nimmt den Rückstand in Wasser auf, filtriert und kristallisiert aus Methanol um; Ausbeute 53 %, F. 116°C, Summenformel $C_{13}H_{15}NO_4S$.
Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 55,50 | 5,37 | 4,98 |
| gef. (%) | 55,32 | 5,33 | 4,68 |

Beispiel 6

3-p-n-Pentylaminophenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 328)

1. Stufe: 5-Benzyloxymethyl-3-p-nitrophenyl-2-oxazolidinon (Code-Nr. 770 151)

Man erhält diese Verbindung mit der gleichen Arbeitsweise wie in Beispiel 1, wobei man von dem geeigneten Propandiol ausgeht; Ausbeute 78 %, F. 125°C, Summenformel $C_{17}H_{16}N_2O_5$
Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 62,19 | 4,91 | 8,53 |
| gef. (%) | 61,84 | 4,87 | 8,57 |

2. Stufe: 3-p-Aminophenyl-5-hydroxymethyl-2-oxazolidinon-hydrochlorid (Code-Nr. 770 211)

In einem Autoklaven erhitzt man eine Suspension von 25 g (0,076 Mol) der in der vorausgegangenen Stufe hergestellten Verbindung, 2,5 g Palladium auf 10 % Kohle und 12,5 ml Äthanol/6,5 n Chlor-

wasserstoffsäure in 600 ml absolutem Alkohol unter einem Druck von 3 kg Wasserstoff 2 Stunden lang auf 50°C. Dann filtriert man, verdampft das Lösungsmittel und kristallisiert den Rückstand aus Methanol um; Ausbeute 64 %, F. 200°C, Summenformel $C_{10}H_{13}ClN_2O_3$.
Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 49,09 | 5,36 | 11,23 |
| gef. (%) | 48,63 | 5,27 | 11,25 |

3. Stufe: 3-p-n-Pentylaminophenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 328)

Eine Suspension von 6,1 g (0,025 Mol) der in der vorausgegangenen Stufe hergestellten Verbindung, 4,5 g (0,03 Mol) n-Pentylbromid, 10 g Kaliumcarbonat und 0,1 g Natriumjodid in 100 ml Butanol erhitzt man 12 Stunden lang unter Rückfluß. Dann filtriert man, verdampft das Lösungsmittel und kristallisiert in einem Äther/Isopropylalkohol-Gemisch; Ausbeute 10 %, F. 124°C, Summenformel $C_{15}H_{22}N_2O_3$.
Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 64,72 | 7,97 | 10,07 |
| gef. (%) | 64,47 | 7,97 | 10,02 |

Beispiel 7

3-p-(m-Nitrophenoxymethyl)phenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 771 263)

1. Stufe: 3-p-Formylphenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 054)

Eine Mischung von 65,4 g 3-p-Formylanilino-1,2-propandiol, 43,6 g Diäthylcarbonat und 16 ml Natriummethylat (10 %ige Lösung in Methanol) in 830 ml Dioxan erhitzt man unter Rückfluß (wobei man den gebildeten Alkohol abdestilliert). Dann filtriert man, dampft das Filtrat ein, nimmt den Rückstand in Chloroform auf und wäscht mit einer verdünnten Chlorwasserstoffsäurelösung. Dann trocknet man, verdampft das Lösungsmittel und chromatographiert den Rückstand an einer Siliciumdioxidkolonne, was zu dem gewünschten Produkt führt; Ausbeute 23 %, F. 123°F, Summenformel $C_{11}H_{11}NO_4$, Molekulargewicht 221,21.

Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 59,72 | 5,01 | 6,33 |
| gef. (%) | 59,49 | 4,66 | 6,20 |

2. Stufe: 3-p-Formylphenyl-tert.-butylcarbonyloxymethyl-2-oxazolidinon (Code-Nr. 771 213)

Zu einer Lösung von 15,5 g der in der vorausgegangenen Stufe hergestellten Verbindung in 180 ml Pyridin gibt man langsam 12,2 ml tert.-Buttersäurechlorid zu. Nach 1 Stunde bei Umgebungstemperatur verdünnt man mit Wasser, filtriert den gebildeten Niederschlag, trocknet ihn und kristallisiert ihn aus Äthanol um; Ausbeute 90 %, F. 134°C, Summenformel $C_{16}H_{19}NO_5$, Molekulargewicht 305,32.

Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 62,94 | 6,27 | 4,59 |
| gef. (%) | 62,64 | 6,57 | 4,46 |

3. Stufe: 3-p-Hydroxymethylphenyl-5-tert.-butylcarbonyloxymethyl-2-oxazolidinon (Code-Nr. 771 214)

Zu einer Suspension von 11,3 g der in der vorausgegangenen Stufe hergestellten Verbindung in 200 ml Methanol gibt man langsam 0,7 g Natriumborhydrid zu. Nach 10 Minuten dampft man das Lösungsmittel ein, nimmt den Rückstand in Äthylacetat auf, wäscht mit Wasser, trocknet, verdampft das Lösungsmittel und kristallisiert den Rückstand aus einem Äther/Isopropanol-Gemisch um; Ausbeute 80 %, F. 102°C, Summenformel $C_{16}H_{21}NO_5$, Molekulargewicht 307,34. Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 62,52 | 6,89 | 4,56 |
| gef. (%) | 62,58 | 7,01 | 4,32 |

4. Stufe: 3-p-(m-Nitrophenoxymethyl)phenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 771 263)

Zu einer Lösung von 11,7 g der in der vorausgegangenen Stufe erhaltenen Verbindung in 150 ml Methylenchlorid gibt man bei 0°C 10,6 ml Triäthylamin und 6 ml Mesylchlorid zu. Dann verdünnt man nach 3-stündigem Kontakt bei Umgebungstemperatur mit Wasser, dekantiert und dampft die organische Phase ein. Man gibt den dabei erhaltenen Rückstand (gelöst in 100 ml Dimethylformamid) zu einer Lösung von 3,7 g m-Nitrophenol und 1,25 g 50 %igem Natriumhydrid in 50 ml Dimethylformamid und erhitzt die Mischung 3 Stunden lang auf 60°C. Dann gießt man die Mischung in Wasser, extrahiert mit Äthylacetat, trocknet, verdampft das Lösungsmittel und behandelt den Rückstand mit einer Lösung von 0,6 g Kaliumhydroxid

in 120 ml Methanol. Nach 1 Stunde unter Rückfluß gießt man die Mischung in Wasser, filtriert den gebildeten Niederschlag ab und kristallisiert aus Methanol und dann aus Äthanol um; Ausbeute 44 %, F. 142°C, Summenformel $C_{17}H_{16}N_2O_6$, Molekulargewicht 344,31.

Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 59,30 | 4,68 | 8,14 |
| gef. (%) | 59,44 | 4,38 | 7,99 |

Beispiel 8

3-p-[(2-1,3-Dithiolanyl)methoxy]phenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 780 080)

1. Stufe: 3-p-(2,2-Diäthoxy)äthoxyphenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 771 049)

Zu einer Lösung von 21 g 3-p-Hydroxyphenyl-5-hydroxymethyl-2-oxazolidinon in 200 ml Dimethylformamid gibt man 4,8 g 50 %iges Natriumhydrid und dann 30 ml Bromacetaldehyddiäthylacetal zu. Man erhitzt die Mischung 13 Stunden lang auf 50°C, gießt sie danach in Eiswasser, extrahiert mit Äthylacetat, wäscht mit Wasser, dampft das Lösungsmittel ein und chromatographiert den Rückstand an einer Siliciumdioxidkolonne. Nach dem Eluieren mit einem $CHCl_3/CH_3OH$ (99/1)-Gemisch erhält man 17 g des gewünschten Produkts; F. 90°C, Summenformel $C_{16}H_{23}NO_6$, Molekulargewicht 325,35.

Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 59,06 | 7,13 | 4,31 |
| gef. (%) | 58,82 | 7,15 | 4,22 |

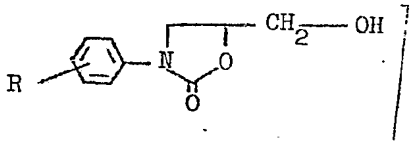
2. Stufe: 3-p-[(2-1,3-Dithiolanyl)methoxy]phenyl-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 780 080)

Man läßt eine Lösung von 2,9 g der in der vorausgegangenen Stufe hergestellten Verbindung, 1,2 ml 1,2-Äthandithiol und 1 ml Bortrifluoridätherat in 35 ml Methylenchlorid 45 Minuten lang bei Umgebungstemperatur stehen. Dann verdünnt man mit Äther und filtriert den gebildeten Niederschlag ab; Ausbeute 60 %, F. 160°C, Summenformel $C_{14}H_{17}NO_4S_2$, Molekulargewicht 327,42.
Elementaranalyse:

| | C | H | N |
|---|---|---|---|
| ber. (%) | 51,35 | 5,23 | 4,28 |
| gef. (%) | 51,51 | 5,28 | 4,00 |

Nach dem gleichen Verfahren, jedoch ausgehend von entsprechenden Reagentien, erhält man die Verbindungen mit den Code-Nummern 780 077 und 780 112, die in der nachfolgenden Tabelle I angegeben sind.

Tabelle I




(I)

Tabelle I

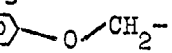
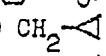
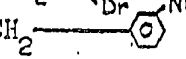
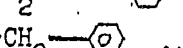
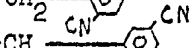
| Code-Nr. | R | Summenformel | Molekulargewicht | Schmelzpunkt (°C) | Ausbeute % | Elementaranalyse ber. (%) C | H | N | gef. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 770365 | 4—CO-Et | $C_{13}H_{15}NO_4$ | 249,26 | 186 | 62 | 62,64 | 6,07 | 5,62 | 62,87 | 6,25 | 5,41 |
| 770423 | 4-$COC_3H_7n$ | $C_{14}H_{17}NO_4$ | 263,28 | 120 | 68 | 63,86 | 6,51 | 5,32 | 63,75 | 6,67 | 5,20 |
| 770152 | 4 $CF_3$ | $C_{11}H_{10}F_3NO_3$ | 261,19 | 88 | 20 | 50,58 | 3,86 | 5,36 | 50,74 | 3,83 | 5,32 |
| 770696 | 4  | $C_{17}H_{17}NO_4$ | 299,31 | 140 | 10 | 68,21 | 5,73 | 4,68 | 68,22 | 5,57 | 4,85 |
| 770388 | 4-O $CH_2$  | $C_{14}H_{17}NO_4$ | 263,28 | 134 | 76 | 63,86 | 6,51 | 5,32 | 63,91 | 6,57 | 5,30 |
| 770788 | 4 O-$CH_2$  | $C_{15}H_{19}NO_4$ | 277,31 | 108 | 48 | 64,96 | 6,91 | 5,05 | 64,66 | 6,89 | 4,94 |
| 770467 | 4 O-$CH_2$  | $C_{16}H_{21}NO_4$ | 291,34 | 130 | 30 | 65,96 | 7,27 | 4,81 | 66,04 | 7,24 | 4,53 |
| 770466 | 4-O-$CH_2$  | $C_{16}H_{19}NO_4$ | 289,32 | 119 | 81 | 66,42 | 6,62 | 4,84 | 66,14 | 6,44 | 4,84 |
| 770196 | 4 O-$(CH_2)_3$- CH=$CH_2$ | $C_{15}H_{19}NO_4$ | 277,31 | 102 | 51 | 64,96 | 6,91 | 5,05 | 64,93 | 7,00 | 5,18 |
| 770154 | 4 O $CH_2$-CO-  | $C_{15}H_{19}NO_5$ | 293,31 | 137 | 58 | 61,42 | 6,53 | 4,78 | 61,27 | 6,56 | 4,66 |
| 770131 | 4 $O(CH_2)_2$- CN | $C_{13}H_{14}N_2O_4$ | 262,26 | 131 | 39 | 59,53 | 5,38 | 10,68 | 59,06 | 5,24 | 10,37 |
| 770126 | 4-O-$CH_2$—C(=N-OH)—$CH_3$ | $C_{13}H_{16}N_2O_5$ | 280,27 | 164 | 75 | 55,71 | 5,75 | 10,00 | 55,44 | 5,70 | 10,09 |
| 770501 | 4-S $CH_2$ CO $CH_3$ | $C_{13}H_{15}NO_4S$ | 281,32 | 116 | 55 | 55,50 | 5,37 | 4,98 | 55,32 | 5,33 | 4,68 |
| 770328 | 4-NH-$C_5H_{11}n$ | $C_{15}H_{22}N_2O_3$ | 278,34 | 124 | 10 | 64,72 | 7,97 | 10,07 | 64,47 | 7,97 | 10,02 |
| 770155 | 3-N($CH_3$)($CH_3$) | $C_{12}H_{16}N_2O_3$ | 236,26 | 110 | 60 | 61,00 | 6,83 | 11,86 | 61,02 | 6,76 | 11,75 |
| 770230 | 3-$OCH_2$ CO $CH_3$ | $C_{13}H_{15}NO_5$ | 265,26 | 102 | 53 | 58,86 | 5,70 | 5,28 | 58,61 | 5,78 | 5,27 |
| 770231 | 3-O $CH_2$ CN | $C_{12}H_{12}N_2O_4$ | 248,23 | 110 | 71 | 58,06 | 4,87 | 11,29 | 58,08 | 4,88 | 11,35 |
| 760557 | 4-O-$CH_2$  | $C_{17}H_{16}BrNO_4$ | 378,27 | 136 | 70 | 53,98 | 4,26 | 3,70 | 54,07 | 4,25 | 3,71 |
| 770234 | 4-$OCH_2$  | $C_{17}H_{16}N_2O_6$ | 344,31 | 135 | 55 | 59,30 | 4,68 | 8,14 | 59,22 | 4,45 | 8,16 |
| 770318 | 4-O-$CH_2$  | $C_{18}H_{16}N_2O_4$ | 324,32 | 135 | 72 | 66,66 | 4,97 | 8,64 | 66,48 | 4,84 | 8,75 |
| 770222 | 4-O-$CH_2$  | $C_{18}H_{16}N_2O_4$ | 324,32 | 138 | 78 | 66,66 | 4,97 | 8,64 | 66,48 | 4,94 | 8,57 |

Tabelle I - 1. Fortsetzung

| Code-Nr. | R | Summenformel | Molekulargewicht | Schmelzpunkt (°C) | Ausbeute (%) | Elementaranalyse | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ber. (%) | | | gef. (%) | | |
| | | | | | | C | H | N | C | H | N |
| 770569 | 4-OCH$_2$-C$_6$H$_4$-NH CO CH$_3$ | $C_{19}H_{20}N_2O_5$ | 356,37 | 212 | 50 | 64,03 | 5,66 | 7,86 | 64,33 | 5,69 | 7,79 |
| 770268 | 4-O-CH$_2$-C$_6$H$_3$Cl$_2$ | $C_{17}H_{15}Cl_2NO_4$ | 368,21 | 140 | 40 | 55,45 | 4,11 | 3,80 | 55,66 | 4,13 | 3,68 |
| 770354 | 4-O CH$_2$-C$_6$H$_3$Cl$_2$ | $C_{17}H_{15}Cl_2NO_4$ | 368,21 | 138 | 36 | 55,45 | 4,11 | 3,80 | 55,70 | 4,19 | 3,84 |
| 770416 | 4-O-CH$_2$-C$_6$H$_3$Cl$_2$ | $C_{17}H_{15}Cl_2NO_4$ | 368,21 | 135 | 25 | 55,45 | 4,11 | 3;80 | 55,43 | 4,12 | 3,75 |
| 770572 | 4-OCH$_2$-C$_6$H$_3$ClF | $C_{17}H_{15}ClFNO_4$ | 351,75 | 110 | 50 | 58,04 | 4,30 | 3,98 | 57,83 | 4,21 | 3,88 |
| 770672 | 4-OCH$_2$-C$_6$H$_3$Cl-NO$_2$ | $C_{17}H_{15}ClN_2O_6$ | 378,76 | 132 | 75 | 53,90 | 3,99 | 7,40 | 53,97 | 3,80 | 7,41 |
| 770790 | 4-OCH$_2$-C$_6$H$_3$Cl-NO$_2$ | $C_{17}H_{15}ClN_2O_6$ | 378,76 | 114 | 22 | 53,90 | 3,99 | 7,40 | 54,27 | 3,76 | 7,49 |
| 770789 | 4-OCH$_2$-C$_6$H$_3$CN-F | $C_{18}H_{15}FN_2O_4$ | 342,32 | 93 | 49 | 63,15 | 4,42 | 8,18 | 63,54 | 4,58 | 8,23 |
| 770298 | 4-OCH$_2$-C$_5$H$_4$N | $C_{16}H_{16}N_2O_4$ | 300,30 | 138 | 33 | 63,99 | 5,37 | 9,33 | 64,05 | 5,44 | 9,44 |
| 770221 | 4-OCH$_2$-C$_5$H$_4$N | $C_{16}H_{16}N_2O_4$ | 300,30 | 162 | 42 | 63,99 | 5,37 | 9,33 | 64,08 | 5,59 | 9,63 |
| 770299 | 4-OCH$_2$-C$_5$H$_4$N | $C_{16}H_{16}N_2O_4$ | 300,30 | 144 | 46 | 63,99 | 5,37 | 9,33 | 64,28 | 5,30 | 9,46 |
| 770673 | 4-OCH$_2$-C$_4$H$_3$S | $C_{15}H_{15}NO_4S$ | 305,34 | 153 | 70 | 59,00 | 4,95 | 4,59 | 59,01 | 4,93 | 4,52 |
| 770889 | 4 OCH$_2$-C$_4$H$_3$O | $C_{15}H_{15}NO_5$ | 289,28 | 162 | 48 | 62,28 | 5,23 | 4,84 | 62,26 | 5,12 | 4,52 |
| 760904 | 4-OCH$_2$-OCH$_3$ | $C_{12}H_{15}NO_5$ | 253,25 | 110 | 32 | 56,91 | 5,97 | 5,53 | 56,87 | 6,04 | 5,48 |
| 750601 | 4-O(CH$_2$)$_2$-C$_5$H$_4$N | $C_{16}H_{22}N_2O_5$ | 322,35 | 121 | 40 | 59,61 | 6,88 | 8,69 | 59,67 | 6,88 | 8,68 |
| 770180 | 4-SC$_5$H$_{11}$ n | $C_{15}H_{21}NO_3S$ | 295,39 | 113 | 73 | 60,99 | 7,17 | 4,74 | 61,15 | 7,06 | 4,80 |
| 770645 | 4-O-CH$_2$-C$_5$H$_4$N | $C_{15}H_{15}N_3O_4$ | 301,30 | 148 | 32 | 59,79 | 5,02 | 13,95 | 59,51 | 4,79 | 13,83 |

Tabelle I - 2. Fortsetzung

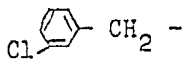
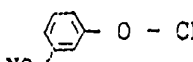
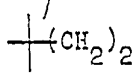
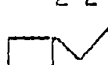
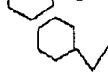
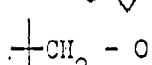
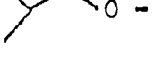
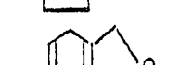
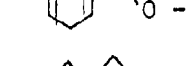
| Code-Nr. | R | Summenformel | Molekulargewicht | Schmelzpunkt (°C) | Ausbeute (%) | Elementaranalyse ber. (%) C | H | N | gef. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 77 1181 |  | $C_{18}H_{15}ClNO_3$ | 331,79 | 123 | 62 | 65,16 | 5,47 | 4,22 | 65,29 | 5,76 | 3,92 |
| 77 1263 |  | $C_{17}H_{16}N_2O_6$ | 344,31 | 142 | 44 | 59,30 | 4,68 | 8,14 | 59,44 | 4,38 | 7,99 |
| 77 1082 |  | $C_{15}H_{21}NO_4$ | 279,33 | 100 | 53 | 64,49 | 7,59 | 5,01 | 64,24 | 7,80 | 4,85 |
| 77 1246 |  | $C_{16}H_{23}NO_4$ | 293,35 | 92 | 22 | 65,50 | 7,90 | 4,78 | 65,53 | 8,12 | 4,64 |
| 77 1245 |  | $C_{17}H_{23}NO_4$ | 305,36 | 108 | 35 | 66,86 | 7,59 | 4,59 | 66,89 | 7,85 | 4,53 |
| 77 0949 |  | $C_{18}H_{25}NO_4$ | 319,39 | 84 | 73 | 67,69 | 7,89 | 4,39 | 67,81 | 7,71 | 4,03 |
| 77 1249 |  | $C_{15}H_{21}NO_4$ | 279,33 | 136 | 15 | 64,49 | 7,58 | 5,01 | 64,64 | 7,62 | 4,91 |
| 77 1197 |  | $C_{16}H_{23}NO_4$ | 293,35 | 86 | 82 | 65,50 | 7,90 | 4,78 | 65,20 | 8,16 | 4,07 |
| 78 0076 |  | $C_{17}H_{23}NO_4$ | 305,36 | 99 | 43 | 66,86 | 7,59 | 4,59 | 66,85 | 7,50 | 4,35 |
| 77 0984 |  | $C_{17}H_{19}NO_4$ | 301,33 | 128 | 32 | 67,76 | 6,36 | 4,65 | 67,49 | 6,47 | 4,49 |
| 78 0259 |  | $C_{14}H_{16}N_2O_4$ | 276,28 | 94 | 55 | 60,86 | 5,84 | 10,14 | 60,66 | 5,85 | 9,98 |
| 77 0962 |  | $C_{14}H_{17}NO_6$ | 295,28 | 154 | 62 | 56,94 | 5,80 | 4,74 | 56,93 | 5,91 | 4,80 |
| 78 0030 |  | $C_{18}H_{25}NO_4$ | 319,39 | 111 | 80 | 67,68 | 7,89 | 4,39 | 67,76 | 8,12 | 4,07 |

Tabelle I - 3. Fortsetzung

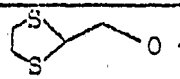
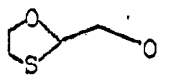
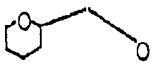
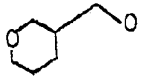
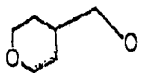
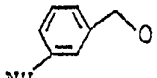
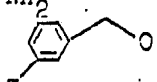
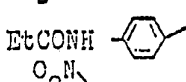
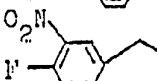
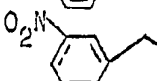
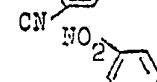
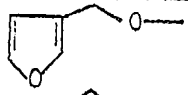
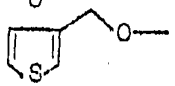
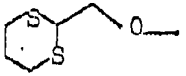
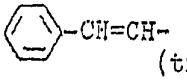
| Code-Nr. | R | Summenformel | Molekulargewicht | Schmelzpunkt °C | Ausbeute % | Elementaranalyse ber. (%) C | H | N | gef. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 78 0080 |  | $C_{14}H_{17}NO_4S_2$ | 327,42 | 160 | 60 | 51,35 | 5,23 | 4,28 | 51,51 | 5,28 | 4,00 |
| 78 0112 |  | $C_{14}H_{17}NO_5S$ | 311,35 | 118 | 55 | 54,00 | 5,50 | 4,50 | 54,13 | 5,52 | 4,38 |
| 77 0900 |  | $C_{16}H_{21}NO_5$ | 307,34 | 112 | 54 | 62,52 | 6,89 | 4,56 | 62,58 | 6,84 | 4,45 |
| 78 0034 |  | $C_{16}H_{21}NO_5$ | 307,34 | 130 | 65 | 62,52 | 6,89 | 4,56 | 62,46 | 7,21 | 4,87 |
| 77 1301 |  | $C_{16}H_{21}NO_5$ | 307,34 | 160 | 72 | 62,52 | 6,89 | 4,56 | 62,29 | 7,02 | 4,43 |
| 77 1240 |  | $C_{17}H_{18}N_2O_4$ | 314,33 | 132 | 88 | 64,95 | 5,77 | 8,91 | 64,71 | 6,00 | 8,71 |
| 77 1321 |  | $C_{17}H_{16}INO_4$ | 425,21 | 145 | 76 | 48,02 | 3,79 | 3,29 | 47,85 | 3,56 | 3,45 |
| 78 0182 |  | $C_{19}H_{20}N_2O_6$ | 372,37 | 202 | 47 | 61,28 | 5,41 | 7,52 | 60,71 | 5,72 | 7,94 |
| 78 0443 |  | $C_{20}H_{22}N_2O_5$ | 370,39 | 208 | 32 | 64,85 | 5,98 | 7,56 | 64,78 | 6,04 | 7,70 |
| 77 0955 |  | $C_{17}H_{15}FN_2O_6$ | 362,31 | 110 | 82 | 56,35 | 4,17 | 7,73 | 56,16 | 4,40 | 7,43 |
| 77 1125 |  | $C_{18}H_{15}N_3O_6$ | 369,32 | 176 | 85 | 58,53 | 4,09 | 11,38 | 58,03 | 3,85 | 11,37 |
| 77 1199 |  | $C_{17}H_{15}ClN_2O_6$ | 378,76 | 178 | 78 | 53,90 | 3,99 | 7,40 | 53,47 | 3,90 | 6,72 |

Tabelle I - 4. Fortsetzung

| Code-Nr. | R | Summenformel | Molekulargewicht | Schmelzpunkt °C | Ausbeute % | Elementaranalyse ber. (%) | | | Elementaranalyse gef. (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | C | H | N |
| 77 0979 |  | $C_{15}H_{15}NO_5$ | 289,28 | 131 | 47 | 62,28 | 5,23 | 4,84 | 61,98 | 5,22 | 4,72 |
| 77 1067 |  | $C_{15}H_{15}NO_4S$ | 305,34 | 144 | 23 | 59,00 | 4,95 | 4,59 | 59,04 | 4,98 | 4,43 |
| 78 0077 |  | $C_{15}H_{19}NO_4S_2$ | 341,44 | 142 | 58 | 52,76 | 5,61 | 4,10 | 52,98 | 5,85 | 4,02 |
| 78 0562 |  | $C_{15}H_{18}N_2O_4$ | 290,31 | 68 | 35 | 62,05 | 6,25 | 9,65 | 61,75 | 6,25 | 9,70 |
| 78 0564 |  (trans) | $C_{18}H_{17}NO_3$ | 295,32 | 215 | 71 | 73,20 | 5,80 | 4,74 | 72,92 | 5,72 | 4,66 |

Die Verbindungen der Formel (I) wurden an Versuchstieren untersucht und es zeigte sich, daß sie Aktivitäten auf dem psychotropen Gebiet als potentielle Antidepressionsmittel aufwiesen. Diese Aktivitäten wurden durch die nachfolgend beschriebenen Tests nachgewiesen:

Test A

Potenzierung von generellem Zittern bei der Maus, hervorgerufen durch eine intraperitoneale Injektion (200 mg/kg) von dl-5-Hydroxytryptophan nach dem von C. Gouret und G. Raynaud in "J. Pharmacol. (Paris)", 1974, 5, 231, beschriebenen Versuch.

Test B

Antagonismus gegenüber Ptosis, die 1 Stunde nach der intravenösen Injektion (2 mg/kg) von Resorpin bei der Maus beobachtet wurde, nach dem von C. Gouret und J. Thomas in "J. Pharmacol. (Paris)", 1973, 4, 401, beschriebenen Versuch.

Test C

Verminderung der Dichte der Hinterhaupt-Pontogenicul-Punkte (P.G.O.), hervorgerufen durch eine intravenöse Injektion (0,5 mg/kg) von Resorpin bei der Katze nach dem von von A. Coston und C. Gouret in "J. Pharmacol. (Paris)", 1976, 7, 409, beschriebenen Versuch.

Die Ergebnisse dieser drei Tests sowie diejenigen einer notorisch bekannten Vergleichssubstanz, dem Toloxatone, sind in der nachfolgenden Tabelle II zusammengefaßt.

Tabelle II

| getestete Verbindungen | Test A DE 50 (mg/kg/p.o.) | Test B DE 50 (mg/kg/p.o.) | Test C DE 50 (mg/kg/i.p.) |
|---|---|---|---|
| a) erfindungsgemäß | | | |
| 770 365 | 29 | 25 | - |
| 770 423 | 35 | 25 | 5 |
| 770 152 | 20 | 25 | 15 |
| 770 696 | 15 | 20 | - |
| 770 388 | 9 | 12,5 | 4,5 |
| 770 788 | 6,25 | 12,5 | - |
| 770 467 | 2,8 | 1,2 | 3 |
| 770 466 | 9,6 | 6,2 | 9 |
| 770 196 | 20 | 15 | 16 |
| 770 154 | 50 | 50 | 20 |
| 770 131 | 2,5 | 3 | 5,5 |
| 770 126 | 8 | 11 | 16,5 |
| 760 904 | 50 | 50 | 8,5 |
| 750 601 | 70 | 8 | 31 |
| 770 180 | 35 | 45 | 45 |
| 770 501 | 22 | 25 | - |
| 770 328 | 25 | 35 | - |
| 770 155 | 50 | 22,5 | 35 |
| 770 230 | - | 6,25 | 16 |
| 770 231 | 40 | 50 | 14 |
| 760 557 | 7,3 | 3,3 | 110 |
| 770 234 | 1,5 | 0,7 | 9 |
| 770 318 | 25 | 16 | - |
| 770 222 | 2,8 | 1,2 | 5,2 |
| 770 569 | 5 | 2,5 | 6 |
| 770 268 | 7 | 8,5 | - |
| 770 354 | 25 | 30 | 30 |
| 770 416 | 6,2 | 10 | 3 |
| 770 572 | 6,3 | 3,12 | 8,5 |
| 770 672 | 25 | 19 | - |
| 770 790 | 50 | 25 | - |
| 770 789 | 3 | 2 | - |
| 770 298 | 55 | 12,5 | - |

Tabelle II - Fortsetzung

| getestete Verbindungen | Test A DE 50 (mg/kg/p.o.) | Test B DE 50 (mg/kg/p.o.) | Test C DE 50 (mg/kg/i.p.) |
|---|---|---|---|
| a) erfindungsgemäß | | | |
| 770 221 | 11,8 | 3,12 | 15 |
| 770 299 | 20 | 12,5 | - |
| 770 673 | 16 | 35 | 8 |
| 770 845 | 6,25 | 12,5 | - |
| 771 181 | 6,25 | 6,25 | - |
| 771 263 | 4 | 3,1 | - |
| 771 082 | 1,3 | 0,7 | - |
| 771 246 | 17 | 23 | - |
| 771 245 | 1,5 | 2 | - |
| 770 949 | 10 | 16 | - |
| 771 249 | 22,5 | 50 | - |
| 771 197 | 25 | 16 | - |
| 780 030 | 3 | 5,3 | - |
| 780 076 | 2,3 | 7 | - |
| 770 984 | 10 | 25 | - |
| 780 259 | 1,25 | 3,2 | - |
| 770 962 | 26 | 50 | - |
| 780 080 | 50 | 50 | - |
| 780 112 | 5 | 5,2 | - |
| 770 900 | 50 | 25 | - |
| 780 034 | 4,4 | 6,2 | - |
| 771 301 | 1,9 | 3 | - |
| 771 240 | 35 | 50 | - |
| 771 321 | 25 | 20 | - |
| 780 182 | 40 | 25 | - |
| 780 443 | 3,7 | 12,5 | - |
| 770 955 | 13 | 7 | - |
| 771 125 | 3,12 | 1,56 | - |
| 771 199 | 1,1 | 0,8 | - |
| 780 562 | 0,8 | - | - |
| 770 979 | 14 | 35 | - |
| 771 067 | 7,5 | 12,5 | - |
| 780 077 | 25 | 44 | - |
| b) Vergleich | | | |
| TOLOXATONE | 50 | | 28 |

Wie aus den vorstehend angegebenen Ergebnissen und denjenigen, die in der nachfolgenden Tabelle III angegeben sind, hervorgeht, ist der Abstand zwischen den letalen Dosen und den pharmakologisch aktiven Dosen ausreichend groß, um die therapeutische Verwendung der erfindungsgemäßen Verbindungen zu erlauben.

Tabelle III

| getestete Verbindungen | akute Toxizität bei der Maus | | |
|---|---|---|---|
| | verabreichte Dosis (mg/kg/p.o.) | Mortalität(%) | DL 50 (mg/kg/p.o.) |
| a) erfindungsgemäß | | | |
| 770 131 | 1000 | 0 | – |
| 770 222 | 1000 | 0 | – |
| 770 234 | 1000 | 0 | – |
| 760 652 | 1000 | 0 | – |
| 760 557 | " | " | – |
| 771 082 | – | – | >2000 |
| 771 245 | – | – | " |
| 771 301 | – | – | " |
| 770 955 | 2000 | 17 | – |
| b) Vergleich | | | |
| TOLOXATONE | – | – | 1850 |

Wie aus den in den vorstehenden Tabellen angegebenen Ergebnissen hervorgeht, haben die erfindungsgemäßen Verbindungen der Formel (I) eine Aktivität (Wirksamkeit), die derjenigen der Vergleichsverbindung überlegen oder zumindest gleich ist. Sie sind indiziert bei endogenen und exogenen depressiven Zuständen und sie können auf oralem Wege in Form von Tabletten, Dragees, Kapseln, in einer mittleren Dosis von 500 mg aktivem Prinzip pro Tag verabreicht werden. Sie können auch in Form von injizierbaren Lösungen in einer Menge von 5 bis 50 mg aktivem Prinzip pro Tag verabreicht werden, wobei das verwendete Lösungsmittel aus binären oder ternären Mischungen besteht, die beispielsweise Wasser, Polypropylenglykol oder Polyäthylenglykol (Sorte 300 bis 400) oder irgendein anderes physiologisch verträgliches Lösungsmittel enthalten; die relativen Mengenverhältnisse der verschiedenen Lösungsmittel werden in Abhängigkeit von der verabreichten Dosis eingestellt.

Die Erfindung wurde zwar vorstehend unter Bezugnahme auf bevorzugte Ausführungsformen näher erläutert, es ist jedoch für den Fachmann selbstverständlich, daß sie darauf keineswegs beschränkt ist, sondern daß diese in vielfacher Hinsicht abgeändert und modifiziert werden können, ohne daß dadurch der Rahmen der vorliegenden Erfindung verlassen wird.

Die oben angegebenen Synthese-Zwischenprodukte der Formeln (X), (XI), (XIII), (XV), (XVII), (XVIII), (XXI), (XXII), (XXIII), (XXIV), (XXV) und (XXVI) stellen neue Verbindungen dar und bilden einen weiteren Gegenstand der Erfindung.

(12) UK Patent Application (19) GB (11) 2 140 687 A

(43) Application published 5 Dec 1984

(21) Application No 8334189

(22) Date of filing 22 Dec 1983

(30) Priority data

(31) 493760 (32) 11 May 1983 (33) US

(71) Applicant
Alza Corporation, (USA—California),
950 Page Mill Road, Palo Alto, California 94304,
United States of America

(72) Inventors
Patrick S. L. Wong, Joseph C. Deters,
Brian Barclay, Felix Theeuwes

(74) Agent and/or address for service
F. J. Cleveland & Company, 40—43 Chancery Lane,
London, WC2A 1JQ

(51) INT CL³
A61K 9/00 A61M 31/00

(52) Domestic classification
A5B 829 832 835 M Q

(56) Documents cited

| | | | |
|---|---|---|---|
| GB A | 2116842 | EP A2 | 0040899 |
| GB | 1551898 | EP A1 | 0010876 |
| GB | 1511614 | US | 4327725 |
| GB | 1385521 | US | 4111202 |

(58) Field of search
A5B

# (54) Osmotic drug delivery system

(57) An osmotic system is disclosed comprising a wall 12, 23 formed in at least a part of a semipermeable material that surrounds a compartment 14. The compartment contains a first osmotic composition 15, 16, 17 comprising a beneficial agent 15, and a second and different osmotic composition 18, 19. A passageway 13 in the wall connects the first composition with the exterior of the system.

FIG. 2

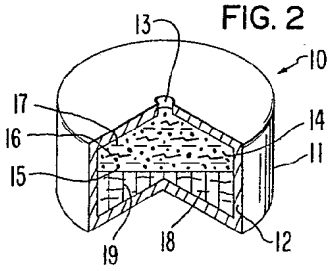
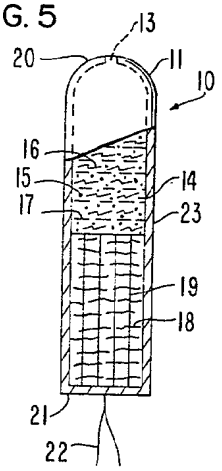



FIG. 5




GB 2 140 687 A

2140697

FIG. 1

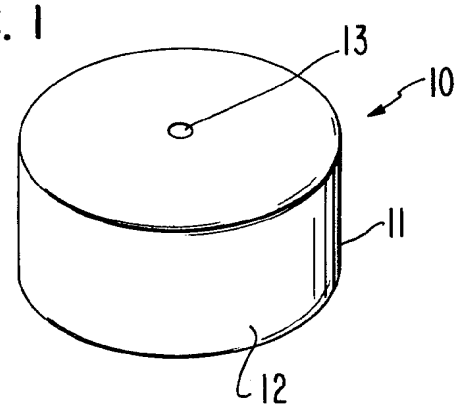



FIG. 2

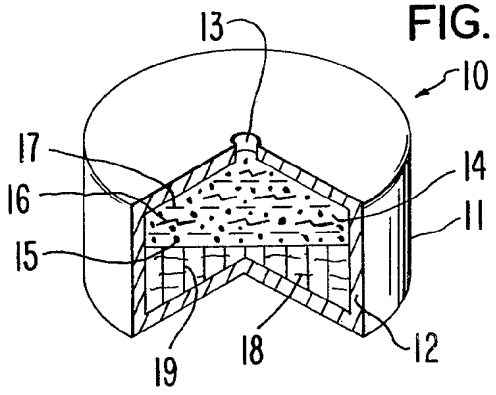



FIG. 3

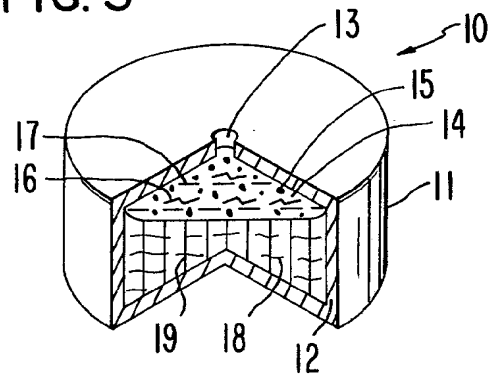



FIG. 4

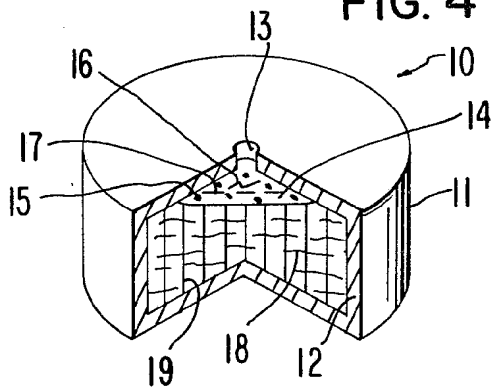



FIG. 5

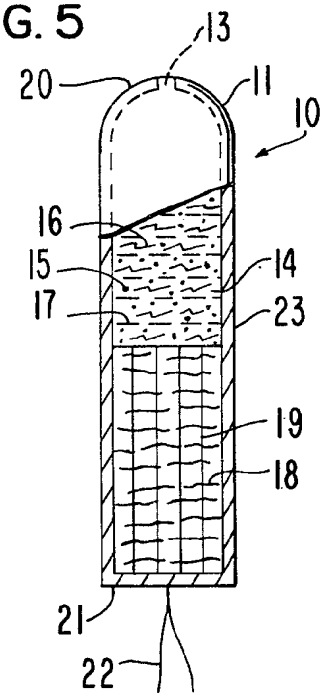



FIG. 6

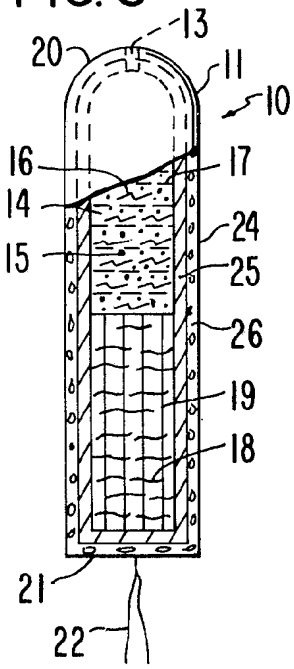
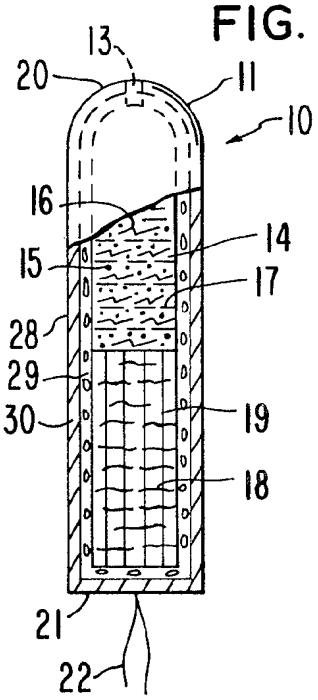



FIG. 7



2140637

FIG. 8

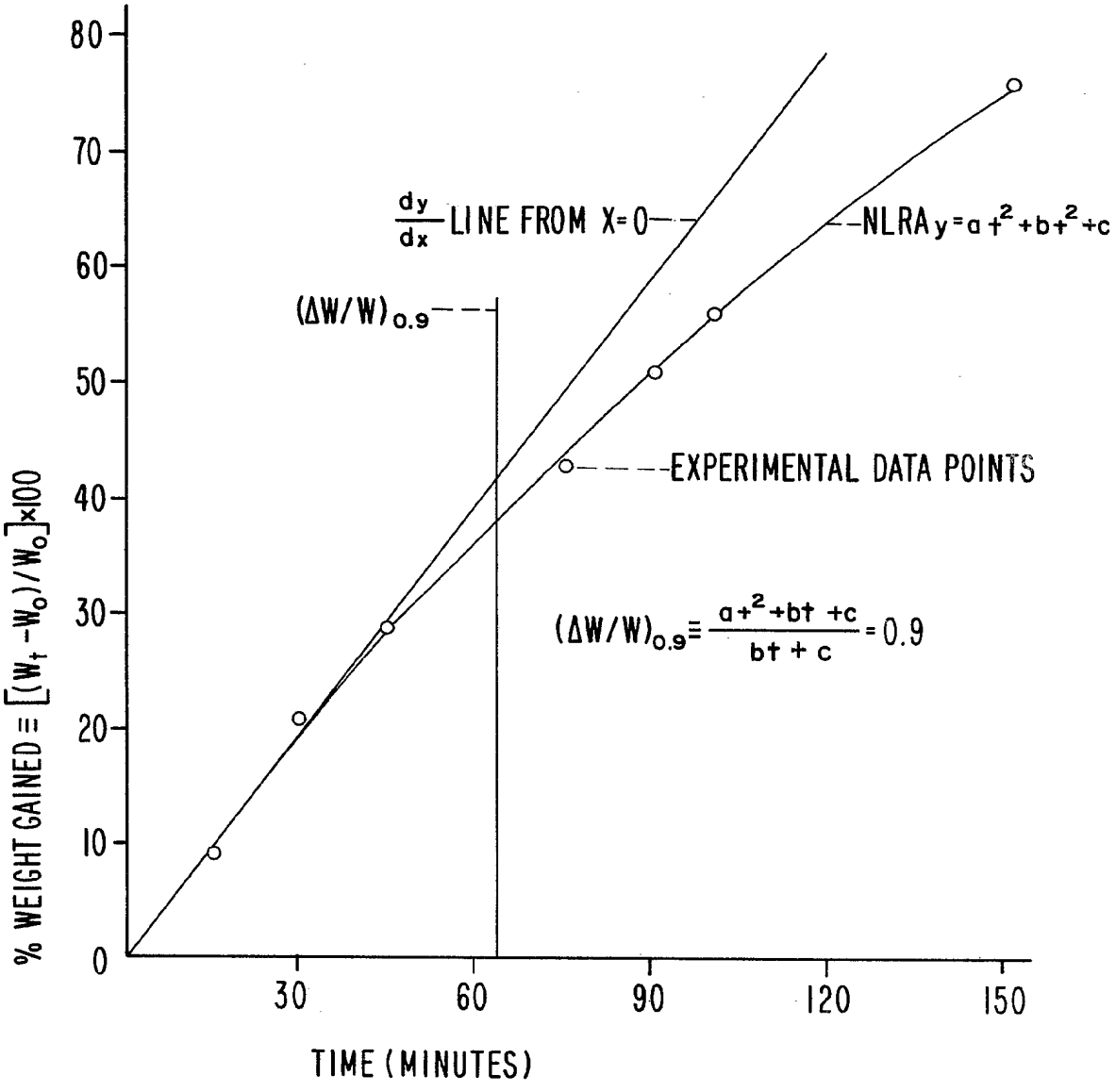


FIG. 9

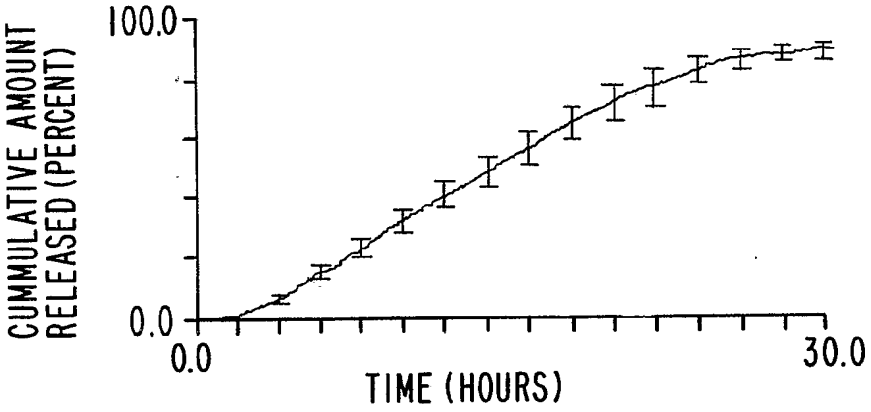
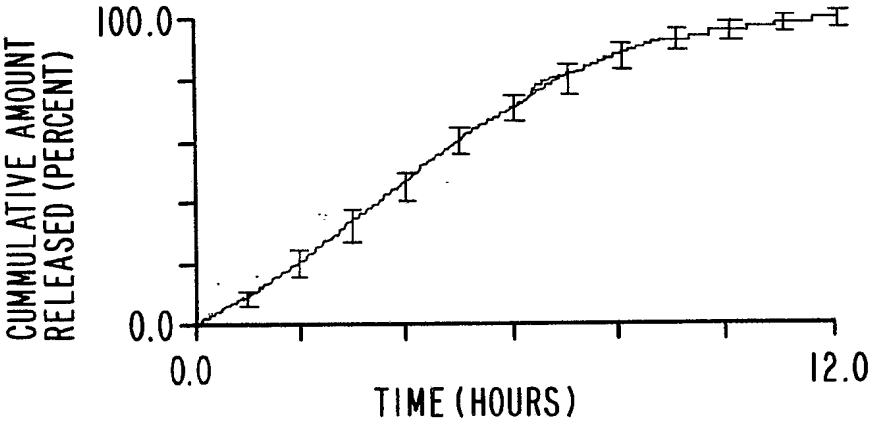

100.0
0.0
0.0
30.0
CUMMULATIVE AMOUNT RELEASED (PERCENT)
TIME (HOURS)

FIG. 10


100.0
0.0
0.0
12.0
CUMMULATIVE AMOUNT RELEASED (PERCENT)
TIME (HOURS)

2140637

FIG. II

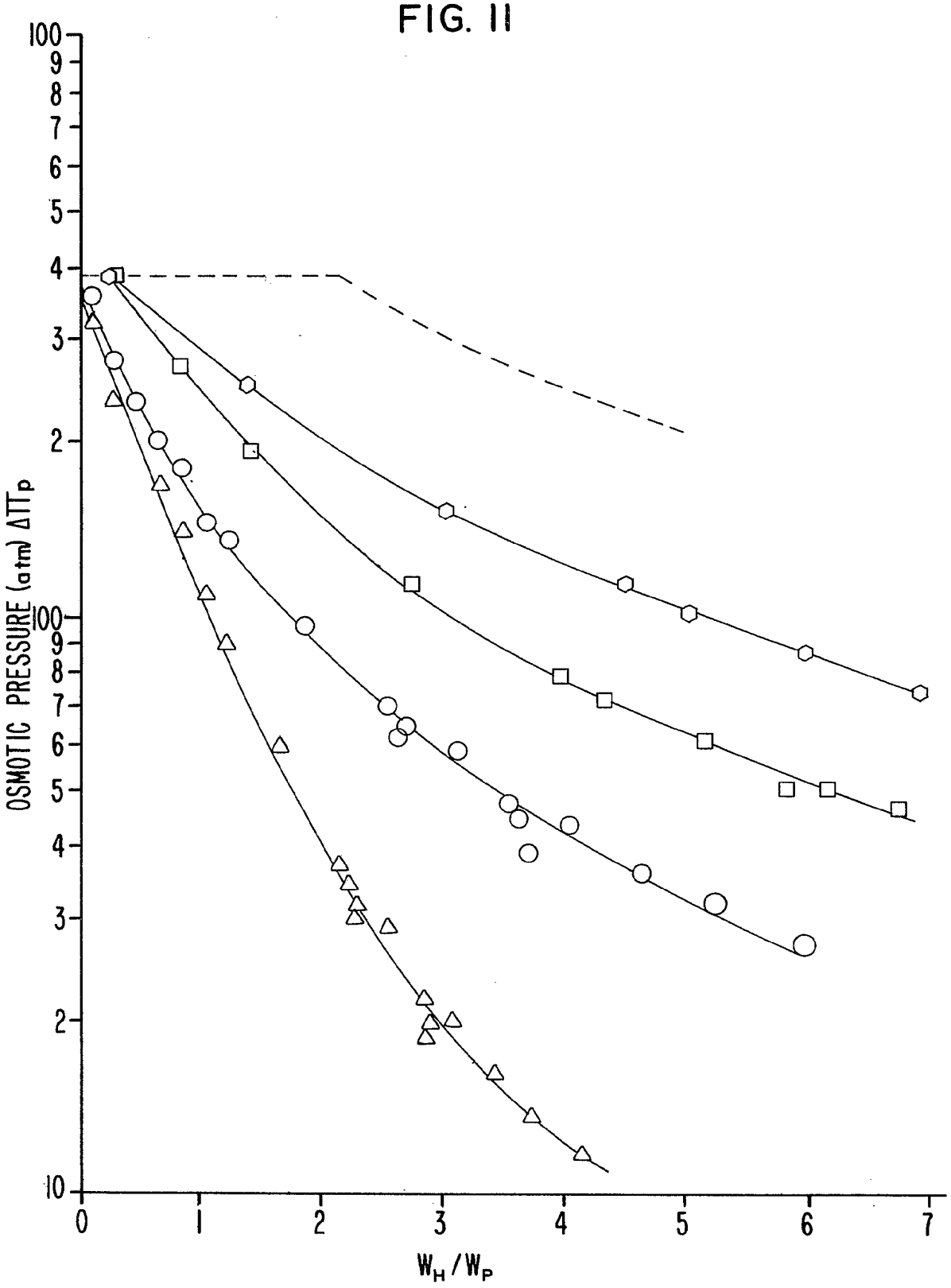


FIG. 12

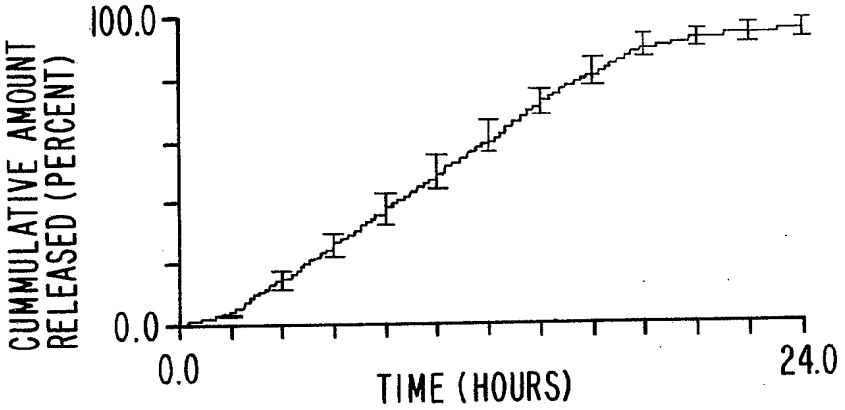



FIG. 13

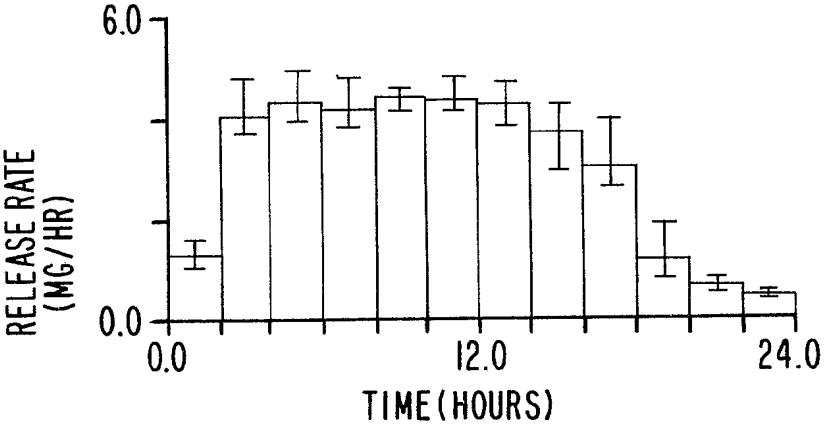



FIG. 14

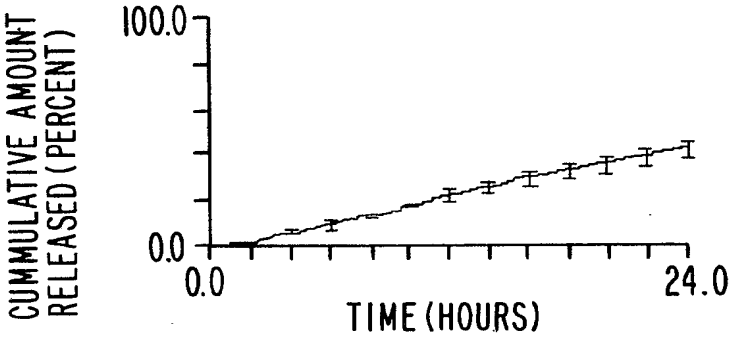
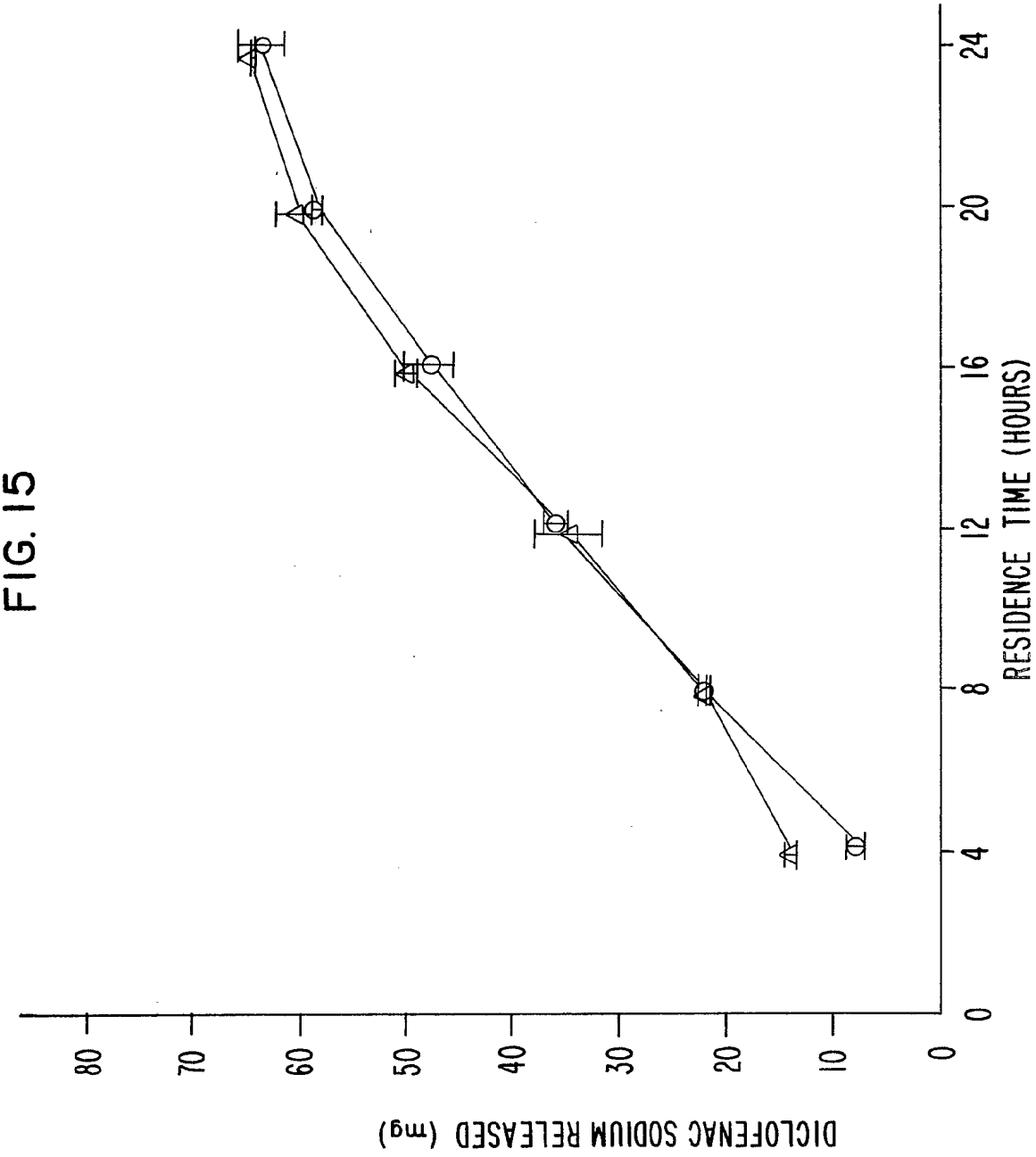
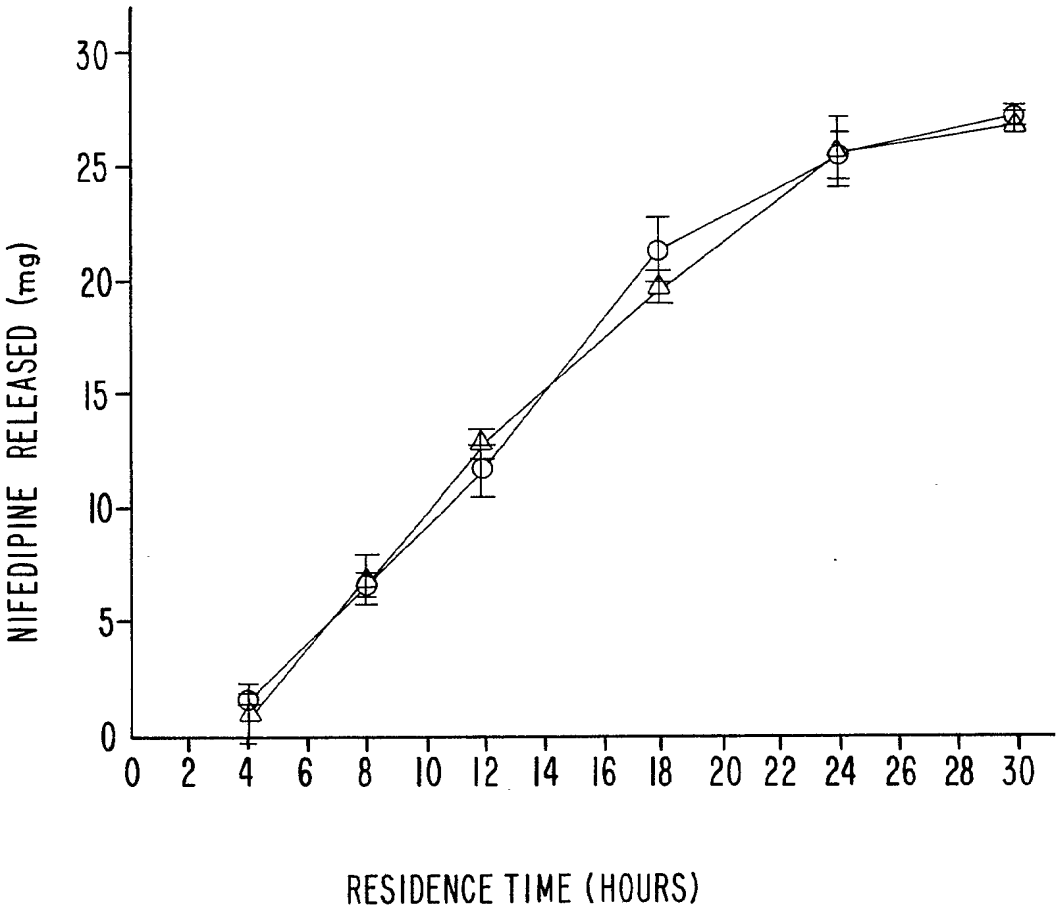


FIG. 15


DICLOFENAC SODIUM RELEASED (mg)
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
RESIDENCE TIME (HOURS)

2140637

FIG. 16



SPECIFICATION

**Osmotic Device With Dual Thermodynamic Activity**

This invention pertains to both a novel and unique delivery system. More particularly, the invention relates to an osmotic device comprising a wall formed in at least a part of a semi-permeable material that surrounds a compartment comprising: (1) a first osmotic composition comprising a beneficial agent, and preferably an osmagent and/or an osmopolyer, said composition in contacting arrangement with (2) a second osmotic composition comprising an osmagent and an osmopolymer. A passageway through the wall connects the exterior of the osmotic device with the first osmotic composition containing the beneficial agent for delivering the first composition from the osmotic device. The osmotic device is useful for delivering beneficial agents that because of their solubilities are difficult to deliver in a known amount at a controlled rate from an osmotic dispensing system.

Background of the Invention

Since the beginning of antiquity, both pharmacy and medicine have sought a delivery system for administering a beneficial drug. The first written reference to a dosage form is in the Eber Papyrus, written about 1552 B.C. The Eber Papyrus mentions dosage forms such as anal suppositories, vaginal pessaries, ointments, oral pill formulations, and other dosage preparations. About 2500 years passed without any advance in dosage form development, when the Arab physician Rhazes, 865—925 A.D., invented the coated pill. About a century later the Persian Avicenna, 980—1037 A.D., coated pills with gold or silver for increasing patient acceptability and for enhancing the effectiveness of the drug. Also around this time, the first tablet was described in Arabian manuscrips written by al-Zahrawi, 936—1009 A.D. The manuscrips described a tablet formed from the hollow impressions in two facing tablet molds. Pharmacy and medicine waited about 800 years for the next innovation in dosage forms, when in 1883 Mothes invented the capsule for administering drug. The next quantum leap in dosage forms came in 1972 with the invention of the osmotic delivery device by inventors Theeuwes and Higuchi as disclosed in United States Pat. Nos. 3,845,770 and 3,916,899. The osmotic devices disclosed in those patents comprise a semi-permeable wall that surrounds a compartment containing a useful agent. The wall is permeable to the passage of an external fluid, and it is substantially impermeable to the passage of useful agent. There is a passageway through the wall for delivering the useful agent from the osmotic device. These devices release useful agent by fluid being imbibed through the semi-permeable wall into the compartment at a rate determined by the permeability of the semi-permeable wall and the osmotic pressure gradient across the semi-permeable wall to produce an aqueous solution containing useful agent that is dispensed through the passageway from the device. These devices are extraordinarily effective for delivering a useful agent that is soluble in the fluid and exhibits an osmotic pressure gradient across the semi-permeable wall against the external fluid.

A pioneer advancement in osmotic delivery devices was presented to the dispensing arts by inventor Felix Theeuwes In United States Patent No. 4,111,202. In this patent, the delivery kinetics of the osmotic device is enhanced for delivering useful agents that are insoluble to very soluble in the fluid, by manufacturing the osmotic device with a useful agent compartment and an osmagent compartment separated by a film. The film is movable from a rested to an expanded state. The osmotic device delivers agent by fluid being imbibed through the semi-permeable wall into the osmagent compartment producing a solution that causes the compartment to increase in volume and act as a driving force that is applied against the film. This force urges the film to expand against the useful agent compartment and correspondingly diminish the volume of the useful agent compartment, whereby useful agent is dispensed through the passageway from the osmotic device. While this device operates successfully for its intended use, and while it can deliver numerous useful agents of varying solubilities, its use can be limited because of the manufacturing steps and costs needed for fabricating and placing the movable film in the compartment of the osmotic device.

In United States Patent No. 4,327,725 patentees Richard Cortese and Felix Theeuwes provided an osmotic dispensing device for delivering beneficial agents, that because of their solubilities in aqueous and biological fluids, are difficult to deliver in meaningful amounts at controlled rates over time. The osmotic devices of this patent comprise a semi-permeable wall surrounding a compartment containing a beneficial agent that is insoluble to very soluble in aqueous and biological fluids, and an expandable hydrogel. In operation the hydrogel expands in the presence of external fluid that enters the device thereby causing the beneficial agent to be dispensed through the passageway from the device. This device operates successfully for its intended use, and it delivers many difficult to deliver beneficial agents for their intended purpose. Now it has been observed, its use can be limited because the hydrogel lacks a present ability to imbibe sufficient fluid for the maximum self-expansion needed for urging the beneficial agent from the device.

It will be appreciated by those versed in the dispensing art, that if an osmotic device can be provided that exhibits a high level of osmotic activity for delivering a beneficial agent by generating in situ an expanding force sufficient for delivering the maximum amount of agent at a controlled rate from an osmotic device, such an osmotic device would have a positive value and represent an advancement in the dispensing art. Likewise, it will be immediately appreciated by those versed in the dispensing art

that if an osmotic device is made available possessing dual thermodynamic osmotic activity for delivering increased amounts of a beneficial agent, said osmotic device would find practical application in the fields of pharmacy and medicine.

Object of the Invention

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide an osmotic system that represents a further improvement and advancement in the dispensing art.

Another object of the invention is to provide an osmotic system manufactured in the form of an osmotic device for delivering in vivo a beneficial drug that is difficult to deliver and now can be delivered by the osmotic device provided by this invention in therapeutically effective amounts over time.

Another object of the invention is to provide an osmotic system possessing dual osmotic activity, which system comprises a compartment containing a first osmotic composition comprising a drug, and preferably an osmagent and/or an osmopolymer, and a second osmotic composition comprising an osmagent and an osmopolymer, with the compositions acting in concert for delivering the drug from the osmotic device.

Yet another object of the invention is to provide an osmotic device having means for high loading of a water-insoluble or a slightly water-soluble drug and means for delivering the drug in either instance at a controlled rate and continuously over time.

Yet another object of the invention is to provide an osmotic device that can deliver a pH dependent beneficial agent by providing a neutral medium for delivering the beneficial agent in a finely dispersed form for increasing its surface area and for maximizing the dissolution rate of the beneficial agent.

Still yet another object of the invention is to provide an osmotic system for delivering a drug having a very low dissolution rate that is the rate-limiting step for delivering the drug from the system, but now can be delivered by using an osmotic composition that functions in situ as a wetting agent and a solubilizing agent for increasing the dissolution rate and the solubility of the drug, thereby enhancing its delivery from the osmotic system.

Still yet another object of the invention is to provide an osmotic system comprising means for maintaining a high level of osmotic activity of a polymer used for delivering a beneficial agent from the osmotic system.

Still a further object of the invention is to provide an osmotic, therapeutic device that can administer a complete pharmaceutical dosage regimen comprising poorly soluble to very soluble agents, at a controlled rate and continuously, for a particular time period, the use of which requires intervention only for the initiation and possible termination of the regimen.

Other objects, features, aspects and advantages of the invention will be more apparent to those versed in the dispensing art from the following detailed specification taken in conjunction with the figures and the accompanying claims.

Brief Description of the Drawings

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Figure 1 is an isometric view of an osmotic device designed for orally administering a beneficial agent to the gastrointestinal tract;

Figure 2 is an opened view of the osmotic device of Figure 1 illustrating the structure of the osmotic device of Figure 1;

Figure 3 is an opened view of the osmotic device of Figure 1 illustrating the osmotic device in operation and delivering a beneficial agent from the osmotic device;

Figure 4 is an opened view of the osmotic device of Figure 1 considered with Figure 3 illustrating the osmotic device in operation and delivering a major amount of a beneficial agent from the osmotic device;

Figure 5 shows an osmotic therapeutic device with its wall partially broken away, designed for delivering a beneficial agent into a body passageway, such as the ano-rectal and vaginal passageways;

Figure 6 shows the osmotic device of Figure 5 with a different wall structure;

Figure 7 shows the osmotic device of Figure 5 depicting a different wall structure than the wall structure depicted in Figure 6.

Figure 8 represents the weight gain as a function of time for a polymer encapsulated in a semi-permeable membrane when the encapsulated polymer is placed in water;

Figure 9 depicts the cumulative amount of drug released from a device comprising an osmopolymer having two different molecular weights;

Figure 10 depicts the cumulative amount of drug released from a device using a different set of osmopolymers;

Figure 11 depicts the osmotic pressure curves for a number of osmagent and a number of osmopolymer/osmagent compositions;

Figure 12 depicts the cumulative release profile for an osmotic system using two different osmopolymers;

Figure 13 depicts the release rate per hour for an osmotic system different from Figure 9 containing an osmopolymer having two different molecular weights;

Figure 14 depicts the cumulative amount released from a single composition device comprising only one layer;

Figure 15 illustrates the in vivo and in vitro cumulative release for one drug delivered by the osmotic device;

Figure 16 illustrates the in vivo and in vitro cumulative release for a different drug delivered by an osmotic device.

In the drawings and the specification, like parts in related figures are identified by like parts. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further detailed elsewhere in the disclosure.

Detailed Description of the Drawings

Turning now to the drawings in detail, which are examples of various osmotic devices provided by the invention, and which examples are not to be construed as limiting, one example of an osmotic device is seen in Figure 1. In Figure 1, osmotic device 10 is seen comprising a body member 11 having a wall 12 and a passageway 13 for releasing a beneficial agent from osmotic device 10.

In Figure 2, osmotic device 10 of Figure 1 is seen in opened section. In Figure 2, osmotic device 10 comprises a body 11, a semipermeable wall 12 that surrounds and forms internal compartment 14, that communicates through a passageway 13 with the exterior of osmotic device 10. Compartment 14 contains a first osmotic composition comprising a beneficial agent 15, represented by dots, and it can be from insoluble to very soluble in fluid imbibed into compartment 14, an osmagent 16, represented by wavy lines, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across semi-permeable wall 12 against an external fluid, and, an osmopolymer 17, represented by horizontal dashes, that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across semi-permeable wall 12 against an exterior fluid present in the environment of use. Wall 12 is formed of a semi-permeable composition that is substantially permeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of agent 15, osmagent 16 and osmopolymer 17. Semi-permeable wall 12 is non-toxic and it maintains its physical and chemical integrity during the delivery life of device 10.

Compartment 14 also houses a second osmotic composition that is distant from passageway 13 and in contacting relation with the first composition. The second composition is an expandable driving force that acts in co-operation with the first osmotic composition for delivering the maximum amount of beneficial agent 15 from osmotic device 10. The second osmotic composition comprises an osmagent 18, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across wall 12 against an external fluid, blended with an osmopolymer 19 that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across wall 12 against external fluid. Osmopolymers 17 and 19 are hydrophilic water soluble or lightly cross-linked water insoluble polymers, and they possess osmotic properties such as the ability to imbibe external fluid, exhibit an osmotic pressure gradient across the semipermeable wall against the external fluid, and swell or expand in the presence of the fluid. Osmopolymers 17 and 19 are mixed with osmagent 16 and 18 for imbibing the maximum volume of external fluid into compartment 14. This fluid is available to osmopolymers 17 and 19 to optimize the volumetric rate and for total expansion of osmopolymers 17 and 19. That is, osmopolymers 17 and 19 absorb fluid imbibed into compartment 14 by the osmotic imbibition action of osmopolymers 17 and 19 supplemented by the osmotic imbibition action of osmagents 16 and 18 for effecting the maximum expansion of osmopolymers 17 and 19 to an enlarged state.

In operation, the delivery of beneficial agent 15 from osmotic device 10 is carried out, in one presently preferred embodiment, by (1) imbibition of fluid by the first composition to form a suspension in situ and delivery of the suspension through the passageway; and concurrently by (2) imbibition of fluid by the second composition causing the second composition to swell and co-operate with the first composition for driving the agent suspension through the passageway. According to the operation described, the osmotic device may be treated as a cylinder, with the second composition expanding like the movement of à piston for aiding in delivering the agent suspension from the osmotic device. Although the shape of the osmotic device as depicted in Figs. 1 and 2 is not a true cylinder, it is approximate enough for the following physical analysis. In this analysis, the volume rate delivered by the osmotic device $F_t$ is composed of two sources; the water imbibition rate by the first composition F, and the water imbibition rate by the second composition Q wherein:

$$F_t=F+Q \qquad (1)$$

Since the boundary between the first composition and the second composition hydrates very

little during the functioning of the osmotic device, there is insignificant water migration between the compositions. Thus, the water imbibition rate of the second composition, Q, equals the expansion of its volume,

$$\frac{dv_p}{dt}=Q \quad (2)$$

The total delivery rate from the osmotic device is then,

$$\frac{dm}{dt}=F_t \cdot C=(F+Q)C \quad (3)$$

wherein C is the concentration of beneficial agent in the delivered slurry. Conservation of the osmotic device volume, V, and the surface area, A, gives equation 4 and 5:

$$V=V_d+V_p \quad (4)$$

$$A=A_d+V_p \quad (5)$$

wherein $V_d$ and $V_p$ equal the volumes of the first composition and the second composition respectively; and wherein $A_d$ and $A_p$ equal the surface area contact with the wall by the first composition and the second composition respectively. In operation, both $V_p$ and $A_p$ increase with time while $V_d$ and $A_d$ decrease with time as the device delivers beneficial agent.

The volume of the second composition that expands with time when fluid is imbibed into the compartment is given by equation 7:

$$V_p=\int\left(\frac{W_H}{W_p}\right) \quad (7)$$

wherein, $W_H$ is the weight of fluid imbibed by the second composition, $W_p$ is the weight of the second composition initially present in the device, $W_H/W_p$ is the ratio of fluid to initial solid of the second composition, $V_p$ equals

$$\left(1+\frac{W_H}{W_p}\right)\ \frac{W_p}{e}$$

wherein e is the density of the second composition corresponding to $W_H/W_p$. Thus, based on the geometry of a cylinder, where r is radius of the cylinder, the area of imbibition is related to the volume of the swollen second composition as follows:

$$A_p=r^2+\frac{2\,W_p}{r\ e}\ 1+\ \frac{W_H}{W_p} \quad (8)$$

$$A_d=A-A_p \quad (9)$$

The fluid imbibition rates into each compartment are:

$$F=\left(\frac{k}{h}\right)(A_d\ \Delta\pi_d) \quad (10)$$

$$Q=\left(\frac{k}{h}\right)(A_p\ \Delta\pi_p) \quad (11)$$

wherein k equals the osmotic permeability of the wall, h equals the wall thickness, $\Delta\pi_d$ and $\Delta\pi_p$ are the osmotic gradients for the first composition and the second composition respectively.

The total delivery rate, therefore, is:

$$\frac{dm}{dt} = \frac{k}{h} C A - \pi r^2 - \frac{2}{Y} \frac{W_p}{p} 1 + \frac{W_H}{W_p} \Delta\pi d + \pi p^2 + \frac{2}{r} \frac{W_p}{p} 1 + \frac{W_H}{W_p} \Delta\pi p \quad (12)$$

Figures 3 and 4 illustrate the osmotic device in operation as described for Figures 1 and 2. In Figures 3 and 4, for osmotic device 10, fluid is imbibed by the first composition at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall. The imbibed fluid continuously forms a solution containing beneficial agent, or a solution or of gel osmagent and osmopolymer containing beneficial agent in suspension, which solution or suspension in either operation is released by the combined operations of device 10. These operations include the solution, or the suspension being osmotically delivered through the passageway due to the continuous formation of solution or suspension, and by the swelling and increasing volume of the second composition, represented by the increase in height of the vertical lines in Figure 3 and 4. This latter swelling and increase in volume applies pressure against the solution or suspension thereby aiding the first composition and simultaneously causing delivery of beneficial agent to the exterior of the device.

The first composition and the second composition act together to substantially insure that delivery of beneficial agent from the compartment is constant over a prolonged period of time by two methods. *First,* the first composition imbibes external fluid across the wall, thereby forming either a solution or a suspension, the latter fraction of which would be substantially delivered at non-zero order (without the second composition present), since the driving force decays with time. *Second, the second composition* operates by two simultaneous operations: first, the second composition operates to continuously concentrate beneficial agent by imbibing some fluid from the first composition to help keep the concentration of beneficial agent from falling below saturation, and second, the second composition by imbibing external fluid across the wall continuously increases in volume, thereby exerting a force against the first composition and diminishing the volume of benefical agent, thusly directing beneficial agent to the passageway in the compartment. Additionally, since the extra solution or suspension formed in the first comparment is squeezed out, the osmotic composition cosely contacts the internal wall and generates a constant osmotic pressure, and therefore a constant delivery rate, in conjunction with the second composition. The swelling and expansion of the second composition, with its accompanying increase in volume, along with the simultaneous corresponding reduction in volume of the first composition, assures the delivery of beneficial agent at a controlled rate over time.

Device 10 of Figures 1 through 4 can be made into many embodiments including the presently preferred embodiments for oral use, for releasing either a locally or systemically acting therapeutic agent in a gastrointestinal tract. Oral system 10 can have various conventional shapes and sizes such as round with a diameter or 3/16 inches to 1/2 inch. In these forms, system 10 can be adapted for administering beneficial agent to numerous animals, including warm-blooded animals, humans, avains, reptiles and pisces.

Figures 5, 6 and 7 show another embodiment, an osmotic device 10 designed for placement in a body passageway, such as a vagina, or the ano-rectal canal. Device 10 has an elongated, cylindrical, self-sustaining shape with a rounded lead end 20, a trailing end 21, and it is equipped with manually controlled strings 22 for easily removing device 10 from a biological passageway. Device 10 is structurally identical with device 10 as described above and it operates in a like manner. In Figure 5, device 10 is depicted with a semi-permeable wall 23, in Figure 6 with a laminated wall 24 comprising an inner semi-permeable lamina 25 adjacent to compartment 14, and an external microporous lamina 26 distant from compartment 14. In Figure 7, device 10 comprises a laminated wall 28 formed of a microporous lamina 29 next to compartment 14, and a semi-permeable lamina 30 facing the environment of use and in laminar arrangement with microporous lamina 29. Device 10 delivers a beneficial agent for absorption by the vaginal mucosa, or the ano-rectal mucosa, to produce an in vivo local or systemic effect over a prolonged period of time.

The osmotic devices of Figures 1 through 7 can be used for delivering numerous agents including drugs at a controlled rate independent of the drug pH-dependency, or where the dissolution rate of the agent can vary between low and high in fluid environments, such as gastric fluid and intestinal fluid. The osmotic devices also provide for the high loading of agents of low solubility and their delivery at meaningful, therapeutic amounts. And, while Figures 1 through 7 are illustrative of various osmotic devices that can be made according to the invention, it is to be understood these devices are not to be construed as limiting, as the devices can take a wide variety of shapes, sizes and forms for delivering beneficial agents to the environment of use. For example, the devices include buccal, implant, artifical gland, cervical intrauterine, ear, nose, dermal, subcutaneous and blood delivery devices. The devices also can be sized, shaped, structured and adapted for delivering an active agent in streams, aquariums, field, factories, reservoirs, laboratory facilities, hot houses, transportation means, naval means, military means, hospitals, veterinary clinics, nursing homes, farms, zoos, sickrooms, chemical reactions, and other environments of use.

Detailed Description of the Invention

In accordance with the practice of this invention, it has now been found that osmotic delivery device 10 can be manufactured with a first osmotic composition and a second osmotic composition mutually housed in co-operative relationship in the compartment of the device. The compartment is formed by a wall comprising a material that does not adversely affect the beneficial agent, osmagent, osmopolymer and the like. The wall is permeable to the passage of an external fluid such as water and biological fluids, and it is substantially impermeable to the passage of agents, osmagents, osmopolymers, and the like. The wall is formed of a material that does not adversely affect an animal or a host, and the selectively semi-permeable materials used for forming the wall are non-erodible and they are insoluble in fluids. Typical materials for forming the wall are in one embodiment cellulose esters, cellulose ethers and cellulose ester-ethers. These cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di and tricellulose alkanylates, mono, di and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of 32 to 39.8; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%; and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioclanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioclanoate, cellulose dipentale, coesters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional semi-permeable polymers include ethyl cellulose, cellulose nitrate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate dimethyl aminoacetate, semi-permeable polyamides, semi-permeable polyurethanes, semi-permeable sulfonated polystyrenes, cross-linked selectively semi-permeable polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006; and 3,546,142; semi-permeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; lightly cross-linked polystyrene derivatives; cross-linked poly(sodium styrene sulfonate), cross-linked poly(vinylbenzyltrimethyl amonium chloride), semi-permeable polymers exhibiting a fluid permeability of $10^{-5}$ to $10^{-1}$ (cc.mil/cm$^2$.hr.atm) expressed per atmosphere $10^{-8}$ of hydrostatic or osmotic pressure difference across the semi-permeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, Ohio.

The laminated wall comprising a semi-permeable lamina and a microporous lamina are in laminar arrangement and they act in concert to form an integral laminated wall, that maintains its physical and chemical integrity and does not separate into lamina through the operative agent release history of an osmotic device. The semi-permeable lamina is made from the semi-permeable polymeric materials presented above, the semi-permeable homopolymers, the semi-permeable copolymers and the like.

Microporous lamina suitable for manufacturing an osmotic device generally comprises performed microporous polymeric materials, and polymeric materials that can form a microporous lamina in the environment of use. The microporous materials in both embodiments are laminate to form the laminate wall. The preformed materials suitable for forming the microporous lamina are essentially inert, they maintain their physical and chemical integrity during the period of agent release and they can be generically described as having a sponge-like appearance that provides a supporting structure for a semi-permeable lamina and also provide a supporting structure for microscopic-sized interconnected pores or voids. The materials can be isotropic wherein the structure is homogenous throughout a cross-sectional area, or they can be anisotropic wherein the structure is non-homogenous throughout a cross-sectional area. The pores can be continuous pores that have an opening on both faces of a microporous lamina, pores interconnected through tortuous paths of regular and irregular shapes including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, microporous lamina are defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and the number of pores. The pore size of a microporous lamina is easily ascertained by measuring the observed pore diameter at the surface of the material under the electron microscope. Generally, materials possessing from 5% to 95% pores and having a pore size of from 10 angstroms to 100 microns can be used for making a microporous lamina. The pore size and other parameters characterizing the microporous structure also can be obtained from flow measurements, where a liquid

flux, J, is produced by a pressure difference $\Delta P$, across the lamina. The liquid flux through a laminate with pores of uniform radius extended through the membrane and perpendicular to its surface with area A is given by relation 13:

$$J=\frac{N\pi^4\Delta P}{8\eta\Delta x} \qquad (13)$$

wherein J is the volume transported per unit time and lamina area containing N number of pores of radius r, $\eta$ is the viscosity of the liquid, and $\Delta P$ is the pressure difference across the lamina with thickness $\Delta x$. For this type of lamina, the number of pores N can be calculated from relation 14, wherein $\varepsilon$ is the porosity defined as the ratio of void volume to total volume of the lamina: and A is the cross-sectional area of the lamina containing N pores.

$$N=\frac{\varepsilon A}{\pi r^2} \qquad (14)$$

The pore radius then is calculated from relation 15:

$$r=8\eta\frac{\Delta x\,\tau}{\Delta p\,\varepsilon} \qquad (15)$$

wherein J is the volume flux through the lamina per unit area produced by the pressure difference $\Delta P$ across the lamina, $\eta$, $\varepsilon$ and $\Delta x$ have the meaning defined above and $\tau$ is the turtuosity defined as the ratio of the diffusional path length in the lamina to the lamina thickness. Relations of the above type are discussed in *Transport Phenomena In Membranes*, by Lakshiminatayanaiah, N, Chapter 6, 1969, published by Academic Press, Inc., New York.

As discussed in this reference on page 336, in Table 6.13, the porosity of the lamina having pores with radius r can be expressed relative to the size of the transported molecule having a radius a, and as the ratio of molecular radius to pore radius a/r decreases, the lamina becomes porous with respect to this molecule. That is, when the ratio a/r is less than 0.3, the lamina becomes substantially microporous as expressed by the osmotic reflection coefficient $\sigma$ which decreases below 0.5. Microporous lamina with a reflection coefficient $\sigma$ in the range of less than 1, usually from 0 to 0.5 and preferably less than 0.1 with respect to the active agent are suitable for fabricating the system. The reflection coefficient is determined by shaping the material in the form of a lamina and carrying out water flux measurements as a function of hydrostatic pressure difference and as a function of the osmotic pressure difference caused by the active agent. The osmotic pressure difference creates a hydrostatic volume flux, and the reflection coefficient is expressed by relation 16:

$$\sigma=\frac{\text{osmotic volume flux}}{\text{hydrostatic volume flux}} \qquad (16)$$

Properties of microporous materials are described in *Science,* Vol. 170 pages 1302 to 1305, 1970; *Nature,* Vol. 214 page 285, 1967; *Polymer Engineering and Science* Vol. 11 pages 284—288, 1971; U.S. Pat. Nos. 3,567,809 and 3,751,536; and in *Industrial Processing With Membranes* by Lacey R. E. and Loeb Sidney pages 131 to 134, 1972, published by Wiley, Interscience, New York.

Microporous materials having a preformed structure are commercially available and they can be made by art-known methods. The microporous materials can be made by etching, nuclear tracking, by cooling a solution of flowable polymer below the freezing point whereby solvent evaporates from the solution in the form of crystals dispersed in the polymer and then curing the polymer followed by removing the solvent crystals, by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a soluble component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte processes. Processes for preparing microporous materials are described in *Synthetic Polymer Membranes*, by R. E. Kesting, Chapters 4 and 5, 1971 published by McGraw Hill, Inc.; *Chemical Reviews,* Ultrafiltration, Vol. 18, pages 373 to 455, 1934; *Polymer Eng. and Sci.,* Vol. 11, No. 4, pages 284 to 288, 1971; *J. Appl. Poly Sci.,* Vol. 15, pages 811 to 829, 1971; and in U.S. Pat. Nos. 3,565,259; 3,615,024; 3,751,536; 3,801,692; 3,852,224 and 3,849,528.

Microporous materials useful for making the lamina include microporous polycarbonates comprises of linear polyesters of carbonic acid in which carbonate groups recur in the polymer chain, microporous materials prepared by the phosgenation of a dihydroxyl aromatic such as bisphenol A, microporous poly(vinylchloride), microporous polyamides such as polyhexamethylene adipamide, microporous modacrylic copolymers including those formed from poly(vinylchloride) 60% and

acrylonitrile, styrene-acrylic and its copolymers, porous polysulfones characterised by diphenylene sulfone groups in a linear chain thereof, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by exterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolic polyesters, microporous poly(saccharides), microporous poly(saccharides) having substituted and unsubstituted anhydroglucose units and preferably exhibiting an increased permeability to the passage of water and biological fluids than semi-permeable lamina, asymmetric porous polymers, cross-linked olefin polymers, hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and materials described in U.S. Pat. Nos. 3,597,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,061; 3,852,224; 3,853,601; and 3,852,388 in British Pat. No. 1,126,849 and in *Chem. Abst.,* Vol. 71 4274F, 22572F, 22573F, 1969.

Additional microporous materials include poly(urethanes), cross-linked, chain-extended poly(urethanes), microporous poly(urethanes) in U.S. Pat. No. 3,524,753 poly(imides), poly(benzimidazoles), collodion (cellulose nitrate with 11% nitrogen), regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols as in U.S. Pat. No. 3,565,259, anisotropic permeable microporous materials of ionically associated polyelectrolytes, porous polymers formed by the coprecipitation of a polycation and a polyanion as described in U.S. Pat. Nos. 3,276,589; 3,541,055; 3,541,066 and 3,546,142 derivatives of poly(styrene) such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), the microporous materials disclosed in U.S. Pat. No. 3,615,024 and U.S. Pat. Nos. 3,646,178 and 3,852,224.

Further, the microporous forming material used for the purpose of the invention, includes the embodiment wherein the microporous lamina is formed in situ, by a pore-former being removed by dissolving or leaching it to form the microporous lamina during the operation of the system. The pore-former can be a solid or a liquid. The term liquid, for this invention, embraces semi-solids and viscous fluids. The pore-formers can be inorganic or organic. The pore-formers suitable for the invention include pore-formers that can be extracted without any chemical change in the polymer. The pore-forming solids have a size of about 0.1 to 200 micrometres and they include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate and the like. The alkali earth metal salts include calcium phosphate, calcium nitrate and the like. The transition metal salts include ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, manganese fluoride, manganese fluorosilicate, and the like. The pore-formers include organic compounds such as polysaccharides. The polysaccharides include the sugars sucrose, glucose, fructose, mannitol, mannose, galactose, aldohexose, altrose, talose, sorbitol, lactose, monosaccharides and disaccharides. Also, organic aliphatic and aromatic oils and solids, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly($\alpha$-$\omega$)-alkylenediols esters or alkylene glycols and the like; water soluble cellulosic polymers such as hydrosyloweralkyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, methylethyl cellulose, hydroxyethyl cellulose and the like; water soluble polymers such as polyvinylpyrrolidone, sodium carboxymethylcellulose and the like. The pore-formers are nontoxic and on their removal form the lamina channels are formed through the lamina. In a preferred embodiment, the nontoxic pore-forming agents are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly($\alpha$-$\omega$)-alkylenediols, esters of alkylene glycols, glycols, and water soluble cellulosic polymers, useful for forming a microporous lamina in a biological environment. Generally, for the purpose of this invention, when the polymer forming the lamina contains more than 25% by weight of a pore-former, the polymer is a precursor microporous lamina that on removing the pore-former, yields a lamina which is substantially microporous, at concentrations less than this, the lamina behaves like a semi-permeable lamina or membrane.

The expression passageway as used comprises means and methods suitable for releasing the agent or drug from the osmotic system. The expression includes aperture, orifice, hole, or bore through the semi-permeable wall or the laminated wall. The passageway can be formed by mechanical drilling, laser drilling, or by eroding an erodible element, such as a gelatin plug, in the environment of use. A detailed description of osmotic passageways, and the maximum and minimum dimensions for a passageway are disclosed in United States Pat. Nos. 3,845,770 and 3,916,899.

The osmotically effective compounds that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across a semi-permeable wall, or across a semi-permeable microporous laminated wall, against an external fluid. The osmotically effective compounds (along with the osmopolymers) imbibe fluid into the osmotic device thereby making available in situ fluid for imbibition by an osmopolymer to enhance its expansion, and/or for forming a solution or suspension containing a beneficial agent for its delivery from the osmotic device. The osmotically effective compounds are known also as osmotically effective solutes, or osmagents. The osmotically effective compounds are used by mixing them with a beneficial agent and osmopolymer for forming a solution, or suspension containing the beneficial agent that is osmotically delivered from the device. The expression limited solubility as used herein means the agent has a solubility of about less than 5% by weight in the aqueous fluid present in the environment. The osmotic

solutes are used by homogenously or heterogenously mixing the solute with the agent or osmopolymer, and then charging them into the reservoir. The solutes and osmopolymers attract fluid into the reservoir producing a solution of solute in a gel which is delivered from the system concomitantly transporting undissolved and dissolved beneficial agent to the exterior of the system. Osmotically effective solutes used for the former purpose include magnesium sulfate, magnesium chloride, sodium chloride, potassium chloride, lithium chloride, potassium sulfate, sodium sulfate, lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, d-mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, $\alpha$-d-lactose monohydrate, and mixtures thereof. The amount of osmagent in the compartment will generally be from 0.01% to 30%, or higher in the first composition, and usually from 0.01% to 40% or higher in the second compartment.

The osmotic solute is initially present in excess and it can be in any physical form that is compatible with the beneficial agent and the osmagent. The osmotic pressure of saturated solutions of various osmotically effective compounds and for mixtures of compounds at 37°C, in water, is listed in Table 1. In the table, the osmotic pressure $\pi$, is in atmospheres, ATM. The osmotic pressure is measured in a commercially available osmometer that measures the vapor pressure difference between pure water and the solution to be analyzed, and according to standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. In Table 1, osmotic pressures of from 20 ATM to 500 ATM are set forth; of course, the invention includes the use of lower osmotic pressures from zero, and higher osmotic pressures than those set forth by way of example in Table 1. The osmometer used for the present measurements is identified as Model 320B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard Co., Avonadale, Penna.

TABLE 1

| Compound or Mixture | Osmotic Pressure ATM |
|---|---|
| Lactose-Fructose | 500 |
| Dextrose-Fructose | 450 |
| Sucrose-Fructose | 430 |
| Mannitol-Fructose | 415 |
| Sodium Chloride | 356 |
| Fructose | 355 |
| Lactose-Sucrose | 250 |
| Potassium Chloride | 245 |
| Lactose-Dextrose | 225 |
| Mannitol-Dextrose | 225 |
| Dextrose-Sucrose | 190 |
| Mannitol-Sucrose | 170 |
| Dextrose | 82 |
| Potassium Sulfate | 39 |
| Mannitol | 38 |
| Sodium Phosphate Tribasic · $12H_2O$ | 36 |
| Sodium Phosphate Dibasic · $7H_2O$ | 31 |
| Sodium Phosphate Dibasic · $12H_2O$ | 31 |
| Sodium Phosphate Dibasic Anhydrous | 29 |
| Sodium Phosphate Monobasic · $H_2O$ | 28 |

The osmopolyers suitable for forming the first osmotic composition, and also suitable forming the second osmotic composition are osmopolymers that exhibit fluid imbibition properties. The osmopolymers are swellable, hydrophilic polymers which interact with water and aqueous biological fluids and swell, or expand to an equilibrium state. The osmopolymers exhibit the ability to swell in water and retain a significant portion of the imbibed water within the polymer structure. The osmopolymers swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. The swellable, hydrophilic polymers are in one presently preferred embodiment lightly cross-linked, such cross-links being formed by covalent or ionic bonds. The osmopolymers can be of plant, animal, or synthetic origin. The osmopolymers are hydrophilic polymers. Hydrophilic polymers suitable for the present purpose include poly(hydroxyalkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; poly(vinylpyrrolidone) having a molecular weight of from 10,000 to 360,000; anionic and cationic hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) having a low acetate residual, cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization from 200 to 30,000; a mixture of methyl cellulose, cross-linked agar and carboxymethyl cellulose; a water-insoluble, water-swellable copolymer produced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene ethylene, propylene, butylene or isobutylene cross-linked with from 0.001 to about 0.5 moles of polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer; water-swellable polymers of N-vinyl lactams and the like.

Other osmopolymers include polymers that form hydrogels such as Carbopol acidic carboxy polymers having a molecular weight of 450,000 to 4,000,000; Cyanamer polyacrylamides; cross-linked water-swellable indene-maleic anhydride polymers; Good-rite polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox polyethylene oxide polymers having a molecular weight of 100,000 to 5,000,000; starch graft copolymers; Aqua-Keeps acrylate polymer; diester cross-linked polyglucan; and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Pat. No. 3,865,108 issued to Hartop; U.S. Pat. No. 4,002,173 issued to Manning; U.S. Pat. No. 4,207,893 issued to Michaels; and in *Handbook of Common Polymers* by Scott and Roff, published by the Chemical Rubber Co., Cleveland, Ohio. The amount of osmopolymer in the first osmotic composition is about .01 to 90% and the amount of osmopolymer in the second osmotic composition is 15 to 95%. In a presently preferred embodiment, the molecular weight of the osmopolymer in the second osmotic composition is larger than the molecular weight of the osmopolymer in the first osmotic composition.

Osmopolymer fluid imbibition determination for a chosen polymer can be made by following the procedure described below. A 1/2 inch round disc, fitted with a 1/2 inch diameter stainless steel plug, is charged with a known quantity of polymer with the plugs extending out either end. The plugs and the die were placed in a Carver press with plates between 200° and 300°F. A pressure of 10,000 to 15,000 PSI was applied to the plugs. After 10 to 20 minutes of heat and pressure, the electrical heating to the plates were turned off, and tap water circulated through the plates. The resulting 1/2 inch discs were placed in an air suspension coater charged with 1.8 kg saccharide cores and coated with cellulose acetate having an acetyl content of 39.8% dissolved in 94:6 w/w, $CH_2Cl_2/CH_3OH$, to yield a 3% w/w solution. The coated systems were dried overnight at 50°C the coated discs were immersed in water at 37°C and periodically removed for a gravimetric determination of water imbibed. The initial imbibition pressure was calculated by using the water transmission constant for the cellulose acetate, after normalizing imbibition values for membrane surface area and thickness. The polymer used in this determination was the sodium derivative of Carbopol-934 polymer, prepared according to the procedure of B. F. Goodrich Service Bulletin GC-36, "Carbopol Water-Soluble Resins", page 5, published by B. F. Goodrich, Akron, Ohio. The cumulative weight gain values, y, as a function of time, t, for the water soluble polymer disc coated with the cellulose acetate were used to determine the equation of the line $y=c+bt+at^2$ passing through those points by a least square fitting technique.

The weight gain for the Na Carbopol-934 is given by the equation 17 that follows: Weight Gain equals $0.359+0.665t-0.00106t^2$ wherein t is elapsed time in minutes. The rate of water flux at any time will be equal to the slope of the line, that is given by the following equation 18 and 19:

$$\frac{dy}{dt} = \frac{d(0.359+0.665t-0.00106t^2)}{dt} \qquad (18)$$

$$\frac{dy}{dt} = 0.665-0.00212t \qquad (19)$$

To determine the initial rate of water flux the derivative is evaluated at t=0, and dy/dt=0.665 $\mu$l/min, which is equal to the coefficient b. Then, normalizing the imbibition rate for time, membrane surface area and thickness, and the membrane permeability constant to water, K, $\pi$ may be determined according to the following equation 20:

$$K\pi = 0.665\ \mu l/min \times \left(\frac{60\ min}{hr}\right) \times \left(\frac{1\ ml}{1000\ \mu l}\right)\left(\frac{0.008\ cm}{2.86\ cm^2}\right) \quad (20)$$

with $K=1.13\times10^{-4}$ cm²/hr. The ($\pi$) value for NaCl was determined with a Hewlett-Packard vapor pressure osmometer to be 345 atm±10%, and the K value for cellulose acetate used in this experiment calculated from NaCl imbibition values was determined to be $1.9\times10^{-7}$ cm²/hr atm.

Substituting these values into the calculated K$\pi$ expression ($1.9\times10^{-7}$/cm²/hr.atm) ($\pi$)=$1.13\times10^{-4}$ cm²/hr gives $\pi$=600 atm at t=0. As a method for evaluating the efficiency of a polymer with respect to duration of zero-order driving force, the % of water uptake was selected before the water flux values decreased to 90% of their initial values. The value of the slope for the equation of a straight line emanating from the % weight gained axis will be equal to the initial value of dy/dt evaluated at t=0, with the y intercept c defining the linear swelling time, with (dy/dt) 0=0.665 and y intercept=0, which yields y=0.665t+0.359. In order to determine when the value of the cumulative water uptake is 90% below the initial rate, the following expression is solved for t,

$$0.9 = \frac{at^2+bt+c}{bt+c} = \frac{\Delta W}{w}0.9 \quad (21)$$

$$\frac{-0.00106t^2+0.665t+0.359}{0.665t+0.359} = 0.9, \text{ and} \quad (22)$$

solving for t,

$$-0.00106t^2+0.0665t+0.0359=0$$

$$t = \frac{-0.0665 \pm [(0.0665)^2-4(-0.00106)(0.0359)]^{1/2}}{2(-0.00106)} \quad (23)$$

t=62 min and the weight gain is $-0.00106(62)^2+(0.665)(62)+0.359=38\ \mu l$, with the initial sample weight=100 mg, thus ($\Delta$w/w) 0.9×100=38%. The results are presented in Figure 8 for a graphical representation of the values. Other methods available for studying the hydrogel solution interface include rheologic analysis, viscometric analysis, ellipsometry, contact angle measurements, electrokinetic determinations, infrared spectroscopy, optical microscopy, interface morphology and microscopic examination of an operative device.

The expression active agent as used herein, includes any beneficial agent, or beneficial compound, that can be delivered from the device to produce a benefical and useful result. The agent can be insoluble to very soluble in the exterior fluid that enters the device and it can be mixed with an osmotically effective compound and an osmopolymer. The term active agent includes pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, antioxidants, plant growth, promoters, plant growth inhibitors, preservatives, disinfectants, sterilization agents, catalysts, chemical reactants, fermentation agents, sex sterilants, fertility inhibitors, fertility promoters, air purifiers, micro-organism attenuators, and other agents that benefit the environment of use.

In the specification and the accompanying claims, the term beneficial agent includes drug, and the term drug includes any physiologically or pharmacologically active substance that produces a local or systemic effect, in animals, including warm blooded mammals, humans and primates, avians, household, sport and farm animals, laboratory animals, fishes, reptiles and zoo animals. The term physiologically as used herein denotes the administration of a drug to produce normal levels and functions. The term pharmacologically denotes variations in response to amount of drug administered to the host. See *Stedman's Medical Dictionary*; 1966 published by Williams and Wilkins, Baltimore, Md. The phrase drug formulation as used herein means the drug is in the compartment mixed with an osmotic solute and/or an osmopolymer and if applicable, and with a binder and lubricant. The active drug that can be delivered includes inorganic and organic compounds without limitation, including drugs that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine system, hormone systems, immunological system, organ systems, reproductive system, skeletal system, autocoid systems, alimentary and excretory systems, inhibitory of autocoids and histamine systems. The active drug that can be delivered for acting on these animal systems includes depressants, hypnotics, sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatory, local anesthetics, muscle contractants, anti-microbials, anti-malarials, hormonal agents, contraceptives, sympathomimetics, diuretics, anti-parasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents and cardiovascular drugs.

Exemplary drugs that are very soluble in water and can be delivered by the devices of this

invention include prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproternol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, mechacholine chloride, pilocarpine hydrochloride, atropine sulfacte, methascopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol hydrochloride, metoprolol tartrate, imetidine hydrochloride, theophylline cholinate, cephalexin hydrochloride and the like.

Exemplary drugs that are poorly soluble in water and that can be delivered by the devices of this invention include diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythrityl tetranitrate, dizoxin, isofurophate, reserpine, acetazolamide, ethazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, profestins, esterogenic progestational, corticosteroids, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, triamcinolone, methyltesterone 17$\beta$-estradiol, ethinyl estradiol, prazosin hydrochloride ethinyl estradiol 3-methyl ether, pednisolone, 17$\beta$-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethiderone, progesterone, norgesterone, norethynodrel and the like.

Examples of other drugs that can be delivered by the osmotic device include aspirin, indomethacin, naproxen, fenoprofen, sulidac, diclofenac, indoprofen, nitroglycerin, propanolol, metoprolol, valproate, oxprenolol, timolol, atenolol, alprenolol, cimetidine, imipramine, levodopa, chloropromazine, reserpine, methyl-dopa, dihydroxyphenylalanine, pivaloyloxyethyl, ester of $\alpha$-methyldopa hydrochloride, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, proszin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, $\alpha$-blocking agents, calcium-channel blocking drugs such as nifedipine, diliazen, verapamil, betablockers and the like. The beneficial drugs are known to the art in *Pharmaceutical Sciences,* edited by Remington 14th Ed., 1979 published by Mack Publishing Co., Easton, Penna.; *The Drug, The Nurse, The Patient, Including Current Drug Handbook*, 1974—1976 by Falconer, et al., published by Saunder Company, Philadelphia, Penna.; and *Medicinal Chemistry,* 3rd Ed., Vol. 1 and 2 by Burger, published by Wiley-Interscience, New York.

The drug can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic drugs, salts of metals, amines or organic cations, for example quaternary ammonium, can be used. Derivatives of drugs such as esters, ethers and amides can be used. Also, a drug that is water insoluble can be used in a form that is a water soluble derivative thereof to serve as a solute and on its release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original biologically active form. The agent including drug, can be present in the compartment with a binder, dispersant, wetting agent, suspending agent, lubricant and dye. Representative of these include suspending agents such as acacia, agar, calcium carrageenan, alginic acid, algin, agarose powder, collagent, colloidal magnesium silicate, colloidal silicon dioxide, hydroxyethyl cellulose, pectin, gelatin and calcium silicate; binders like polyvinyl pyrrolidone, lubricants such as magnesium stearate, wetting agents such as fatty amines, fatty quaternary ammonium salts and the like. The phrase drug formulation indicates the drug is present in the compartment accompanied by an osmagent, osmopolymer, a binder and the like. The amount of beneficial agent in a device generally is about from 0.05 ng to 5 g or more, with individual devices containing for example, 25 ng, 1 mg, 5 mg, 125 mg, 250 mg, 500 mg, 750 mg, 1.5 g, and the like. The devices can be administered once, twice or thrice daily.

The solubility of a beneficial agent in the fluid can be determined by known techniques. One method consists of preparing a saturated solution comprising the fluid plus the agent as ascertained by analyzing the amount of agent present in a definite quantity of the fluid. A simple apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature and pressure, in which the fluid and agent are placed and stirred by a rotating glass spiral. After a given period of stirring, a weight of the fluid is analyzed and the stirring continued an additional period of time. If the analysis shows no increase of dissolved agent after successive period of stirring, in the presence of excess solid agent in the fluid, the solution is saturated and the results are taken as the solubility of the product in the fluid. If the agent is soluble, an added osmotically effective compound optionally may not be needed; if the agent has limited solubility in the fluid, then an osmotically effective compound can be incorporated into the device. Numerous other methods are available for the determination of the solubility of an agent in a fluid. Typical methods used for the measurement of solubility are chemical and electrical conductivity. Details of various methods for determining solubilities are described in United States *Public Health Service Bulletin,* No. 67 of the Hygenic Laboratory; *Encyclopedia of Science and Technology,* Vol. 12, pages 542 to 556, 1971, published by McGraw-Hill, Inc., and *Encyclopedia Dictionary of Physics,* Vol. 6, pages 547 to 557, 1962 published in Pergamon Press, Inc.

The osmotic devices of the invention is manufactured by standard techniques. For example, in

one embodiment, the beneficial agent is mixed with an osmagent and osmopolymer, and pressed into a solid possessing dimensions that correspond to the internal dimensions of the compartment adjacent to the passageway; or the beneficial agent and other formulation forming ingredients and a solvent are mixed into a solid or a semisolid by conventional methods such as ballmilling, calendering, stirring or rollmilling and then pressed into a preselected shape. Next, a layer of a composition comprising an osmagent and an osmopolymer is placed in contact with the layer of beneficial agent formulation, and the two layers surrounded with a semi-permeable wall. The layering of the beneficial agent composition and the osmagent/osmopolymer can be accomplished by conventional two-layer tablet press techniques. The wall can be applied by molding, spraying or dipping the pressed shaped into wall-forming material. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the pressed compositions in a current of air and a wall forming composition until the wall surrounds and coats the two pressed compositions. The procedure is repeated with a different lamina forming composition to form a laminated wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.,* Vol. 48, pages 451 to 459, 1979; and ibid, Vol. 49, pages 82 to 84, 1960. Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia,* Vol. 46, pages 62 to 70, 1969; and in *Pharmaceutical Sciences,* by Remington, 14th Edition, pages 1626 to 1678, 1970, published by Mack Publishing Co., Easton, Penna.

Exemplary solvents suitable for manufacturing the laminates and láminae include inert inorganic and organic solvents that do not adversely harm the materials and the final laminated wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water and mixtures thereof such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

Detailed Description of Examples

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An osmotic delivery device manufactured as an osmotic tablet shaped, sized and adapted for oral admittance into the gastrointestional tract is made as follows: a first osmotic drug composition is prepared by screening 355 g of poly(ethylene oxide) having an approximate molecular weight of 200,000 through a 40 mesh stainless steel screen, then 100 g of nifedipine is passed through the 40 mesh screen, 25 g of hydroxypropylmethylcellulose is passed through the 40 mesh screen, and finally 10 g of potassium chloride is passed through the 40 mesh screen. Next, all the screened ingredients are added to the blowl of a laboratory blender and the ingredients dry blended for 15—20 minutes to produce a homogeneous blend. Then a granulation fluid is prepared comprising 250 ml of ethanol and 250 ml of isopropyl alcohol and the granulating fluid added to the blending blowl; a first 50 ml is sprayed into the bowl with constant blending then 350 ml of the granulation fluid is added slowly to the bowl and the wet mass blended for another 15 to 20 minutes. Then the wet granules are passed through a 16 mesh screen and dried at room temperature for 24 hours, and the dry granules passed through a 16 mesh screen. Next, 10 g of magnesium stearate is added to the dry granules, and the ingredients roll-mixed for 20—30 minutes on a standard two roll mill.

Next, a second osmotic composition is prepared as follows: first, 170 g of poly(ethylene oxide) having a molecular weight of 5,000,000 is screened through a 40 mesh screen, then 72.5 g of sodium chloride is passed through the 40 mesh screen and the ingredients added to a mixing bowl and blended for 10—15 minutes. Then a granulation fluid is prepared by mixing 350 ml of methanol and 150 ml of isopropyl alcohol and the granulation fluid added to the blending bowl in two steps. First, 50 ml of the granulation fluid is sprayed into the bowl with constant blending, then 350 ml of the granulation fluid is slowly added to the bowl and the wet blend mixed for 15—20 minutes to a homogeneous blend. Then, the wet blend is passed through a 16 mesh screen, spread on a stainless steel tray and dried at room temperature of 22.5°C for 24 hours. The dried blend is passed through a 16 mesh screen, the roll milled with 5 g of magnesium stearate on a two roll mill for 20—30 minutes.

A number of drug cores are prepared by pressing the two compositions on Manesty Layerpress. The drug containing composition is fed into the cavity mold of the press and compressed into a solid

layer. Then, the second osmotic composition is fed into the cavity overlaying the compressed layer and pressed into a solid layer to form a two layered drug core.

The drug cores next are coated with a semi-permeable wall-forming composition comprising 95 g of cellulose acetate having an acetyl content of 39.8% and 5 g of poly(ethylene glycol) 4000 in a solvent comprising 1960 ml of methylene chloride and 820 ml of methanol. The drug cores are coated with the semi-permeable wall forming composition until the wall surrounds the drug core. A Wurster air suspension coater is used to form the semi-permeable wall. The coated cores are then spread on a tray and the solvent evaporated in a circulating air oven at 50°C for 65 hours. After cooling to room temperature a 0.26 mm diameter passageway is laser drilled through the semi-permeable wall connecting the exterior of the osmotic device with the composition containing the drug. The osmotic device weighed 262 mg and it contained 30 mg of drug in the first composition weighing 150 mg, the second composition weighed 75 mg and the semi-permeable wall weighed 37 mg. The first osmotic composition of the osmotic device comprises 30 mg of nifedipine, 106 mg of poly(ethylene oxide), 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate. The second osmotic composition comprises 51 mg of poly(ethylene oxide), 22 mg of sodium chloride, and 1.5 mg of magnesium stearate. The device has a diameter of 8 mm, a surface area of 1.8 $cm^2$ and the semi-permeable wall is 0.17 mm thick. The cumulative amount of drug released is depicted in Figure 9.

EXAMPLE 1A

Osmotic delivery systems are prepared having a first composition comprising 25 to 100 mg of nifedipine, 100 to 325 mg of poly(ethylene oxide) having a molecular weight of 200,000, 2 to 10 mg of potassium chloride, 5 to 30 mg of hydroxypropylmethylcellulose and 2 to 10 mg of magnesium stearate; and a second composition comprising 30 to 175 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 20 to 75 mg of sodium chloride and 1 to 5 mg of magnesium stearate. The procedure of Example 1 is repeated for preparing osmotic devices having the following compositions: (a) an osmotic device having a first composition comprising 60 mg of nifedipine, 212 mg of poly(ethylene oxide), 6 mg of potassium chloride, 15 mg of hydroxypropylmethylcellulose and 6 mg of magnesium stearate; and a second composition comprising 102 mg of poly(ethylene oxide), 44 mg of sodium chloride, and 3 mg of magnesium stearate; and (b) an osmotic device having a first composition comprising 90 mg of nifedipine, 318 mg of poly(ethylene oxide), 9 mg of potassium chloride, 22.5 mg of hydroxypropylmethylcellulose, and 9 mg of magnesium stearate, and a second composition comprising 102 mg of poly(ethylene oxide), 66 mg of sodium chloride, and 4.5 mg of magnesium stearate. In an embodiment, the osmotic device described in (a) and (b) further comprise a pulse coated on the outer semi-permeable wall. The pulse coat comprises 30 mg of nifedipine and hydroxypropylmethylcellulose. In operation in the fluid environment of use, the pulse coat provides instant drug availability for instant drug therapy.

EXAMPLE 2

The procedure of Example 1 is repeated with all conditions as previously described except that the drug in the compartment is replaced with a member from the group consisting of a beta-blocker, anti-inflammatory, analgesic, sympathomimetic, antiparkinson or a diuretic drug.

EXAMPLE 3

An osmotic therapeutic device for the controlled and the continuous oral release of the beneficial calcium channel blocker drug verapamil is made as follows: 90 mg of verapamil, 50 mg of sodium carboxyvinyl polymer having a molecular weight of 200,000 and sold under the trademark Carbopol® polymer, 3 mg of sodium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate are mixed thoroughly as described in Example 1, and pressed in a Manesty press with a 5/16 inch punch using a pressure head of 1-1/2 tons to produce a layer of the drug composition. Next, 51 mg of the carboxyvinyl polymer having a molecular weight of 3,000,000 and sold under the trademark Carbopol® polymer 22 mg of sodium chloride and 2 mg of magnesium stearate are blended thoroughly and added to the Manesty press, and pressed to form a layer of expandable, osmotic composition in contact with the layer of osmotic drug composition.

Next, a semi-permeable wall is formed by blending 170 g of cellulose acetate having an acetyl of 39.8% with 900 ml of methylene chloride and 400 ml of methanol and spray coating the two layered compartment forming member in an air suspension machine until a 5.1 mil thick semi-permeable wall surrounds the compartment. The coated device is dried for 72 hours at 50°C and then a 8 mil passageway is laser-drilled through the semi-permeable wall to connect the layer containing drug with the exterior of the device for releasing drug over a prolonged period of time.

EXAMPLE 4

The procedure of Example 3 is repeated with all conditions as described except that the drug in the osmotic device is fendiline, diazoxide, prenylamine or diltiazen.

EXAMPLE 5

An osmotic, therapeutic device for the delivering of the drug sodium diclofenac for uses as an anti-inflammatory is prepared by first pressing in a Manesty press an osmotic drug composition containing 75 mg of sodium diclofenac, 300 mg of sorbitol, 30 mg of sodium bicarbonate, 26 mg of pectin, 10 mg of polyvinyl pyrrolidone and 5 mg of stearic acid and pressing the composition in a cavity to a solid layer. Next, the cavity is charged with a second and greater force generating composition comprising 122 mg of pectin having a molecular weight of 90,000 to 130,000, 32 mg of mannitol, 20 mg of polyvinyl pyrrolidone and 2 mg of magnesium stearate and pressed to form a second layer in contacting relation with the first layer. The second layer had a density of 1.28 g/cm$^3$ and a hardness score of greater than 12 kg. Next, the two layer core is surrounded with a semi-permeable wall comprising 85 g of cellulose acetate having an acetyl content of 39.8%, and 15 g of polyethylene glycol 4000, 3 wt/wt % solid in a wall forming solvent comprising 1960 ml of methylene chloride and 819 ml of methanol. The coated device is dried for 72 hours at 50°C, and then a 0.26 mm diameter passageway is laser-drilled through the wall. The semi-permeable wall is 0.1 mm thick, the device has an area of 3.3 cm$^2$, and it has an average rate of drug release of 5.6 mg per hour over a 12 hour period. The cumulative amount released is illustrated in Figure 10. The small vertical bars represent the minimum and maximum drug release for five systems measured at that time.

EXAMPLE 5A

The procedure of Example 5 is followed for providing an osmotic device wherein the compartment contained a blend of osmopolymers. The compartment contained a first composition weighing 312 mg and consists of 48% sodium diclofenac drug, 38% poly(ethylene oxide) osmopolymer having a molecular weight of 200,000, 10% poly(ethylene glycol) osmopolymer having a molecular weight of 20,000, 2% sodium chloride, and 2% sodium chloride, and 2% magnesium stearate; and a second composition weighing 150 mg and consisting of 93% poly(ethylene oxide) having a molecular weight of 5,000,000, 5% sodium chloride, and 2% magnesium stearate.

EXAMPLE 6

In this example, the increase in osmotic pressure for a number of compositions comprising an osmagent and as osmopolymer are made for demonstrating the operative advantage provided by the invention. The measurements are made by measuring the amount of water imbibed across the semi-permeable wall of a bag containing as osmagent, or an osmopolymer, or a composition comprising an osmagent and an osmopolymer. The semi-permeable wall of the bag is formed of cellulose acetate having an acetyl content of 39.8%. The measurements are made by weighing the dry ingredients of the semi-permeable bag, followed by weighting the blotted semi-permeable bag, after the bag is in a water bath at 37°C for various lengths of time. The increase in weight is due to water imbibition across the semi-permeable wall caused by the osmotic pressure gradient across the wall. The osmotic pressure curves are illustrated in Figure 11. In Figure 11, the curved line with the triangles represents the osmotic pressure for poly(ethylene) oxide having a molecular weight of 5,000,000; the curved line with the circles represents the osmotic pressure for a composition comprising poly(ethylene) oxide having a molecular weight of 5,000,000 and sodium chloride with the ingredients present in the composition in the ratio of 9.5 parts osmopolymer to 0.5 parts osmagent; the curved line with squares represents a composition comprising the same osmopolymer and osmagent in the ratio of 9 parts osmopolymer to one part osmagent; the curved lines with hexagon represents the same composition comprising the osmopolymer and osmagent in the ratio of 8 parts to 2 parts; and the dashed lines represents the osmagent sodium chloride. The mathematical calculations are made using the formula $dw/dt=A(K\Delta\pi)/h$, wherein dw/dt is the rate of water imbibition over time, A is the area of the semi-permeable wall, and K is the permeability coefficient. Also, in Figure 11, $W_H/W_p$ is the amount of water imbibed divided by the weight of osmopolymer plus osmagent.

EXAMPLE 7

An osmotic therapeutic device for dispensing sodium diclofenac is prepared by screening through a 40 mesh screen a composition comprising 49% of sodium diclofenac, 44% poly(ethylene) oxide having a molecular weight of 100,00, 2% sodium chloride and 3% hydroxypropylmethylcellulose, and then blending the screened composition with an alcohol solvent used in the ratio of 75 ml of solvent to 100 g of granulation. The wet granulation is screened through a 16 mesh screen, dried at room temperature for 48 hours under vacuum, passed through a 16 mesh screen and blended with 2% 80 mesh screened magnesium stearate. The composition is compressed as described above.

Next, a composition comprising 73.9% of pectin, having a molecular weight of 90,000 to 130,000, 5.8% microcrystalline cellulose, 5.8% polyvinyl pyrrolidone, 14.3% sodium chloride and 2% sucrose is passed through a 40 mesh screen, blended with an organic solvent in the ratio of 100 ml of solvent to 100 g of granulation for 25 minutes, passed through a 16 mesh screen, dried for 48 hours at room temperature under vacuum, again passed through a 16 mesh screen, blended with 2% magnesium stearate, and then compressed onto the compressed layer described in the above paragraph. The dual layered drug core is coated by dipping in a wall forming composition comprising

80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 4000, and 10% hydroxypropylmethylcellulose. A passageway is drilled through the wall communicating with the drug containing composition. The passageway diameter is 0.38 mm. The theoretical cumulative release profile for the device is depicted in Figure 12. Figure 13 depicts the theoretical release rate in mg per hour for the osmotic device.

EXAMPLE 8

The procedure of Example 7 is repeated with all conditions as described except that the osmopolymer in the drug composition is polyoxyethylene polyoxypropyleneblock copolymer having a molecular weight of about 12,500.

EXAMPLE 9

An osmotic device is made by following the above procedures. The device of this example comprises a single composition comprising 50% of sodium diclofenac, 46% of poly(ethylene) oxide having a molecular weight of 100,000, 2% sodium chloride and 2% magnesium stearate. The device has a semi-permeable wall comprising 90% cellulose acetate comprising 39.8% acetyl, and 10% polyethylene glycol 4000. The cumulative amount released for this device comprising the single composition is 40% of the device comprising two compositions. The cumulative amount released is illustrated in Figure 14.

EXAMPLE 10

The *in vivo* and *in vitro* mean cumulative releases of diclofenac sodium from an osmotic device comprising a first osmotic composition comprising 75 mg of diclofenac sodium 67 mg of poly(ethylene) oxide having a molecular weight of 100,000, 3.0 mg of sodium chloride, 4.5 mg of hydroxypropylmethylcellulose and 3.0 mg of magnesium stearate; a second osmotic composition distant from the releasing passageway comprising 51 mg of poly(ethylene) oxide having a molecular weight of 5,000,000, 22.5 mg of sodium chloride and 1.5 mg of magnesium stearate; and, surrounded by a semi-permeable wall comprising 90% cellulose acetate having an acetyl content of 39.8% and 10% polyethylene glycol 4000 was measured in vivo and in vitro in laboratory dogs. The amounts of drug released at various times in vivo were determined by administering a series of devices to the animal and measuring the amount released from the corresponding device at the appropriate residence time. The results are depicted in Figure 15, wherein the circles with the bars are the in vitro mean cumulative releases and the triangles with the bars are the in vivo mean cumulative releases.

The in vivo and in vitro mean cumulative release for a device containing nifedipine was measured as described immediately above. The osmotic device comprised a composition adjacent to the passageway comprising 30 mg of nifedipine, 106.5 mg of poly(ethylene) oxide having a molecular weight of 200,000, 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate; a composition distant form the passageway comprising 52 mg of poly(ethylene) oxide having a molecular weight of 5,000,000, 22 mg of sodium chloride and 1.5 mg of magnesium stearate; and a semi-permeable wall comprising 95% cellulose acetate having an acetyl content of 39.8% and 5% hydroxypropylmethylcellulose. Figure 16 depicts the release from the system. In Figure 16 the circles represent the in vivo cumulative release and the triangles represent the in vitro means cumulative release.

EXAMPLE 11

The procedure of Example 10 is followed for making an osmotic therapeutic delivery system comprising: a first or drug composition weighing 638 mg and consisting 96% cephalexin hydrochloride, 2% Poviclone (polyvinyl pyrrolidone) and 2% magnesium stearate; a second, or osmotic deriving composition weighing 200 mg and consisting of 68.5% poly(ethylene oxide) having a molecular weight of $5 \times 10^6$, 29.5% sodium chloride, and 2% magnesium stearate; a semi-permeable wall weighing 55.8 mg consisting of 80% cellulose acetate having an acetyl content of 39.8%, 14% polyethylene glycol 4000, and 14% hydroxypropylmethylcellulose; and an osmotic orifice having a diameter of 0.039 mm. The device has an average rate of release of about 54 mg per hour over a period of 9 hours.

The novel osmotic system of this invention uses dual means for the attainment of precise release rate of drugs that are difficult to deliver in the environment of use, while simultaneously maintaining the integrity and the character of the system. While there has been described and pointed out features and advantages of the invention as applied to the presently preferred embodiments, those skilled in the dispensing art will appreciate that various modifications, changes, additions and omissions in the system illustrated and described can be made without departing from the spirit of the invention.

CLAIMS

1. A device for the delivery at a controlled rate a beneficial agent to an environment of use, the device comprising:

a). a wall formed in at least a part of a composition permeable to the passage of an exterior fluid present in the environment of use, the wall surrounding and forming;

b). a compartment;

c). a first composition in the compartment, said first composition comprising a beneficial agent, an osmagent and an osmopolymer;

d). a second composition in the compartment, said second composition comprising an osmagent and an osmopolymer; and

e). a passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent from the device.

2. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the wall forming composition comprises a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, hydroxypropylmethylcellulose, hydroxyloweralkylcellulose, methylcellulose, methylethylcellulose and mixtures thereof.

3. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

4. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

5. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

6. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the beneficial agent is a drug.

7. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the wall is a laminate comprising a semi-permeable lamina and a microporous lamina.

8. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the composition forming the wall contains polyethylene glycol.

9. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the osmopolymer in the first composition is poly(ethylene oxide).

10. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the osmopolymer in the second composition is poly(ethylene oxide).

11. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the agent is the drug nifedipine, verapamel, diltiazen, diclofenae, propanolol, proszin, ibuprofen, ketoprofen, haloperiodol, indomethacin, and cephalexin.

12. A device as claimed in claim 1 and substantially as herein described and/or with reference to the accompanying drawings.

13. Each and every novel embodiment herein set forth either separately or in combination.

New claims or amendments to claims filed on 3.7.84
Superseded claims 1—13
New or amended claims:—

1. A device for the delivery at a controlled rate a beneficial agent to an environment of use, the device comprising:

a) a wall formed in at least a part of a composition permeable to the passage of an exterior fluid present in the environment of use, the wall surrounding and forming;

b) a compartment;

c) a first composition in the compartment, said first composition comprising a beneficial agent and an osmopolymer;

d) a second composition in the compartment, said second composition comprising an osmagent and an osmopolymer; and

e) a passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent from the device.

2. The device for the delivery at a controlled rate the beneficial agent according to claim 2, wherein the wall forming composition comprises a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, hydroxypropylmethylcellulose, hydroxyloweralkylcellulose, methylcellulose, methylethylcellulose and mixtures thereof.

3. The device for the delivery at a controlled rate the beneficial agent according to either of claims 1 or 2, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

4. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

5. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

6. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the beneficial agent is a drug.

7. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the wall is a laminate comprising a semi-permeable lamina and a microporous lamina.

8. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the composition forming the wall contains polyethylene glycol.

9. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the osmopolymer in the first composition is poly(ethylene oxide).

10. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the osmopolymer in the second composition is poly(ethylene oxide).

11. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the agent is the drug nifedipine, verapamel, diltiazen, diclofenae, propanolol, proszin, ibuprofen, ketoprofen, haloperiodol, indomethacin, and cephalexin.

12. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the first composition comprises an osmagent.

13. A device as claimed in claim 1 and substantially as herein described and/or with reference to the accompanying drawings.

14. Each and every novel embodiment herein set forth either separately or in combination.

Printed in the United Kingdom for Her Majesty's Stationery Office, Demand No. 8818935, 12/1984. Contractor's Code No. 6378.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 127 902**
**A2**

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 84106400.9

(22) Date of filing: 05.06.84

(51) Int. Cl.³: C 07 D 263/20
C 07 D 263/24, A 61 K 31/42

(30) Priority: 07.06.83 US 501897
14.02.84 US 578332

(43) Date of publication of application:
12.12.84 Bulletin 84/50

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY
1007 Market Street
Wilmington Delaware 19898(US)

(72) Inventor: Gregory, Walter Adelman
104 Rockingham Drive
Wilmington Delaware 19803(US)

(74) Representative: von Kreisler, Alek et al,
Patentanwälte Von Kreisler-Schönwald-Fues-Keller
Selting-Werner Deichmannhaus am Hauptbahnhof
D-5000 Köln 1(DE)

(54) **Aminomethyl oxooxazolidinyl benzene derivatives useful as antibacterial agents.**

(57) Novel aminomethyl oxooxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, such as (I)-N-[3-[4- (methylsulfonyl) phenyl] -2-oxooxazolidin -5- ylmethyl] carbamic acid, methyl ester possess useful antibacterial activity.

EP 0 127 902 A2

0127902

Title BP-6244-A

# AMINOMETHYL OXOOXAZOLIDINYL BENZENE DERIVATIVES USEFUL AS ANTIBACTERIAL AGENTS

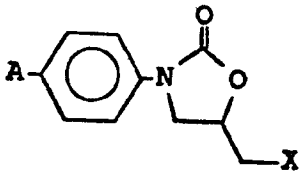
## Technical Field

This invention relates to novel aminomethyl oxooxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, to pharmaceutical compositions containing them, and to methods of using them to alleviate bacterial infections.

## Background of the Invention

At the present time, no existing antibacterial product provides all features deemed advantageous. There is continual development of resistance by bacterial strains. A reduction of allergic reactions and of irritation at the site of injection, and greater biological half-life (i.e., longer in vivo activity) are currently desirable features for antibacterial products.

U.S. Patent 4,128,654 issued to Fugitt et al. on December 5, 1978, discloses, among others, compounds of the formula:




where

A = $RS(O)_n$;

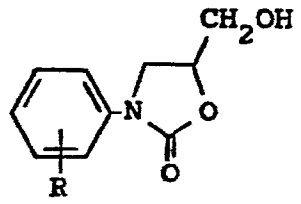
X = Cl, Br or F;

R = $C_1$-$C_3$ alkyl; and

n = 0, 1 or 2.

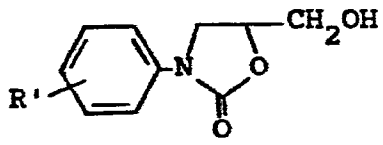
The compounds are disclosed as being useful in controlling fungal and bacterial diseases of plants.

U.S. Reissue Patent 29,607 reissued April 11, 1978 discloses derivatives of 5-hydroxymethyl-3-substituted-2-oxazolidinones of the formula:



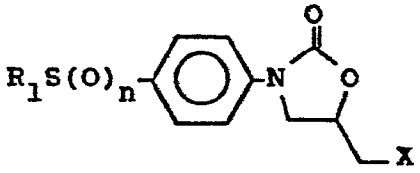
where R is H, F, $CH_3$, or $CF_3$. Such compounds are described as having antidepressive, tranquilizing, sedative, and antiinflammatory properties.

U.S. Patent 4,250,318, which was issued on February 10, 1981, discloses antidepressant compounds of the formula:



where R' can be, among others, a <u>para</u>-<u>n</u>-pentylamino group, an $SR_1$ group where $R_1$ is $C_1$-$C_5$ alkyl, or an acetylmethylthio group.

U.S. Patent 4,340,606, issued to Fugitt et al. on July 20, 1982, discloses antibacterial agents of the general formula:

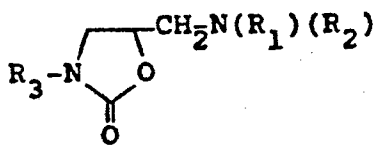


where

$R_1$ = $CH_3$, $C_2H_5$, $CF_2H$, $CF_3$ or $CF_2CF_2H$; and

X = $OR_2$ ($R_2$ = H or various acyl moieties).

U.S. Patent 3,687,965, issued to Fauran et al. on August 29, 1972, discloses compounds of the formula:



where

$-N(R_1)(R_2)$ represents either dialkylamino radical in which the alkyl portions have one to five carbon atoms, or a heterocyclic amino radical which may be substituted by an alkyl radical having one to five carbon atoms or by a pyrrolidinocarbonylmethyl radical, and

$R_3$ represents a phenyl radical which may be substituted by one or more of the following radicals:

an alkoxy radical having one to five carbon atoms;

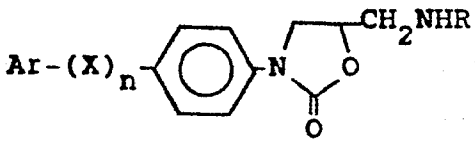
a halogen atom;

a trifluoromethyl radical, or

a carboxyl radical which may be esterified.

The patent states that these compounds possess hypotensive, vasodilatatory, spasmolytic, sedative, myorelaxant, analgesic and antiinflammatory properties. There is no mention of antibacterial properties.

Belgian Patent 892,270, published August 25, 1982, discloses monoamine oxidase inhibitors of the formula



where

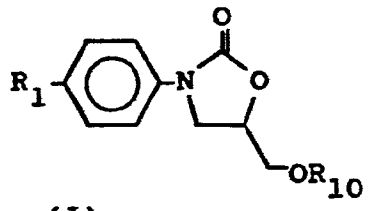
R is H, $C_1$-$C_4$ alkyl or propargyl;

Ar is phenyl, optionally substituted by halo or trifluoromethyl;

n is 0 or 1; and

X is $-CH_2CH_2-$, $-CH=CH-$, an acetylene group or $-CH_2O-$.

Pending U.S. Patent Appln. Serial No. 567,411, filed January 5, 1984, a continuation-in-part of U.S. Patent Application 417,569 filed September 15, 1982 by W. A. Gregory discloses antibacterial agents of the formula



(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

$R_1$ is $R_2SO_2$, $R_3R_4NC(=O)$, or $R_3C(=NR_5)$;

$R_2$ is $-NR_3R_4$, $-N(OR_3)R_4$, $-N_3$, $-NHNH_2$, $-NX_2$, $-NR_6X$, $-NXZ$, $-NHCR_7$ (=O), $-NZCR_7$ (=O) or $-N=S(O)_nR_8R_9$;

$R_3$ and $R_4$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

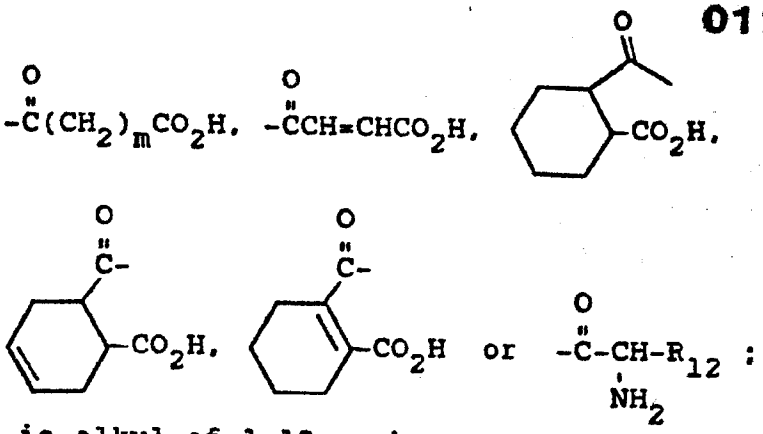
$R_5$ is $NR_3R_4$ or $OR_3$;

$R_6$ is alkyl of 1-4 carbons;

$R_7$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

$R_8$ and $R_9$ are independently alkyl of 1-4 carbons or, taken together are $-(CH_2)_p-$;

$R_{10}$ is H, alkyl of 1-3 carbons, $-CR_{11}$(=O).



$R_{11}$ is alkyl of 1-12 carbons;

$R_{12}$ is H, alkyl of 1-5 carbons, $CH_2OH$ or $CH_2SH$;

X is Cl, Br or I;

Z is a physiologically acceptable cation;

m is 2 or 3;

n is 0 or 1; and

p is 3, 4 or 5;

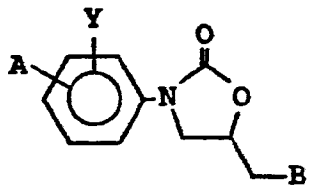
and when $R_{10}$ is alkyl of 1-3 carbons, $R_1$ can also be $CH_3S(O)_q$ where q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

None of the cited references nor any known references suggest the novel antibacterial compounds of this invention.

## Summary of the Invention

The novel compounds of the instant invention possess useful antibacterial activity in both *in vitro* and *in vivo* tests. Specifically, one aspect of this invention relates to compounds having the formula:



(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

A is $-NO_2$, $-S(O)_nR_1$, $-S(O)_2-N=S(O)_pR_2R_3$, $-SH$, $-S\overset{O}{\overset{\|}{C}}R_4$, $-COR_5$, $-CONR_5R_6$, $-\overset{NR_7}{\overset{\|}{C}}-R_5$, $-CN$, $-OR_5$, $-NR_5R_6$, $-\overset{R_5}{\overset{|}{N}}COR_4$, $-\overset{R_5}{\overset{|}{N}}S(O)_nR_4$, alkyl of 1 to 5 carbons, optionally substituted with one or more halogen atoms, alkenyl of 2-5 carbons or cycloalkyl of 3-8 carbons;

$R_1$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms, CN, $NR_5R_6$ or $CO_2R_8$; $C_2$-$C_4$ alkenyl; $-NR_9R_{10}$; $-N_3$; $-NH\overset{O}{\overset{\|}{C}}R_4$; $-NZ\overset{O}{\overset{\|}{C}}R_4$; $-NX_2-$; $NR_9X$ $-{}^{-}NXZ^{+}$;

$R_2$ and $R_3$ are independently $C_1$-$C_2$ alkyl or, taken together, are $-(CH_2)_q-$;

$R_4$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

$R_5$ and $R_6$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

$R_7$ is $-NR_5R_6$ or $-OR_5$;

$R_8$ is H or alkyl of 1-4 carbons;

$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11a}$

$R_{11}$ and $R_{11a}$ are independently H or $C_1$-$C_4$ alkyl, or taken together, are $-(CH_2)_r-$;

X is Cl, Br or I;

Y is H, F, Cl, Br or $NO_2$, or A and Y taken together can be $-O-(CH_2)_tO-$;

Z is a physiologically acceptable cation;

n is 0, 1 or 2;

p is 0 or 1;

q is 3, 4 or 5;

r is 4 or 5;

t is 1, 2 or 3;

B is $-NH_2$, $-N(R_{12})-\overset{O}{\overset{\|}{C}}-R_{13}$, $-N(R_{12})-S(O)_uR_{14}$ or $N_3$;

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and O-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$; $\overset{O}{\overset{\|}{C}}R_{15}$

$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;

$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;

$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_4$ alkyl;

$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s$;

u is 1 or 2;

v is 0, 1 or 2;

m is 2 or 3; and

s is 2, 3, 4 or 5;

or a pharmaceutically suitable salt thereof;

provided that:

1) when A is $CH_3S$-, then B is not $-\overset{CH_3}{\underset{|}{N}}-CO_2CH_3$;

2) when A is $CH_3SO_2$-, then B is not $-\overset{CH_3}{\underset{|}{N}}-COCH_3$ or $-\overset{CH_3}{\underset{|}{N}}-COCF_3$;

3) when A is $H_2NSO_2$- and B is $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}R_{13}$, then $R_{12}$ is H;

4) when A is -CN, B is not $-N_3$;

5) when A is $(CH_3)_2CH$, B is not $NHCOCH_2Cl$.

Preferred, for their high antibacterial activity or ease of synthesis, or both, are compounds of formula I where:

(1) Y is H;

A, substituted in the para position, is $-S(O)_nR_1$, $NO_2$, $-\overset{O}{\overset{\|}{C}}-CH_3$, or $-CH(CH_3)_2$;

$R_1$ is $C_1$-$C_2$ alkyl optionally substituted with one or more halogen atoms or $NR_5R_6$;

$R_5$ is H or $CH_3$;

$R_6$ is H or $CH_3$;

n is 0, 1 or 2 when $R_1$ is alkyl or substituted alkyl; n is 2 when $R_1$ is $NR_5R_6$;

or

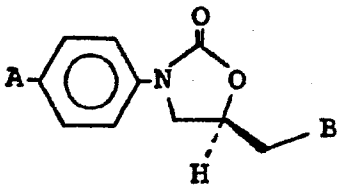
(2) B is $-NH-\overset{O}{\overset{\|}{C}}-R_{13}$;

$R_{13}$ is H, $CH_3$, $OR_{18}$, $CHCl_2$, $CH_2Cl$ or $CH_2OR_{15}$;

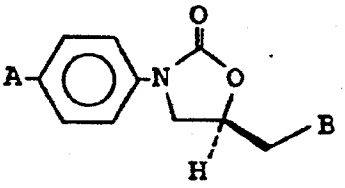
$R_{15}$ is H or $C_1$-$C_4$ alkyl; and

$R_{18}$ is $C_1$-$C_4$ alkyl.

Preferred because of high antibacterial activity are compounds of formula I having the absolute configuration depicted:




More preferred because of high antibacterial activity are compounds of formula I having the absolute configuration depicted:




and where A is $S(O)CH_3$, $SCH_3$, $S(O)_2CH_3$, $SO_2NH_2$, $COCH_3$ or $CH(CH_3)_2$; and

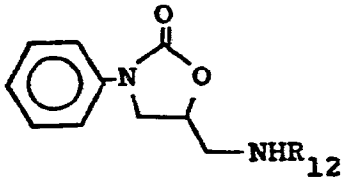
where B is $-NHCOCH_3$, $-NHCO_2CH_3$ or $-NHCOCHCl_2$.

Specifically preferred for their high antibacterial activity are the following compounds:

- (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester;
- (ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester;
- (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]formamide;

- (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(aminosulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(methylsulfinyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-2,2-dichloro-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-isopropylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and
- (ℓ)-N-[3-(4-acetylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

Another aspect of this invention relates to novel intermediates having the formula:

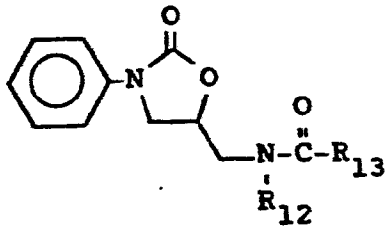


(Ia)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl.

Another aspect of this invention relates to novel intermediates having the formula:



(Ib)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-\overset{O}{\overset{\|}{C}}R_{15}$; $-OR_{18}$; $-SR_{14}$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;

$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;

$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;

$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_4$ alkyl;

$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;

m is 2 or 3; and

v is 0, 1 or 2; and

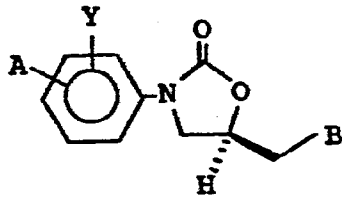
s is 2, 3, 4 or 5.

Another aspect of this invention relates to a pharmaceutical composition comprising a suitable pharmaceutical carrier and an antibacterially effective amount of a compound of formula I. Yet another aspect of the invention relates to a method for alleviating bacterial infection in a mammal which comprises administering to the mammal an antibacterially effective amount of a compound of formula I.

## Detailed Description

The compounds of formulae I, Ia, and Ib contain at least one chiral center, and as such exist as two individual isomers or as a mixture of both. This invention relates to the levorotatory isomer (ℓ), as well as mixtures containing both the d and the ℓ isomers. An additional chiral center is present when A is $R_1S(O)_n$ and n is 1 and this invention relates to both of the possible isomers at that center. Additional chiral centers may be present in the group B and this invention relates to all possible stereoisomers in the group B.

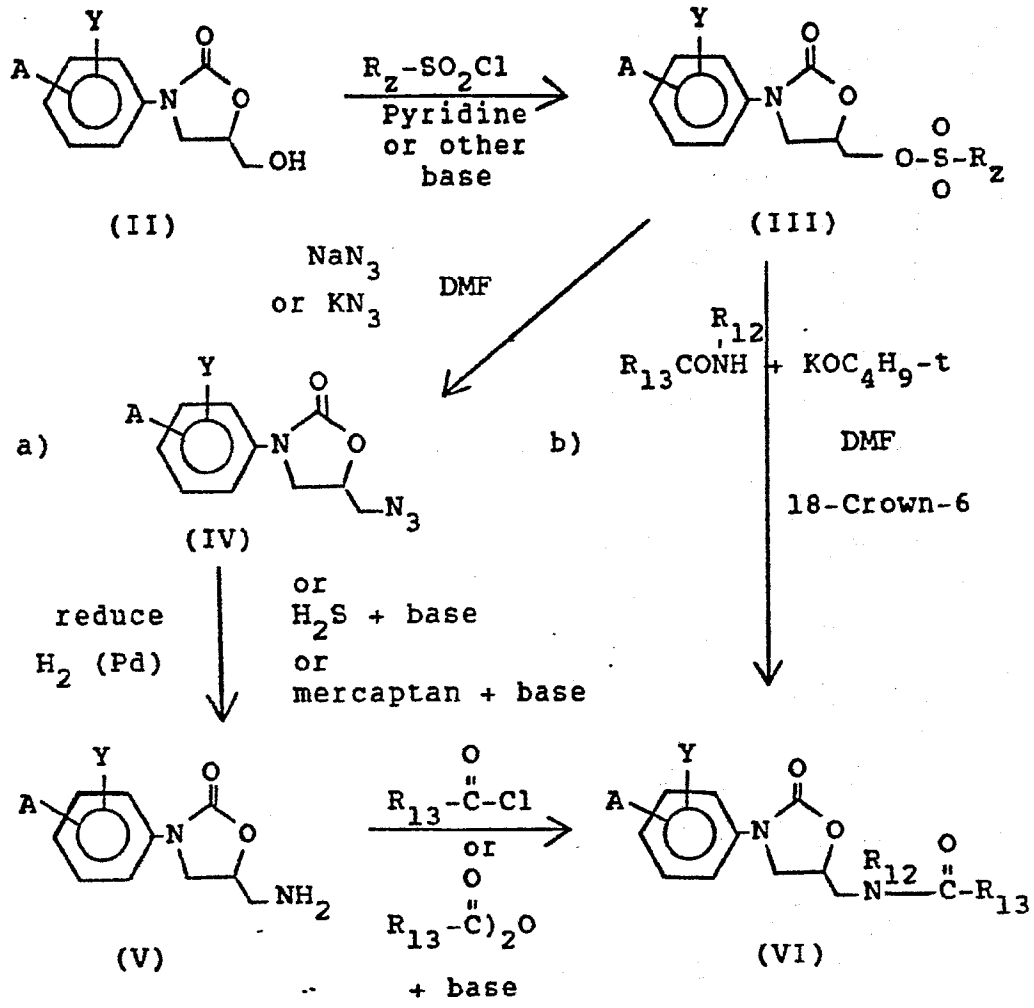
For the purposes of this invention, the ℓ-isomer of compounds of formulae I, Ia, and Ib is intended to mean compounds of the configuration depicted:



Synthesis

Compounds of Formula (I) can be prepared as follows:

Scheme 1:




Where $R_z$ may be 4-tolyl, phenyl, 4-chlorophenyl, $C_1$-$C_4$ alkyl or haloalkyl, such as trifluoromethyl.

When the synthetic path a) is used, the group A may be -H or any of the groups previously shown except where $R_1$ is $-N_3$, $-NX_2$, $-NR_9X$, $-^{-}NXZ^{+}$. When the synthetic path b) is used the group A may be -H or any of the groups previously shown except when A is $R_1S(O)_n$ and $R_1$ is $NR_9R_{10}$, $R_9$, $R_{10}$, $R_{11}$, and $R_{11a}$ cannot be H.

Compounds of Formula (II) may be converted to sulfonate esters (III) by reaction with the appropriate sulfonyl halide or sulfonic anhydride in a solvent plus a base or in a basic organic solvent such as pyridine. It is desirable when the A group has a sulfonamide hydrogen to use pyridine or other mildly basic solvents such as the picolines or collidines. As solvents, 1,2-dimethoxyethane, dioxane, bis-(2-methoxyethyl)ether, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), acetonitrile, or tetramethylenesulfone may be used. As a base, triethylamine, N-methylmorpholine, tributylamine or one of the heterocyclic bases can be used.

Compounds (III) may be reacted with sodium, potassium, lithium, cesium or rubidium azides in a dipolar aprotic solvent such as DMF, N-methylpyrrolidone, DMAc, sulfolane, dimethylsulfoxide, tetramethylurea, hexamethylphosphoramide (HMPA), etc. along with the appropriate catalyst such as 18-crown-6 for sodium and potassium azide and 12-crown-4 for lithium azide. This reaction is carried out from about 60° to 125°C, with the preferred temperatures being 70° to 90°C. The products are azides of structure (IV).

The azides (IV) may be reduced by any of several methods, including hydrogenation over palladium-on-charcoal. It is also possible to reduce the azides by treating with 1,3-propanedithiol and a base such as triethylamine. Azides may also be reduced to amines by hydrogen sulfide and by trivalent phosphorous compounds such as trimethylphosphine and trimethylphosphite, and by mercaptans such as mercaptoacetic acid. Reduction with hydrogen can best be used where A is hydrogen, but it will work where A is a hexavalent sulfur containing group. The reduction is carried out using a solvent such as ethanol, methanol, 1,2-dime-

thoxyethane, acetic acid, trifluoroacetic acid, or isopropanol. A solution may be stirred at ambient temperature with palladium-on-charcoal catalyst present and the hydrogen introduced at atmospheric pressure through a glass frit. In some instances the reduction is exothermic.

The reduction using 1,3-propanedithiol is carried out in methanol or other alcohol solvents containing an equivalent of triethylamine, by warming until $N_2$ evolution occurs. At ambient temperatures, slow reduction occurs. Temperatures of 20° to 100°C may be used; temperatures of 40° to 60°C are preferred. Warming an azide (IV) with trimethylphosphine causes a rapid evolution of $N_2$. The reaction may be carried out in 1,2-dimethoxyethane or bis-(2-methoxyethyl)ether and the crude intermediate, when hydrolyzed with water or acid, gives the desired amine (V).

The aminomethyl compounds (V) are acylated by reaction of the amine with an acid chloride or anhydride in a basic solvent such as pyridine or by reaction in a water miscible solvent such as THF or 1,2-dimethoxyethane in the presence of an aqueous base such as sodium hydroxide or potassium hydroxide, sodium bicarbonate or sodium carbonate. When pyridine is used as solvent for the reaction, the acid chloride or anhydride is added to the mixture at 0° to 10°C. The reaction may be carried out between -30° and 50°C. With very reactive acid chlorides or anhydrides such as trifluoromethanesulfonyl chloride or anhydride the reaction is preferably carried out at -60° to -40°C. The acylations using aqueous bases are done by stirring the amine (V) in a water miscible solvent such as tetrahydrofuran (THF), 1,2-dimethoxyethane, or dioxane and adding 1-5 N NaOH to keep the mixture basic as the acid chloride or anhydride is added, while

keeping the temperature between -5° and 20°C. The compounds (V) can also be acylated by any of the standard peptide synthesis methods where the free acid is reacted with the amine using N,N-dicyclohexylcarbodiimide, or where a mixed anhydride is first formed from the acid using a chloroformate ester and a tertiary base such as triethylamine, followed by reaction with the amine. In the mixed anhydride procedure, the acid to be used is allowed to react with a chloroformate such as ethyl chloroformate or isobutyl chloroformate in a solvent such as THF, DMF or 1,2-dimethoxyethane, in the presence of a tertiary base such as triethylamine or N-methylmorpholine at -30° to 10°C. To this mixture the amine (V) is added and the mixture stirred at -10°C for 1-5 hours. When N,N-dicyclohexylcarbodiimide is used as the condensing agent, the conditions and solvents may be the same but it is often advantageous to add N-hydroxyphthalimide or N-hydroxysuccinimide.

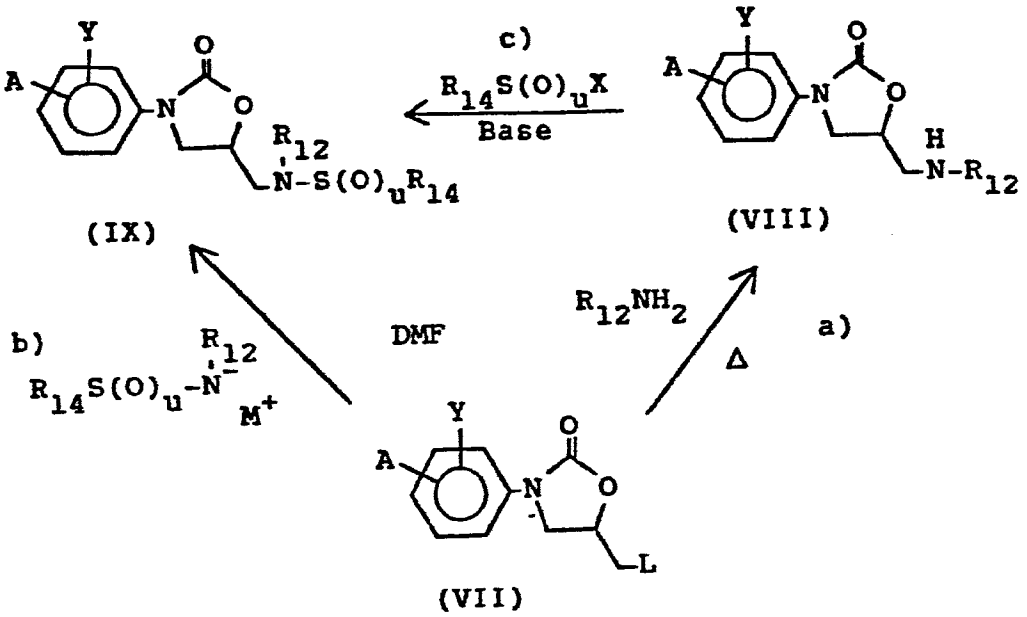
Further, these amines may be acylated by reaction with esters such as methyl dichloroacetate, ethyl trifluoroacetate or n-butyl formate. In this method, the amine (V) is combined with the ester and a solvent such as 1,2-dimethoxyethane, bis-(2-methoxyethyl)ether, or toluene (in some cases the ester may be used as the solvent) and the mixture is heated at reflux until the reaction is shown to be complete by an assay such as thin-layer chromatography. More reactive esters such as p-nitrophenyl esters, pentafluorophenyl esters, thio esters, enol esters, N-hydroxyphthalimide esters, N-hydroxysuccinimide esters, 1-hydroxybenzotriazole esters, 2,4,5-trichlorophenyl esters, and pentachlorophenyl esters, may be used. Further, other acylating agents such as acyl azides, acyl imidazoles and acyl phosphates, may be used.

When synthetic path b) is used, the sulfonate ester (III) is allowed to react with an amide in the form of its sodium or potassium salt, generated using NaH, KH or $KOC_4H_9$-t in a dipolar aprotic solvent such as DMF, DMAc, HMPA, N-methylpyrrolidinone, or tetramethylenesulfone. To the salt preparation is added the sulfonate ester (III) and the mixture is heated to 30° to 150°C. A catalyst such as 18-crown-6 may be used. Heating is continued for 3-50 hours.

In Scheme 1, the starting compound (II) may be dℓ- (the racemate) or the ℓ-isomer. The ℓ-isomer is a precursor for the preferred ℓ-amides (VI).

When the acylating group is derived from an α-amino acid and $R_{13}$ contains an amino function it is necessary to protect that amino function with one of the commonly used protective groups such as benzyloxycarbonyl, t-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, or phthaloyl. Following the acylation, the protective group is removed by one of the standard methods to which the oxazolidinone ring is inert. The benzyloxycarbonyl group may be removed by hydrogenation in a solvent such as methanol, DMF, acetic acid, or mixtures of these solvents, using a catalyst such as 10% palladium-on-carbon or palladium black (100 to 500 mg of catalyst per mmole of compound). Alternatively the benzyloxycarbonyl group may be removed by dissolving the compound in acetic acid, adding an equal volume of 4 N HBr in acetic acid, and keeping the solution at room temperature for 1 to 5 hours. The $N^{\alpha}$-t-butyloxycarbonyl groups are removed by hydrolysis with trifluoroacetic acid at room temperature.

Scheme 2:



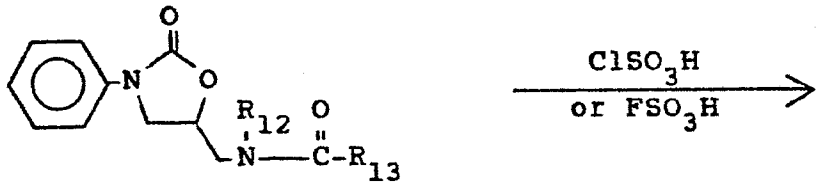

Compounds of formula (I) which may be made using the procedures of Scheme 2 are those where A is H or any of the groups previously shown except that when A is $R_1S(O)_n$ and $R_1$ is $NR_9R_{10}$, $R_9$, $R_{10}$, $R_{11}$ and $R_{11a}$ cannot be H. L may be any suitable leaving group such as I, Br, Cl, benzenesulfonyloxy, 4-toluenesulfonyloxy, methanesulfonyloxy or trifluoromethanesulfonyloxy. In route a) the compound (VII) is allowed to react with ammonia or an amine in a solvent such as ethanol at temperatures of 50° to 150°C. Where the amine or solvent is low-boiling, the reaction is carried out in a sealed vessel to allow the desired temperature to be reached. The solvent may be ethanol, DMF, DMAc, N-methylpyrrolidinone, tetramethylenesulfone, or HMPA. The reaction time may be 1 to 24 hours. Where (VII) is optically active (i.e., the ℓ-isomer) the product is optically active. The acylation of product VIII is carried out as described for Scheme 1, Path a).

The reaction of (VII) with the anion of a sulfonamide shown in Scheme 2, Path b) is carried out in a polar solvent such as DMF, DMAc, N-methylpyrrolidinone, tetramethylenesulfone, or HMPA. In some cases the use of a catalyst such as 18-crown-6 may improve the reaction. Temperatures of 50° to 150°C are employed; the time for the reaction can vary between 2 to 48 hours.

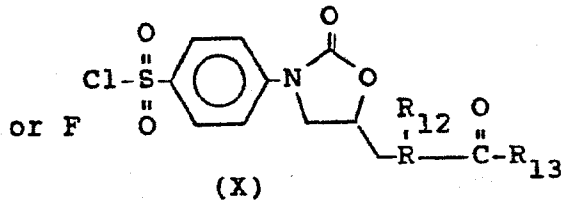
Alternatively, the sulfonamides (IX) can be prepared by reaction of the amine (VIII) with a sulfonyl halide in the presence of a base such as triethylamine or a basic solvent such as pyridine [Path c)].

Scheme 3:

a)

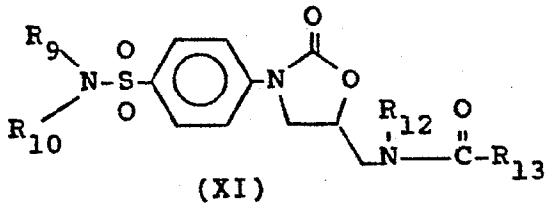



(VI; A=H)



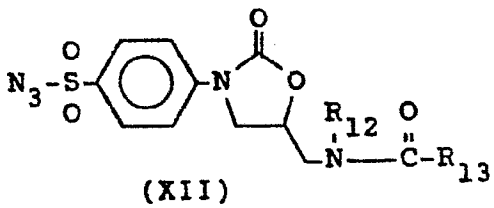

(X)

b) (X) $\xrightarrow{R_9R_{10}NH}$

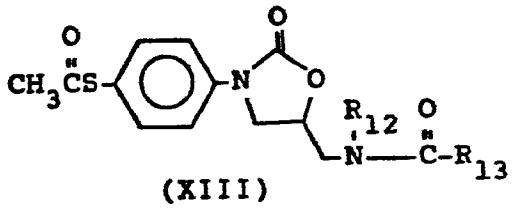


(XI)

c) (X) $\xrightarrow{NaN_3}$



(XII)

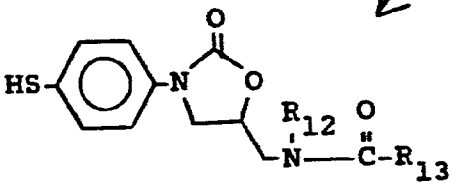
d) (X) —Zn, acetic acid / acetic anhydride→ 

(XIII)

Zn, acetic acid

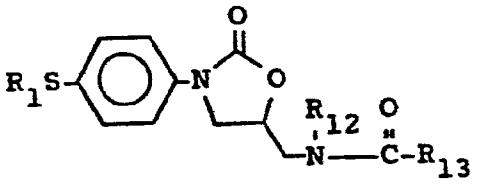
1) base

2) $H^+$



(XIV)

$R_1$-L / base →



(XV)

Compounds of Formula I, where B is $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-R_{13}$ wherein $R_{13}$ is not $CH(OR_{16})OR_{17}$ or $CH_2N_3$ can be prepared as shown in Scheme 3. The halosulfonation (particularly, chlorosulfonation) shown in Scheme 3, Path a), can be carried out by adding the compound of formula VI where A is H to chlorosulfonic acid or fluorosulfonic acid at room temperature in the absence of solvent. The temperature may be 10° to 100°C; preferred temperatures are 15° to 35°C. A solvent inert to chlorosulfonic acid or fluorosulfonic acid may be employed (examples include carbon tetrachloride, nitrobenzene, or a fluorocarbon) but using neat chlorosulfonic acid or fluorosulfonic acid is preferred.

The sulfonyl chloride or fluoride (X) may then be reacted by the procedure of Scheme 3, Path b), with ammonia, a mono- or disubstituted amine, a hydroxylamine or a hydrazine in a solvent such as THF, 1,2-dimethoxyethane, dioxane, bis-(2-methoxyethyl)ether or DMF. The reaction may be run at temperatures of -20° to 40°C; temperatures of -10° to 10°C are preferred.

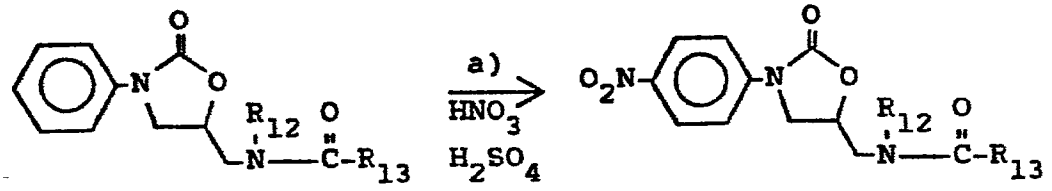
The sulfonyl chloride or fluoride (X), may be reacted with sodium azide or potassium azide in a mixture of acetone and water to give the sulfonyl azide (XII) as shown in Scheme 3, Path c). Other water-miscible solvents such as acetonitrile, DMF, 1,2-dimethoxyethane, THF, or dimethylsulfoxide may be used in place of acetone. An aqueous solution of sodium azide is added to acetone, the mixture is cooled in an ice-bath, the sulfonyl halide (X) is added, and the mixture is allowed to come to room temperature. The reaction may be carried out at -10° to 20°C. Preferred temperatures are -5° to 10°C.

The sulfonyl chlorides (X) may be reduced by several methods, as shown in Scheme 3, path a). The use of zinc metal added to a hot mixture of acetic acid, acetic anhydride and sodium acetate gives the S-acetates (XIII) in good yield. This is carried out at reflux temperature of the mixture, but may be carried out between 50°C to 120°C. Alternatively, the sulfonyl halides may be reduced by using zinc in acetic acid to give the mercaptans (XIV). The reduction may also be carried out using an iodide such as trimethylsilyl iodide or mixtures of trimethylsilyl chloride and sodium iodide in an inert solvent such as dichloromethane, benzene or toluene; stirring in the temperature range of 0°C to 50°C with the preferred temperature 20-30°C. This reduction gives the disulfide which is then reduced by sodium borohydride in an

alcohol solvent such as methanol. The disulfide may also be reduced by dithiothreitol or by zinc and acid. The product is the mercaptans (XIV). If desired the mercaptans may be alkylated with the halides $R_1$-L to give the sulfides (XV). This reaction may be carried out using base such as potassium carbonate, sodium methoxide, sodium ethoxide or potassium t-butoxide. The alkylation can be done using sodium hydroxide in dimethylsulfoxide.

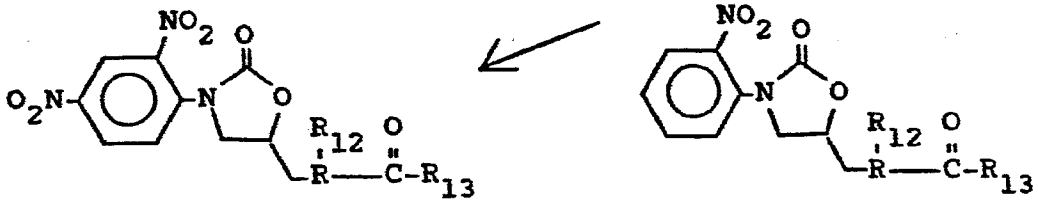
The reactions of Scheme 3 may be carried out starting with the ℓ-isomer of (VI) where A = H to give products of the preferred ℓ-form (the preferred configuration shown above).

Scheme 4:

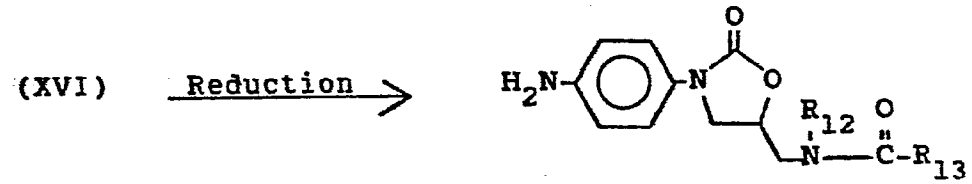



(VI; where A=H) (XVI)

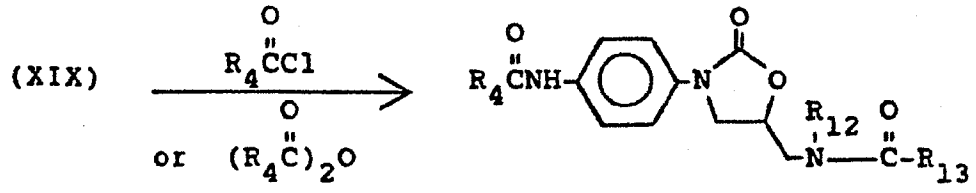
+



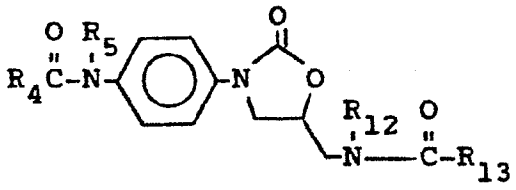
(XVIII) (XVII)



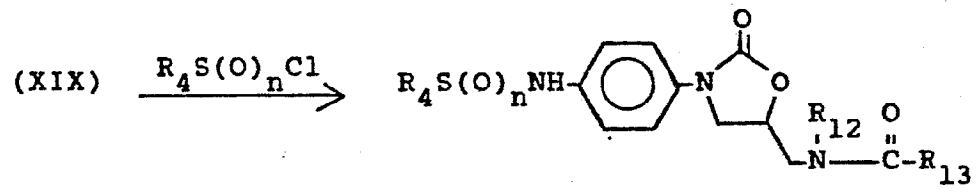

(XIX)



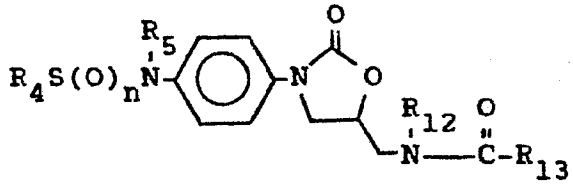
(XX)



(XXI)



(XXII)



(XXIII)

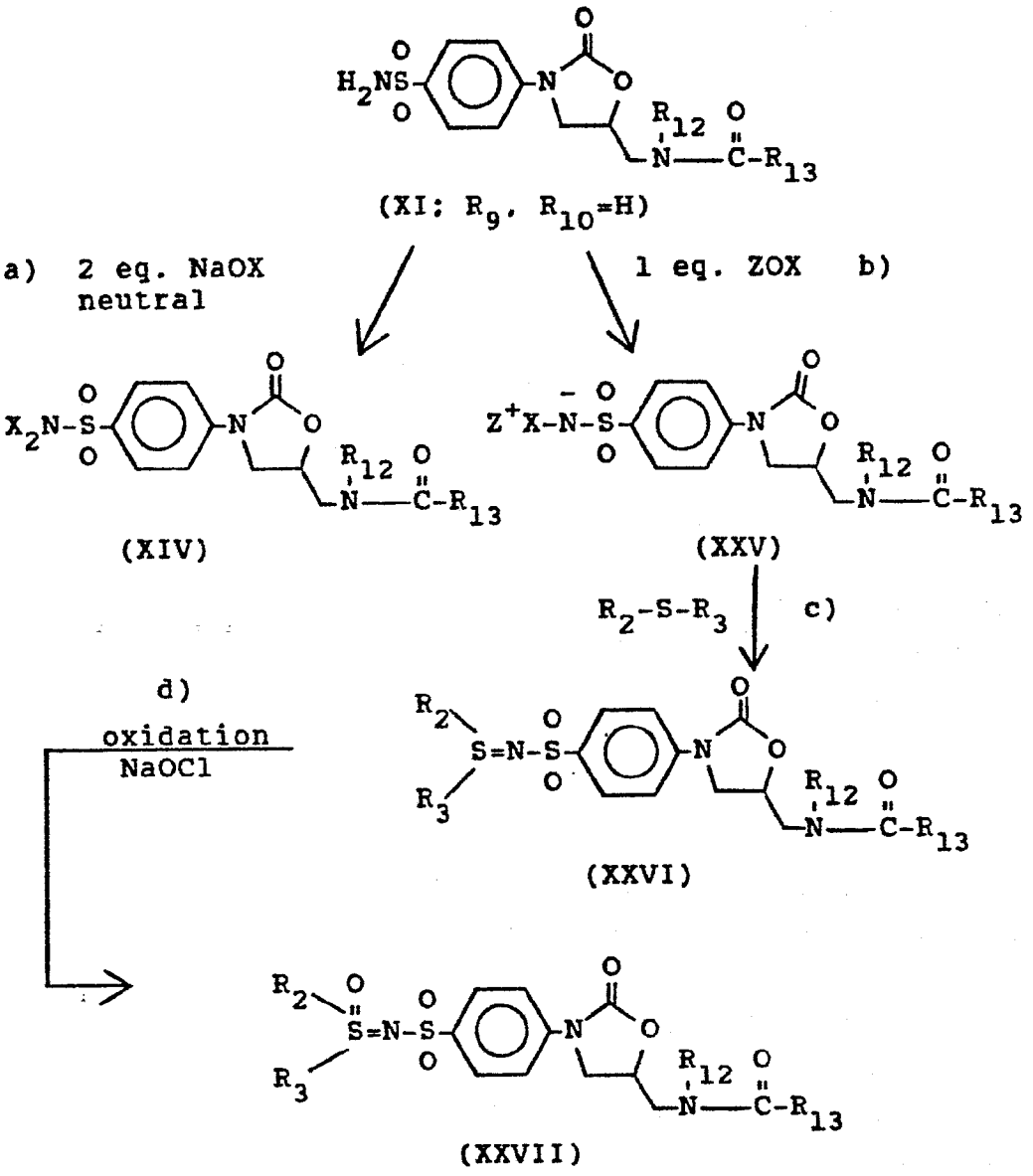
The nitration of Scheme 4, Path a) is carried out by adding the compound of formula (VI) (A=H) to concentrated sulfuric acid containing one equivalent of nitric acid. Nitrate may be added in the form of a salt such as potassium nitrate. The nitration mixture is cooled to about -5°C, kept below 0°C during the addition, and then allowed to warm to room temperature. The nitration may be carried out at temperatures of -20° to 15°C, over time periods of 30 to 180 minutes.

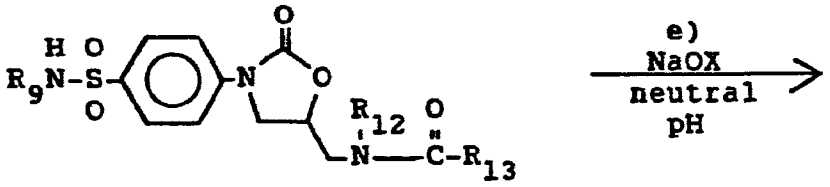
In the nitration shown in Scheme 4 it has been found that some ortho nitration occurs as well as the formation of 2,4-dinitro-compound. These products may be isolated by use of preparative chromography, and/or crystallization. The ortho nitro compound may be made in higher amounts by nitration in acetic acid by generating acetyl nitrate. The dinitro-compound can easily be made by using a higher molar ratio of nitrating agent.

The nitro-compounds (XVI, XVII, XVIII) can be reduced by using Raney nickel catalyst and hydrazine or by catalytic hydrogenation in a Parr shaker under 10-50 lbs. of hydrogen using palladium-on-charcoal as the catalyst. The products are the anilines (XIX). The anilines (XIX) may be acylated using an acyl halide or an acyl anhydride in the presence of an organic base such as pyridine or triethylamine or N-methylmorpholine; or using aqueous sodium hydroxide in an organic solvent such as tetrahydrofuran, 1,2-dimethoxyethane or DMF. A catalyst such as 4-dimethylaminopyridine may be used. In a similar way the anilines may be reacted with a sulfonyl halide to give the sulfonamides. In turn, the amides (XX) and sulfonamides (XXII) may be alkylated using base and the appropriate alkyl halide, alkyl sulfonate or sulfate ester.

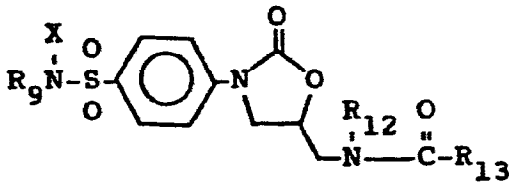
Compounds where $R_1$ is $-NX_2$, $-NR_4X$, $-NXZ$ or $-N=S(O)_pR_2R_3$ may be made as shown in Scheme 5.

Scheme 5:






(Xi: $R_{10}$=H)



(XXVIII)

Part a) of Scheme 5 is carried out by adding the sulfonamide (XI; $R_9$, $R_{10}$=H) to 1.3-2 N sodium or other hypohalite (2 equivalents) while keeping the pH between 6 and 7 by adding a dilute acid solution or acetic acid. This reaction may be carried out at -20° to 50°C; it goes well at room temperatures of 20° to 30°C. The reaction is complete in 30 minutes to 2 hours. To make the metal salts of the haloamide (XXV), Scheme 5, Path b), one keeps the solution basic and uses approximately an equivalent amount of the hypohalite.

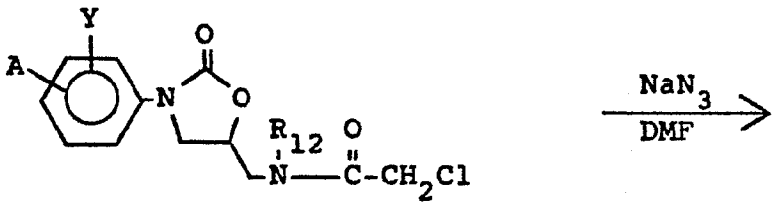
The sulfilimines (XXVI) are made by reacting the haloamide (XXV) with the appropriate sulfide in an alcohol-water mixture at 50° to 70°C. These products may be converted to the sulfoximines by oxidation using an oxidant such as hypochlorite anion in a phase transfer catalyzed system. This oxidation is carried out by stirring (XXVI) in a mixed solvent (ethyl acetate and dichloromethane) with tetra-n-butylammonium bromide while a two-fold excess of aqueous NaOCl are added at room temperature.

The preparation of N-alkyl haloamides (XXVIII) (Scheme 5, step e)) is carried out using the procedure

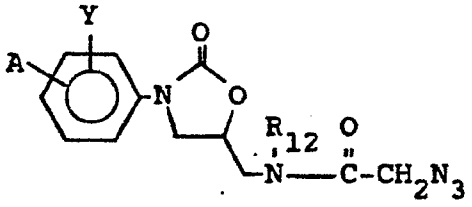
of Scheme 5, Path a), except employing one equivalent of hypohalite.

An alternative synthesis of the glycinamides of Formula I where B is $\overset{R_{12}}{\underset{|}{N}}\!\!-\!\!\overset{O}{\overset{\|}{C}}\!-R_{13}$ wherein $R_{13}$ is $CH_2NH_2$ as well as compounds where $R_{13}$ is $CH_2N_3$ is shown in Scheme 6.

Scheme 6:

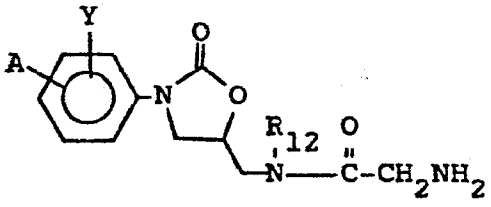



(XXIX)




(XXX)

reduction



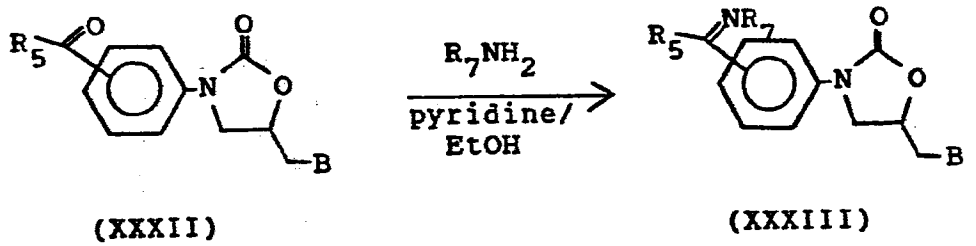

(XXXI)

Glycine amides (XXXI) may be prepared by making the chloroacetyl or bromoacetyl or iodoacetyl compounds (XXIX) followed by reacting these with sodium azide in dimethylsulfoxide or other dipolar aprotic solvents to give the azidoacetyl compounds (XXX). The azidoacetyl compounds then may be reduced by hydrogen

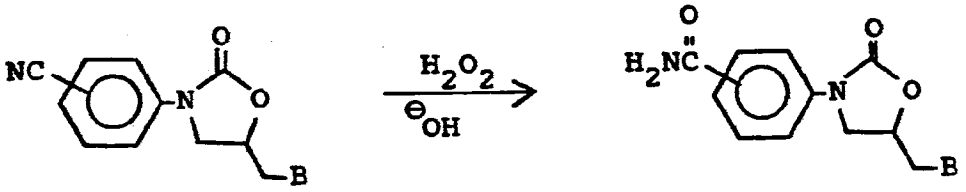
using a palladium catalyst or by any of the other reduction methods such as 1,3-propanedithiol and triethylamine, thioglycolic acid or hydrogen sulfide. The products are the glycine amides (XXXI).

The compounds of Formula I where A is $-\overset{NR_7}{\overset{\|}{C}}-R_5$ or $-\overset{O}{\overset{\|}{C}}NR_5R_6$ are obtained as shown in Scheme 7.

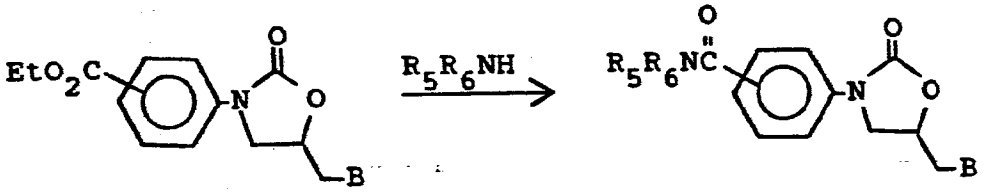
Scheme 7:




(XXXII) (XXXIII)




(XXXIV) (XXXV)



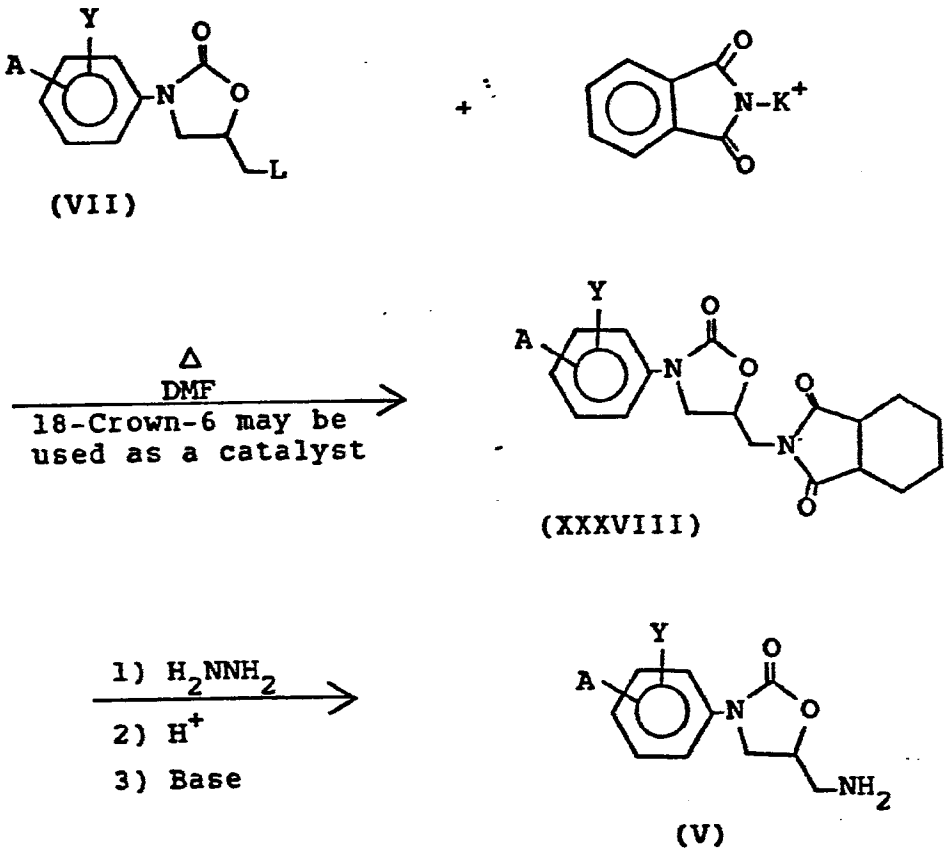

(XXXVI) (XXXVII)

Reaction of the ketones (XXXII) with a hydroxylamine or hydrazine gives the corresponding oxime or hydrazone derivative (XXXIII). The reaction is carried out in a solvent mixture of pyridine in ethanol at a temperature of 50°C to the reflux temperature of the solvent mixture.

The amides (XXXV) can be prepared by hydrolysis of the nitriles (XXXIV) with basic hydrogen peroxide. The reaction is conducted in aqueous alcoholic solvent at a temperature between 0 and 60°C. The substituted amides (XXXVII) can be prepared by aminolysis of the esters (XXXVI). For low boiling amines, the reaction can be carried out under pressure. For higher boiling amines, a mixture of the amine and (XXXVI) is stirred optionally in an alcoholic or polar aprotic solvent at a temperature of 50 to 150°C.

An alternate synthesis of compounds of structure (V) is carried out as shown in Scheme 8.

Scheme 8:

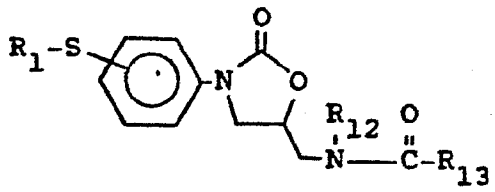



In Scheme 8, A may be H, or any of the groups previously shown except that when A is $R_1S(O)_n$, $R_1$ cannot be $N_3$, and when $R_1$ is $NR_9R_{10}$, $R_9$, $R_{10}$, $R_{11}$ and $R_{11a}$ cannot be H. L may be any suitable leaving group such as I, Br, Cl, benzenesulfonyloxy, 4-toluenesulfonyloxy, methanesulfonyloxy, or trifluoromethanesulfonyloxy. The reaction is carried out by heating at temperatures of 25° to 150°C in a dipolar aprotic solvent such as DMF, DMAc, N-methylpyrrolidinone, tetramethylenesulfone or HMPA. The phthalimide group is then removed by treatment with hydrazine in alcohol at 20°C to 50°C for 5-30 hours followed by adjusting to neutral pH with acid. An alternate method is first

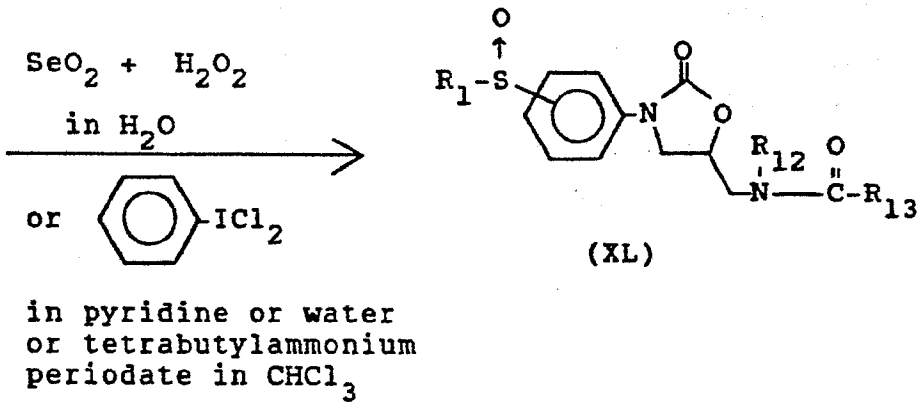
to react (XXXVIII) with sodium sulfide, then to dehydrate with N,N-dicyclohexylcarbodiimide, followed by reaction with hydrazine and then treatment with dilute acid. This last method is very mild.

Compounds where A is $-S(O)R_1$ or $-S(O)_2R_1$ may be made as shown in Scheme 9.

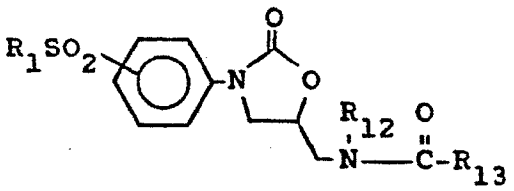
Scheme 9



(XXXIX)




(XL)



(XXXIX) MCPBA

(XLI)

Sulfides of structure (XXXIX) where $R_{12}$ and $R_{13}$ are as defined above may be oxidized to sulfoxides having the structure (XL) by using one equivalent of an oxidant. The preferred oxidant is a water-solution of selenium dioxide containing hydrogen peroxide.

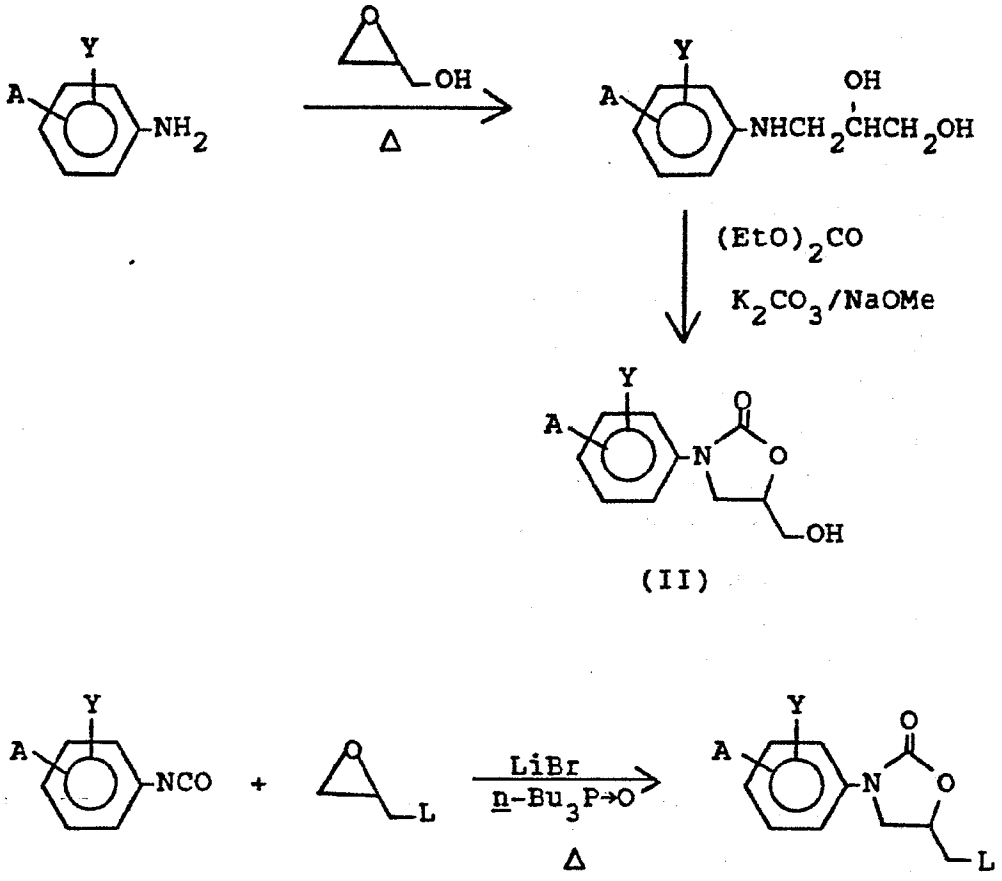
Other oxidants which may be used include iodobenzene dichloride in a pyridine-water mixture, or tetrabutylammonium periodate in refluxing chloroform. Strong oxidants such as m-chloroperoxybenzoic acid or peracetic acid may be used; the mixtures containing varying amounts of sulfide, sulfoxide and sulfone thus obtained may be separated by conventional techniques such as chromatography.

Use of two equivalents of a strong oxidizing agent such as m-chloroperoxybenzoic acid results in the sulfone (XLI).

The alcohols (II) and halides (VII) required as starting materials are readily available by any of a number of standard methods for the preparation of oxazolidones. [M. E. Dyen and D. Swern, Chem. Rev., 67, 197-246 (1967)].

Of these methods, the two which are noteworthy for the variety of compounds prepared are outlined in Scheme 10.

Scheme 10:




Pharmaceutically suitable salts of compounds of formula I can be prepared in a number of ways known in the art. In the definition of $R_1$, cations indicated by Z include alkali and alkaline earth metal ions such as $K^+$, $Mg^{++}$, $Ca^{++}$, $Li^+$, $Na^+$ and tetraalkylammonium. Where B is $-NH_2$ or where $R_{10}$ contains an amino group and A is not $S(O)_nNXZ$, pharmaceutically suitable salts include those resulting from treatment with acetic, hydrochloric, sulfuric, phosphoric, succinic, fumaric, ascorbic, and glutaric acid.

## Example 1

**Preparation of (dℓ)-5-Azidomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone (I; A=4-$CH_3SO_2$, B=$N_3$)**

Part A

**Preparation of (dℓ)-5-Iodomethyl-3-[4-(methylsulfonyl)-phenyl]-2-oxazolidinone**

A mixture of 50 g (345 mmole) of (dℓ)-5-chloromethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone and 100 g of sodium iodide in 300 ml of 2-butanone was refluxed overnight. This was cooled and poured into 1 liter of ice and water; sodium sulfite was added until all the yellow iodine color was gone; the mixture was filtered and washed with water to provide 61.7 g of iodomethyl compound, m.p. 175.5-177°C. This material was recrystallized from 370 ml of acetonitrile to give 44.8 g, m.p. 177.5-179°C.

Part B

A mixture of 7.6 g (20 mmole) of (dℓ)-5-iodomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone and 4 g of sodium azide in 150 ml of (dry) DMAC was heated at 125°C for three hours. It was then poured into ice and water. The product was extracted with chloroform three times and the extracts dried over sodium sulfate and concentrated to a semi-solid paste. The product was stirred with ether, filtered and dried; yield 4.7 g. This was recrystallized from 14 ml of acetonitrile to give 2.2 g of azidomethyl compound, m.p. 152.5-153.5°C.

## Example 2

Preparation of (ℓ)-5-Azidomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone (I; A=4-$MeSO_2$, B=$N_3$)

### Part A

Preparation of (ℓ)-5-Hydroxymethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, 4-methylbenzenesulfonate (I; A=4-$MeSO_2$, B=$OSO_2C_6H_4Me$)

A solution of 5.00 g of (ℓ)-5-hydroxymethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 30 ml of pyridine (dry) was stirred at 0-5°C and a solution of 3.7 g of p-toluenesulfonyl chloride in 10 ml of pyridine was added slowly. At the end of the addition the mixture was stirred one hour; the mixture crystallized to a semi-solid mass. A few drops of water were added with evolution of heat. The mixture was poured onto a water-ice mixture, filtered, and washed with water. The product yield was 4.02 g, m.p. 187.1-188.6°C.

### Part B

A mixture of 3.5 g of (ℓ)-5-hydroxymethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, 4-methylbenzenesulfonate and 2 g of sodium azide in 20 ml of DMF was heated to 90-100°C. At the end of one hour, the mixture was cooled and diluted with ice-water, the product crystallized and was filtered and washed well with water; yield 1.25 g; m.p. 146.5-148.5°C. This product may be crystallized from methanol to give a product melting at 148.9-149.4°C.

Example 3

Preparation of (ℓ)-4-[5-(Azidomethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide (I; A=4-$H_2NSO_2$, B=$N_3$)

Part A

Preparation of (ℓ)-4-[5-(Hydroxymethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide, 4-methylbenzenesulfonate (I; A=4-$H_2NSO_2$, B=$OSO_2C_6H_4Me$)

A mixture of 13.61 g (50 mmole) of (ℓ)-4-[5-hydroxymethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide in 50 ml of dry pyridine was stirred at -5 to 0°C as solution of 9.53 g of 4-methylbenzenesulfonyl chloride in 25 ml of pyridine was added dropwise. The reaction was allowed to warm to room temperature and stirred three hours. It was then poured into ice-water, the crystalline product filtered and washed well with water and dried. The yield of product was 19.0 g, m.p. 213.5-217.5°C.

Part B

A mixture of 18.75g (44 mmole) of (ℓ)-4-[5-(hydroxymethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide, 4-methylbenzenesulfonate and 3 g of sodium azide in 75 ml of DMF was heated at 50°C for three hours. The reaction at this stage was only about one-half done, so further sodium azide (2 g) was added and the reaction heated at 50°C for 6 hours and then at 60°C for one hour. It was poured into ice and water, filtered, washed well with water and dried; yield 11.24 g, m.p. 139.1-140.1°C. This was recrystallized from 50 ml of acetonitrile to give 6.1 g of product, m.p. 139.5-140.1°C.

Using the procedures described in Examples 1-3, the following azides could be prepared.

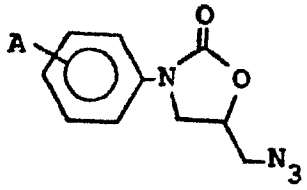


Table 1

| Ex. | A | m.p.(°C) | isomer |
|---|---|---|---|
| 4 | 4-$CH_3S$ | 97.4-98.2° | ℓ |
| 5 | 4-$CH_3CO$ | 101-102° | dℓ |
| 6 | 4-$CF_3$ | | dℓ |
| 7 | 4-$(CH_3)_2CH$ | 63-64° | dℓ |
| 8 | 3-$CH_3CO$ | | dℓ |
| 9 | 4-$CH_3O$ | | dℓ |

Example 10

Preparation of (dℓ)-5-Aminomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone trifluoroacetic Acid Salt (A=4-$CH_3SO_2$, B=$NH_2 \cdot CF_3CO_2H$)

A solution of 1.1 g of (dℓ)-5-azidomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 75 ml of trifluoroacetic acid and 0.5 g of 10% palladium-on-charcoal was shaken under hydrogen pressure (approximately 50 psig) for one hour. The mixture was filtered and concentrated to give 0.8 g of product, m.p. 158-170°C (dec.).

Example 11

Preparation of (ℓ)-5-Aminomethyl-3-[4-(methylsulfonyl)-phenyl]-2-oxazolidinone (I; A=4-$MeSO_2$, B=$NH_2$)

A mixture of 3.48 g (0.0117 mole) of (ℓ)-5-azidomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, 11 ml of 1,3-propanedithiol and 15 ml of triethylamine in 30 ml methanol was warmed to 40-50°C as nitrogen evolution occurred at an appreciable rate. After nitrogen evolution ceased, the solution was concentrated under reduced pressure, the residue stirred with ether, and the solid filtered and dried; yield 3.09 g, m.p. 137-142°C. This was dissolved in about 200 ml of absolute alcohol at reflux (some brown solid did not dissolve) and filtered hot. The product crystallized to yield 2.46 g of product, m.p. 146.6-147.1°C.

Example 12

Preparation of (ℓ)-4-[5-(Aminomethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide (I; A=4-$H_2NSO_2$, B=$NH_2$)

A suspension of 4.5 g (15.1 mmole) of (ℓ)-4-[5-(azidomethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide in 30 ml of methanol and 3 ml of triethylamine was stirred and 3 ml of 1,3-propanedithiol added. Evolution of nitrogen started and the mixture was warmed to reflux. In 15 minutes, all of the solid had dissolved, and heating was continued thirty minutes longer. The methanol was evaporated in a nitrogen stream and ether was added to the residue and a solid crystallized. The filtered solid was dried; yield 5.01 g, m.p. 148-150°C. This was dissolved in 30 ml water by adding acid, filtered and made strongly basic with concentrated ammonium hydroxide and filtered to give 1.32 g of product, m.p. 151.7-152.4°C.

Anal. Calcd. for $C_{10}H_{13}N_3O_4S$: C, 44.27; H, 4.83; N, 15.49. Found: C, 44.00, 44.13; H, 5.06, 4.85; N, 15.21, 15.21.

Example 13

Preparation of (ℓ)-5-Aminomethyl-3-[4-(methylsulfonyl)-phenyl]-2-oxazolidinone (I; A=4-$MeSO_2$, B=$NH_2$)

A 2.00 g (6.75 mmole) portion of (ℓ)-5-azidomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 25 ml of 1,2-dimethoxyethane was stirred under nitrogen as 3.2 ml of trimethylphosphine in 5 ml of 1,2-dimethoxyethane was added. The mixture became warm and a rapid evolution of nitrogen occurred. The mixture was concentrated to leave a brown gum. The gum was stirred with water and solid crystallized. This was dissolved in water by adding dilute acetic acid to pH=4, filtered and the water made basic with concentrated ammonium hydroxide. The yield of product was 0.94 g, m.p. 129-132.8°C.

Example 14

Preparation of (ℓ)-5-Aminomethyl-3-[4-(methylthio)-phenyl]-2-oxazolidinone (I; A=4-MeS, B=$NH_2$)

A mixture of 30.3 g (115 mmole) of (ℓ)-5-azidomethyl-3-[4-(methylthio)phenyl]-2-oxazolidinone, 13.1 ml of 1,3-propanedithiol and 18.2 ml of triethylamine in 150 ml of methanol was stirred at 50°C for eight hours. It was then concentrated. The residue was stirred with aqueous citric acid, filtered, and the filtrate made basic with concentrated ammonium hydroxide. The product was filtered; yield 16.5 g, m.p. 160-162°C.

Using the procedures of Examples 10-14, the following amines could be prepared.

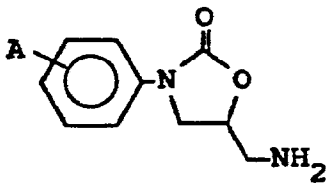



Table 2

| Ex. | A | m.p.(°C) | isomer |
|---|---|---|---|
| 15 | 4-$CH_3CO$ | 115-116° | dℓ |
| 16 | 3-$CH_3CO$ | | dℓ |
| 17 | 4-$(CH_3)_2CH$ | 104.1-105.1 | dℓ acetate salt |
| 18 | 4-$CF_3$ | | dℓ |
| 19 | 4-$CH_3O$ | | dℓ |
| 20 | 4-NC | | dℓ |

Example 21

Preparation of (ℓ)-N-[3-[4-(Methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]formamide (I; A=4-$MeSO_2$, B=NHCHO)

A solution of 1.00 g (3.70 mmole) of (ℓ)-5-aminomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, in 10 ml of 2-propanol containing 2.5 ml of ethyl formate was heated at reflux for twenty-four hours. The mixture was cooled and diluted with ether to give 0.96 g of material which was recrystallized from 9.5 ml of acetonitrile to give 0.65 g of product, m.p. 190-191.6°C.

Example 22

Preparation of (ℓ)-2,2-Dichloro-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=-4-$MeSO_2$, B=$NHCOCHCl_2$)

A mixture of 2.00 g (7.4 mmole) of (ℓ)-5-aminomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, 2 ml methyl dichloroacetate and 10 ml of ethanol was refluxed under nitrogen for five hours. The mixture was concentrated under reduced pressure then stirred with ether and filtered; yield 2.72 g, m.p. 174.0-181.9°. This was stirred with water made acid with acetic acid, filtered and washed with water; yield 2.60 g, m.p. 194.5-196.1°C. This was dissolved in boiling 70% ethanol:water made acid with acetic acid, cooled and filtered; yield of product 1.65 g, m.p. 203.3-204.3°C.

Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_5S$: C, 40.95; H, 3.70; N, 7.35. Found: C, 40.82; H, 3.70; N, 7.10, 7.15.

Example 23

Preparation of (ℓ)-N-[3-[4-(Methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I: A=4-$MeSO_2$. B=$NHCOCH_3$)

A 2.00 g (7.4 mmole) portion of (ℓ)-5-aminomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 10 ml of pyridine was cooled in a ice-bath as 0.72 ml of acetic anhydride was added. The mixture was stirred for 10 to 20 minutes then diluted with ice-water. The product was filtered and washed with water; m.p. 191.9-192.9°C. After recrystallization from acetonitrile, there was obtained 1.01 g of product, m.p. 192.7-193.2°C.

Anal. Calcd. for $C_{13}H_{16}N_2O_5S$: C, 49.99; H, 5.16; N, 8.97. Found: C, 49.48; H, 5.17; N, 8.93, 8.88.

Example 24

Preparation of (ℓ)-N-[3-[4-(Aminosulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]formamide (I: A=4-$H_2NSO_2$. B=NHCHO)

A mixture of 2.00 g (7.37 mmole) of (ℓ)-[5-(aminomethyl)-2-oxooxazolidin-3-yl]benzenesulfonamide, 2 ml of n-butyl formate and 0.5 g of 1,4-diazobicyclo-[2.2.2]octane (DABCO) in 30 ml of DMF was heated at 90-100°C for about 24 hours. It was concentrated under reduced pressure and the residue stirred with 10 ml of water. The product crystallized, 2.60 g, m.p. 184.5-186.5°C. This was recrystallized from 70% ethanol in water followed by recrystallization from acetonitrile. The product melted at 191-192°C (dec.).

Example 25

Preparation of (ℓ)-N-[3-[4-(Methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]methanesulfonamide (I; A=4-$MeSO_2$, B=$NHSO_2Me$)

A solution of 1.00 g (3.70 mmole) of (ℓ)-5-aminomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 50 ml of dry pyridine was stirred in an ice-bath as methanesulfonyl chloride (2.3 ml) was slowly added. After the addition was complete, 3 drops of water were added and the mixture concentrated. The residue was stirred with water and a few drops of concentrated HCl added until the solution was acid. The precipitate was filtered, washed with water and dried. The yield was 0.77 g, m.p. 216.7-220.7°C. This was recrystallized from acetonitrile, water (4:1) to give 0.51 g of product, m.p. 219.7-220.7°C.

Example 26

Preparation of (ℓ)-N-[3-[4-(Methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester (I; A=4-$MeSO_2$, B=$NHCO_2Me$)

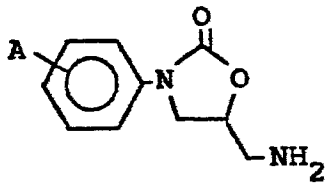
A mixture of 5.41 g (0.02 mole) of (ℓ)-5-aminomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 50 ml of tetrahydrofuran was stirred in an ice-bath as a solution of 2 ml of methyl chloroformate in 10 ml of tetrahydrofuran was added along with 2 N NaOH to keep the pH between 10-11. The mixture was stirred 45 minutes after all of the methyl chloroformate had been added. The organic solvents were removed under reduced pressure and the residue diluted with water and the pH brought to 7, the solid filtered and washed with water; yield 6.5 g, m.p. 210-211°C. This was recrystallized from acetonitrile to give 3.5 g of product, m.p. 214-215°C.

A further recrystallized sample melted at 216.9-217.6°C.

Anal. Calcd. for $C_{13}H_{16}O_6N_2S$: C, 47.55; H, 4.91; N, 8.53. Found: C, 47.55, 47.46; H, 4.88, 4.81; N, 8.73, 8.62.

$[\alpha]_D^{25} = -47.7 \pm 0.4°$ (c = 1 in acetonitrile)

In the same manner, by reacting the appropriate acyl halide, isocyanate, chloroformate ester, or ester with an amine of the structure:



the following compounds could be prepared:

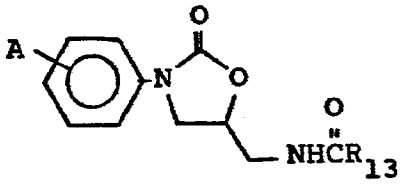


Table 3

| Ex. | A, Y | $R_{13}$ | m.p.°C | Isomer |
|---|---|---|---|---|
| 27 | 4-$CH_3SO_2$, H | $-CH_2CH_3$ | 195.8-197.1 | ℓ |
| 28 | 4-$CH_3SO_2$, H | $-CF_3$ | 239.6-240.3 | ℓ |
| 29 | 4-$CH_3SO_2$, H | $CH_2CH_2CH_3$ | 208.1-208.7 | ℓ |
| 30 | 4-$CH_3SO_2$, H | $C(CH_3)_3$ | 172.3-172.9 | ℓ |
| 31 | 4-$CH_3S$, H | $CH_3$ | 166.7-167.1 | ℓ |
| 32 | 4-$CH_3S$, H | $OCH_3$ | 140.5-141.5 | ℓ |
| 33 | 4-$CH_3S$, H | $OCH_2CH_3$ | 140-142 | ℓ |
| 34 | 4-$CH_3SO_2$, H | $C_6H_5$ | 221.6-221.9 | ℓ |
| 35 | 4-$CH_3SO_2$, H | $NHCH_3$ | 197.8-198.7 | ℓ |
| 36 | 4-$CH_3CO$, H | $CH_3$ | 205-207 | dℓ |
| 37 | 3-$CH_3CO$, H | $CH_3$ | 145-146 | dℓ |
| 38 | 4-$(CH_3)_2CH$, H | $CH_3$ | 142.7-143.3 | dℓ |
| 39 | 4-$(CH_3)_2CH$, H | $OCH_3$ | 107.8-108.3 | dℓ |
| 40 | 4-$CH_3S$, H | $CH=CH_2$ | 172-174 | dℓ |
| 41 | 4-$CF_3$, H | $CH_3$ | 179.0-179.8 | dℓ |
| 42 | 4-$CF_3$, H | $OCH_3$ | 153.3-153.6 | dℓ |
| 43 | 4-$CH_3O$, H | $OCH_3$ | | |
| 44 | 4-$CH_3O$, H | $CH_3$ | 149.0-149.6 | dℓ |
| 45 | 4-$H_2NSO_2$, H | $OCH_3$ | 229.9-230.5 | ℓ |
| 46 | 4-$CH_3NHSO_2$, H | $CH_3$ | 181.5-182 | ℓ |
| 47 | 4-$(CH_3)SO_2$, H | $CHCl_2$ | | |
| 48 | 4-$CH_2CH-CH_2NHSO_2$, H | $CH_2OCH_3$ | | |
| 49 | 4-▷-$NHSO_2$, H | $CHBr_2$ | | |
| 50 | 4-$CH_3ON(CH_3)SO_2$, H | $OC_2H_5$ | | |
| 51 | 4-$(CH_3)_2CH_3$, H | $CH_3$ | 118.9-119.4 | ℓ |
| 52 | 4-$(CH_3)_2CH$, H | $OCH_3$ | 129.0-129.3 | ℓ |
| 53 | 4-$CH_3NHN(CH_3)SO_2$, H | $CHCl_2$ | | |
| 54 | 4-n-$C_4H_9NHSO_2$, H | $CH=CH_2$ | | |
| 55 | 4-cyclooctyl $NHSO_2$, H | $CH_2Br$ | | |
| 56 | 4-$H_2NNHSO_2$, H | $CH(OCH_3)_2$ | | |
| 57 | 4-$CH_3SO_2$, H | $CH_2OCH_3$ | 164.6-165.6 | ℓ |
| 58 | 4-$CF_3S$, H | O-$C_4H_9$-t | | |

Table 3 (continued)

| Ex. | A, Y | $R_{13}$ | m.p.°C | Isomer |
|---|---|---|---|---|
| 59 | 4-NC, H | $CH_3$ | 153-154 | dℓ |
| 60 | 4-$CF_2HSO$, H | $CH{=}CH_2$ | | |
| 61 | 4-$CH_2{=}CH{-}CH_2S$, H | $CH_3$ | | |
| 62 | 3,4-$OCH_2O$- | $CH_3$ | 156-157 | dℓ |
| 63 | 4-$Cl_2CHSO$, H | $CH(OCH_3)_2$ | | |
| 64 | 4-$CH_2FS$, H | $SCH_3$ | | |
| 65 | 4-$CCl_3SO$, H | $CH_2{-}S(O)_2CH_3$ | | |
| 66 | 4-$CH_2BrSO_2$, H | $S{-}C_4H_9{-}n$ | | |
| 67 | 4-$CH_3SO_2$, H | $CH_2Cl$ | 195.1-195.9 | ℓ |
| 68 | 4-$(CH_3)S$, H | $NHCOCOCH_3$ | 142.9-143.5 | ℓ |
| 69 | 4-$CH_3SO_2$, H | $CH{=}CH_2$ | 180-183 | dℓ |
| 70 | 4-$CH_3SO_2$, H | $OCH_2CH_2CH_3$ | 170-173 | dℓ |
| 71 | 4-$CH_3S$, H | ◁ | 197-199 | dℓ |
| 72 | 4-$CH_3SO_2$, H | ◁ | 210-211 | dℓ |
| 73 | 4-$CH_3S$, H | $CH(OCH_3)_2$ | 89-90 | dℓ |
| 74 | 4-$CH_3SO_2$, H | $CH(OCH_3)_2$ | 175-178 | dℓ |
| 75 | 4-$CH_3S$, H | $CH(OC_2H_5)_2$ | 68-69 | dℓ |
| 76 | 4-$CH_3SO_2$, H | $NH_2$ | 146-149 | dℓ |
| 77 | 4-$CH_3SO_2$, H | $CH(NH_2)C_6H_5$ HCl | 250 | dℓ |

The following sulfonamides may also be made:

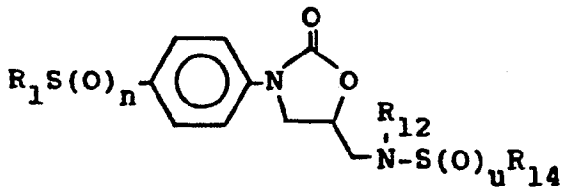


Table 4

| Ex. | n | $R_1$ | $R_{12}$ | u | $R_{14}$ | m.p.(°C) |
|---|---|---|---|---|---|---|
| 78 | 1 | $-CF_3$ | H | 1 | $-CH_3$ | |
| 79 | 0 | $-CH_3$ | H | 2 | $-CF_3$ | |
| 80 | 2 | $-CH_3$ | H | 2 | $-C_3H_7$-n | |

Example 81

Preparation of (ℓ)-2,2-Dichloro-N-[3-[4-(aminosulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$H_2NSO_2$, B=$NHCOCHCl_2$)

Part A

Preparation of (ℓ)-5-hydroxymethyl-3-phenyl-2-oxazolidinone, 4-methylbenzenesulfonate, (I; A=H, B=$OSO_2C_6H_4Me$)

A mixture of 51.5 g of (ℓ)-5-hydroxymethyl-3-phenyl-2-oxazolidinone in 250 ml of dry pyridine was stirred under $N_2$ in an ice-bath as a solution of 53 g of p-toluenesulfonyl chloride in 50 ml of pyridine was added. After the addition, cooling was ceased, the mixture allowed to stand for one hour, and then a few drops of water were added (the temperature rose to 39°C as the water reacted with the excess p-toluenesulfonyl chloride). The reaction mixture was poured into ice water; the white solid was filtered, washed well with water, and dried. The yield of product was

70.0 g, m.p. 146.3-147.8°C. This product was used without further purification.

Part B

Preparation of (ℓ)-5-Azidomethyl-3-phenyl-2-oxazolidinone (I; A=H, B=$N_3$)

A mixture of 5.00 g (14.4 mmole) of (ℓ)-5-hydroxymethyl-3-phenyl-2-oxazolidinone, 4-methylbenzenesulfonate, 2.1 g sodium azide and 1 g 18-crown-6 in 35 ml of DMF was heated at 100°C for three hours. The mixture was poured into ice-water and filtered. The dried yield was 2.47 g, m.p. 71.5-72.5°C. This was recrystallized from diethyl ether to give 1.44 g of product, m.p. 72.5-73°C.

Part C

Preparation of (ℓ)-5-Aminomethyl-3-phenyl-2-oxazolidinone (I; A=H, B=$NH_2$)

A mixture of 37.0 (170 mmole) of (ℓ)-5-azidomethyl-3-phenyl-2-oxazolidinone, 26 ml of triethylamine, 19.5 ml of 1,3-propanedithiol in 150 ml of methanol was warmed to 50°C. Nitrogen was evolved (at the end of 2 hours, 3.9 liters had been measured). The solvent was removed and the residue crystallized on stirring with ether (crude yield, 28.3 g). This material was used without further purification.

Part D

Preparation of (ℓ)-2,2-Dichloro-N-(3-phenyl-2-oxazolidin-5-ylmethyl)acetamide (I; A=H, B=$NHCOCHCl_2$)

A solution of 12.5 g (64.5 mmole) of (ℓ)-5-aminomethyl-3-phenyl-2-oxazolidinone in 45 ml of methyl dichloroacetate and 45 ml of 1,2-dimethoxy-

ethane containing 1 g of 4-dimethylaminopyridine was refluxed four hours. It was concentrated, the residue stirred with ethyl acetate and the product crystallized and was filtered and dried. The yield was 9.18 g, m.p. 142.3-144.8°C. This was recrystallized from ethanol, filtered hot, and cooled to give 7.46 g, m.p. 150.3-151.3°C.

Part E

A 15 ml portion of chlorosulfonic acid was cooled and stirred under nitrogen as 8.77 g (28.9 mmole) of (ℓ)-2,2-dichloro-N-(3-phenyl-2-oxooxazolidin-5-ylmethyl)acetamide was added. Hydrogen chloride bubbled from the acid and the solid dissolved. After one hour the acid solution was poured into ice with good stirring, filtered and dried on the filter under nitrogen for one hour. This solid was added to a mixture of 25 ml of concentrated ammonium hydroxide in 50 ml of tetrahydrofuran. After stirring for four minutes, the resulting mixture was concentrated under reduced pressure; water was added and the product filtered, washed with water, and dried; yield 9.13 g, m.p. 208-209°C. This was recrystallized from 70% ethanol water to give 6.65 g, m.p. 214.8-215.4°C. It was then recrystallized from acetonitrile to yield 6.54 g, m.p. 216.5-217.5°C.

Example 82

Preparation of (ℓ)-N-[3-[4-(aminosulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$H_2NSO_2$, B=$NHCOCH_3$)

Part A

Preparation of (ℓ)-N-(3-Phenyl-2-oxazolidin-5-ylmethyl)acetamide (I; A=H, B=$NHCOCH_3$)

A solution of 12.5 g (65.0 mmole) of (ℓ)-5-aminomethyl-3-phenyl-2-oxazolidinone in 50 ml of dry pyridine was stirred as 7 ml of acetic anhydride was added. The mixture was allowed to stand overnight, then concentrated. The residue was stirred with water and the solid filtered and dried; yield 10.2 g, m.p. 122.4-124.5°C. This was recrystallized from ethanol to give 5.02 g, m.p. 126.8-127.3°C. A second crop was obtained and recrystallized from ethanol to give 3.08 g, m.p. 127.3-127.8°C.

Part B

The chlorosulfonation and amidation procedures of Example 81E were used, starting with 7.91 g (33.8 mmoles) of (ℓ)-N-(3-phenyl-2-oxooxazolidin-5-ylmethyl)acetamide. The yield of product was 6.85 g, m.p. 236.4-236.6°C.

Example 83

Preparation of (ℓ)-N-[3-(4-Azidosulfonylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$N_3SO_2$-, B=NH-$COCH_3$)

A 5.0 g (21.3 mmole) portion of (ℓ)-N-(3-phenyl-2-oxooxazolidin-5-ylmethyl)acetamide was added to 25 ml of chlorosulfonic acid, stirred for 2 hours, poured onto ice, filtered, and washed well. After the pro-

duct was sucked dry on a filter, it was added to a solution made by dissolving 2.0 g sodium azide in 5 ml of water and diluting this with 50 ml of acetone. The mixture was stirred for 2 hours; the acetone was evaporated under reduced pressure. The residue was diluted with water and filtered to provide 5.81 g of product, m.p. 102-104°C (dec.). This was recrystallized from ethanol to give 5.0 g of material, m.p. 122.5-123.4°C (dec.).

Using the chlorosulfonation described in Examples 74 through 76, the following compounds could be prepared.

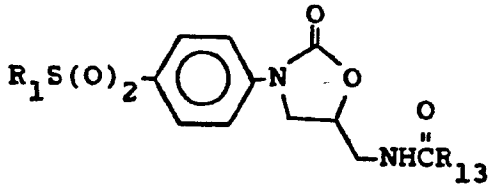


Table 5

| Ex. | $R_1$ | $R_{13}$ | m.p. | isomer |
|---|---|---|---|---|
| 84 | $H_2N$ | $OCH_3$ | 229.9-230.5 | ℓ |
| 85 | $CH_3ON(CH_3)$ | $OCH_3$ | 128.1-129.1 | ℓ |
| 86 | $N_3$ | $OCH_3$ | 107.0-107.5 | ℓ |
| 87 | $CH_3ONH$ | $CH_2CH_3$ | | |
| 88 | $H_2NNH$ | $OCH_2CH_3$ | | |

Example 89

Preparation of (ℓ)-N-[3-[4-(Methylsulfinyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-MeSO, B=$NHCOCH_3$)

A 5.61 g (20 mmole) portion of (ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide in 200 ml of methanol was stirred at 0°C as a solution of 12.3 g of Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in 50 ml of water was added slowly. At the end of the addition the sulfide had all been consumed as determined by thin layer chromatography, and the product was a mixture of sulfoxide and sulfone. The solution was heated with 12 ml of methyl sulfide to reduce the excess Oxone®, concentrated under reduced pressure to give 2.0 g of product, m.p. 188.6-189.9°C. This was recrystallized from 70% ethanol-water to give 1.5 g of the sulfoxide, m.p. 193.7-197°C.

Example 90

Preparation of (ℓ)-N-[3-[4-(Methylsulfinyl)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester (I; A=4-$CH_3SO$, B=$NHCO_2CH_3$)

Using the procedure of Example 89, the title compound could be prepared starting from the compound of Example 32, m.p. 150.5-159.5°C.

Example 91

Preparation of (dℓ)-N-hexyl-N-[3-[4-(methylsulfonyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$MeSO_2$, B=$N(C_6H_{13})COCH_3$)

Part A

Preparation of (dℓ)-5-(Hexylaminomethyl)-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone (I; A=$MeSO_2$, B=$NHC_6H_{13}$)

(dℓ)-5-Bromomethyl-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone (21.92 g) was added to a mixture of 50 ml hexylamine and 25 ml N,N-dimethylformamide. This mixture was heated to 80°C under nitrogen with vigorous stirring overnight, and allowed to cool to room temperature. The mixture was poured into water with vigorous stirring and the product was collected and washed with ethanol and diethyl ether. The dried weight of crude product was 6.25 g which was recrystallized from acetonitrile to give 4.7 g of (dℓ)-5-(hexylaminomethyl)-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, m.p. 132-133°C.

Part B

To a solution of 3.4 g of (dℓ)-5-(hexylaminomethyl)-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 30 ml of pyridine was added 1.8 ml of acetic anhydride. The mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was triturated with dilute aqueous HCl. The product was collected and washed thoroughly with water to give, after drying, 3.4 g of crude product. This was recrystallized from aqueous ethanol to give 2.6 g of (dℓ)-N-hexyl-N-[3-[4-(methylsulfonyl)phenyl]-2-oxo-oxazolidin-5-ylmethyl]acetamide, m.p. 123-124°C.

Example 92

Preparation of (dℓ)-N-hexyl-N-[3-[4-(methylsulfonyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester (I; A=4-$MeSO_2$, B=$N(C_6H_{13})CO_2CH_3$)

In the same manner as in Example 91, Part B, the product of Example 91, Part A is reacted with methyl chloroformate to provide (dℓ)-N-hexyl-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester, m.p. 126-127°C.

Example 93

(dℓ)-N-Cyclohexyl-N-[[3-[4-(methylsulfonyl)phenyl-2-oxooxazolidin-5-yl]methylacetamide (I; A=4-$MeSO_2$, B=$N(C_6H_{11})COCH_3$)

Part A

(dℓ)-5-(Cyclohexylaminomethyl)-3-[4-(methylsulfonyl)-phenyl]-2-oxazolidinone (I; A=4-$MeSO_2$, B=$NHC_6H_{11}$)

(dℓ)-5-Hydroxymethyl-3-[4-(methylsulfonyl)-phenyl]-2-oxazolidinone, 4-methylbenzenesulfonate (15 g) was added to a mixture of 60 ml cyclohexylamine and 30 ml N,N-dimethylformamide and heated gently to 70°C under nitrogen with vigorous stirring overnight. The mixture was allowed to cool to room temperature and was then poured onto water. The product precipitated and was collected and dried; yield 7.48 g.

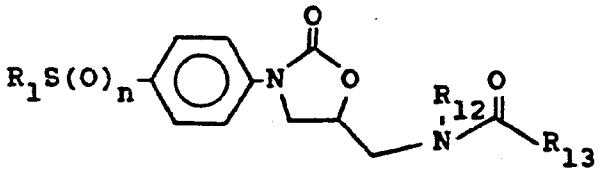
A portion of the solid obtained above (3.75 g) was purified by dissolving in dilute aqueous HCl, washing with ethyl acetate, and precipitating by addition of concentrated ammonium hydroxide. The pure product was washed with water and dried to give 1.1 g of (dℓ)-5-(cyclohexylaminomethyl)-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone, m.p. 154-155°C.

Part B

To a solution of 2.56 g of (dℓ)-5-(cyclohexylaminomethyl)-3-[4-(methylsulfonyl)phenyl]-2-oxazolidinone in 25 ml pyridine was added 2 ml acetic anhydride and the mixture was stirred at room temperature under nitrogen overnight. The mixture was evaporated and the residue was triturated with dilute aqueous HCl. The gummy residue was dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine, and dried over sodium sulfate. Evaporation gave a solid which was triturated with ethyl acetate-diethyl ether and collected to give 2.28 g of (dℓ)-N-cyclohexyl-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide, m.p. 149-151°C.

Using the procedures described above, the following compounds could be prepared.

Table 6



| Ex. | n | $R_1$ | $R_{12}$ | $R_{13}$ | m.p.(°C) | Isomer |
|---|---|---|---|---|---|---|
| 94 | 1 | $-CF_3$ | n-$C_9H_{19}$- | H | | (ℓ)- |
| 95 | 2 | n-$C_4H_9$ | $-CH_3$ | H | | (ℓ)- |
| 96 | 1 | $-C_2H_5$ | $-CH_3$ | $-OCH_3$ | | (ℓ)- |
| 97 | 2 | $-CH_3$ | $-CH_3$ | $-OCH_3$ | 152-155° | (dℓ)- |

Example 98

Preparation of (ℓ)-N-[3-(4-Nitrophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$NO_2$, B=$NHCOCH_3$)

A 30 ml portion of concentrated sulfuric acid was stirred under dry nitrogen and cooled to -10°C; 5 g (21.3 mmole) of (ℓ)-N-(3-phenyl-2-oxazolidin-5-ylmethyl)acetamide was added. When all of the solid dissolved, 2.2 g of potassium nitrate was added at -10° to 0°C. The mixture was then allowed to warm to room temperature over a 2 hour period. The mixture was poured onto ice; the product was filtered, washed well with water, and dried. The yield was 3.47 g. A thin layer chromatogram on silica gel plate eluted with chloroform-methanol (9:1) showed a spot $R_f$=0.37 for the p-nitro- and a spot Rf=0.28 for the o-nitro-compound. The product was recrystallized from acetonitrile to give 2.15 g, m.p. 194.5-195.0°C which showed one spot in the thin layer chromatogram, indicating it to be the para-nitro product.

Example 99

Preparation of (ℓ)-N-[3-(2,4-Dinitrophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$NO_2$ , Y= 2-$NO_2$, B=$NHCOCH_3$).

The nitration shown in Example 98 was repeated starting with 15 g of (ℓ)-N-(3-phenyl-2-oxazolidin-5-ylmethyl)acetamide. The mother liquor from the crystallization of the crude product (9.82 g) was concentrated and purified by preparative chromatography using the Waters "Prep 500" and silica gel columns, eluting with 9:1 chloroform-methanol. A fast moving component was the pure p-isomer. The slow moving product 1.02 g, m.p. 142.2-142.6°C was the 2,4-dinitro compound.

Example 100

Preparation of (ℓ)-N-[3-(2-Nitrophenyl)-2-oxo-oxazolidin-5-ylmethyl]acetamide (I; A=2-$NO_2$, B=$NHCOCH_3$)

A 90 ml portion of concentrated sulfuric was stirred under dry nitrogen as 11 g of potassium nitrate was added. The mixture became warm and it was cooled in an ice bath to 0-10°C as 23.4 g (0.10 mole) of (ℓ)-N-(3-phenyl-2-oxazolidin-5-ylmethyl)acetamide was added slowly. After stirring one hour a thin layer chromatogram showed that there was starting compound left. A further 3 g of potassium nitrate was added and stirring continued two hours. The reaction was poured into ice-water and the product extracted with chloroform. The extract was concentrated and the residue (20 g) was fractionated by preparative chromatography using the Waters Prep 500. The first fraction amounted to 2.8 g, m.p. 130-136°C.

Example 101

Preparation of (ℓ)-N-[3-(4-Aminophenyl)-2-oxo-oxazolidin-5-ylmethyl]acetamide (I; A=4-$H_2N$, B=$NHCOCH_3$)

A mixture of 5.00 g (17.9 mmole) of (ℓ)-N-[3-(4-nitrophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 50 ml absolute ethanol and 3 g of Raney nickel catalyst was stirred and heated to 50°C as a solution of 5 ml of 95% hydrazine diluted with 20 ml of absolute ethanol was added slowly. The temperature rose to reflux and gas was evolved. After refluxing thirty minutes, the solution was filtered and concentrated to a glass which crystallized. This was stirred with acetonitrile and filtered; yield 3.42 g, m.p. 147.5-148.3°C.

Example 102

Preparation of (ℓ)-N-[3-[4-(Acetylamino)phenyl]-2-oxo-oxazolidin-5-ylmethyl]acetamide (I; A=4-$CH_3CONH$, B=$NHCOCH_3$)

A 0.95 g portion of the above aniline (Example 99) in 5 ml of tetrahydrofuran and 5 ml of triethylamine, 2 ml of acetic anhydride, 0.01 g 4-dimethylaminopyridine (DMAP) and 10 ml of dimethylacetamide was warmed, then concentrated under reduced pressure, water added and the white solid filtered and washed with water to yield 0.56 g, m.p. 224.1-224.9°C (dec.). This was recrystallized from 50 ml of acetonitrile to yield 0.44 g, m.p. 225.5-225.8°C (dec).

Example 103

Preparation of (ℓ)-N-[3-[4-(Methylsulfonylamino)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=$CH_3-SO_2-NH-$, B=$-NH-COCH_3$)

A solution of 1.24 g (5 mmole) of the above aniline (Example 99) in 5 ml of pyridine was stirred in an ice-acetone bath under nitrogen as 0.4 ml of methane- sulfonyl chloride was added. An intense red color developed and solid separated. The mixture was stirred one hour, diluted with water and made acidic with hydrochloric acid. This was concentrated under reduced pressure and the residue was stirred with acetonitrile and filtered; yield 0.50 g, m.p. 223.5-224.4°C. This solid is quite water soluble.

Example 104

Preparation of (ℓ)-N-[3-[4-(Acetylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide

(I; A=4-$CH_3\overset{O}{\overset{\|}{C}}S$, B=$NHCOCH_3$).

A 10.0 g (0.0427 mole) portion of (ℓ)-N-(3-phenyl oxooxazolidin-5-ylmethyl)acetamide was chlorosulfonated by adding it to 40 ml of chlorosulfonic acid cooled to 0°C under nitrogen. The mixture was stirred for 1.5 hours, poured on ice and the white solid filtered and washed well with water and dried. The yield was 13 g, m.p. 134.9-135.9°C.

The sulfonyl chloride was added to a mixture of 180 ml of acetic acid, 60 ml of acetic anhydride and 30 g of anhydrous sodium acetate, the mixture heated to 75°C, and zinc dust added slowly. The temperature rose to reflux and the zinc was added until it was no longer consumed (16 g). Reflux was then continued for one and one half hours. The cooled mixture was filtered and concentrated. The residue was stirred with tetrahydrofuran, filtered and concentrated, diluted with ether to give 10.1 g, m.p. 130-180°C. This was dissolved in hot acetonitrile and filtered, concentrated and cooled to yield 5.57 g, m.p. 138.5-139.1°C.

Example 105

Preparation of (ℓ)-N-[3-(4-Mercaptophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, A=4-HS, B=$NHCOCH_3$).

A 4.1 g of (ℓ)-N-[3-[4-(acetylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide in 20 ml of absolute ethanol was stirred at 25°C as 5 ml of pyrrolidine was added. The temperature rose to 40°C, and all of the solid dissolved. Stirring was continued for one hour, the mixture concentrated, diluted with water and filtered to give 3.32 g, m.p. 205-209°C (dec.).

Example 106

Preparation of (ℓ)-N-[3-[4-(Cyanomethylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-N≡CCH$_2$S, B=NHCOCH$_3$).

A suspension of 1.5 g of powdered potassium carbonate in dimethylformamide was stirred under dry nitrogen as 2.5 g (9.4 mmole) of (ℓ)-N-[3-(4-mercaptophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide was added. To this was added 0.65 ml of chloroacetonitrile. After stirring for an hour, the mixture was concentrated. The residue was dissolved in dichloromethane and chromatographed on a 10 inch column of silica gel. The fast moving spot (eluted with 90% dichloromethane, 10% methanol) yield 0.070 g, was recrystallized from ethyl acetate to yield 60 mg, m.p. 90.4°C using a Metler Melting Point apparatus.

Example 107

Preparation of (ℓ)-N-[3-[4-(Acetylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid (I; A=4-CH$_3$CO-S-, B=NHCOOCH$_3$).

A 12.0 g (48 mmole) of (ℓ)-(3-phenyl-2-oxooxazolidin-5-ylmethyl)carbamic acid methyl ester was added to 60 ml of chlorosulfonic acid cooled to -10°C under nitrogen. The solid slowly dissolved. The addition required thirty minutes. The mixture was allowed to warm and at 10°C a very rapid evolution of hydrogen chloride occurred, and all solid dissolved. The stirring was continued two hours at 20-25°C and then the reaction was quenched on ice, the solid was filtered and washed well with water and dried in a nitrogen stream. The yield was 14.6 g, m.p. 155.4°C (Metler apparatus).

The sulfonyl chloride (9 g; 33.7 mmole) was added to a mixture of 145 ml acetic acid, 50 ml acetic anhydride, and 14 g anhydrous sodium acetate and stirred well as 12 g of zinc dust was added. The mixture was refluxed for one hour, cooled, filtered and concentrated. The residue was stirred with water and filtered to give 4.42 g. This was recrystallized from acetonitrile to give 3.22 g, m.p. 156.4-156.8°C.

## Example 108

Preparation of (ℓ)-[3-(4-Mercaptophenyl)-2-oxo-oxazolidin-5-ylmethyl]carbamic acid, methyl ester (I; A=4-HS, B=$NHCOOCH_3$).

A mixture of 2.00 g (6.17 mmole) of (ℓ)-[3-[4-(acetylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester in 10 ml of absolute ethanol was stirred under nitrogen as 2 ml of pyrrolidine was added and then refluxed for thirty minutes, concentrated under reduced pressure, diluted with water and made acid with acetic acid. The white solid was filtered, washed with water and dried; yield 1.7 g, m.p. 131.7-132.6°C.

## Example 109

Preparation of (dℓ)-2-Amino-N-[3-[4-(1-methylethyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; A=4-$(CH_3)_2CH$, B=$NHCOCH_2NH_2$)

Part A

A solution of 5 g (16.1 mmole) of (dℓ)-2-chloro-N-[3-[4-(1-methylethyl)phenyl]-2-oxooxazolidin-5-yl-methyl]acetamide in 50 ml of dry dimethylsulfoxide and 1.5 g sodium azide was stirred and heated to 90°C under dry nitrogen for five hours. The mixture was

concentrated at reduced pressure and the residue stirred with water. A partially crystalline solid separated and solidified on standing, yield 5.8 g. This was recrystallized from ethyl acetate to give 3.4 g, m.p. 122.4-123.4 (dec.). A thin layer chromatogram on silica using 9:1 $CHCl_3$-methanol indicated that this was a mixture of the starting compound and the desired product. This was used in the next step without further purification.

Part B

A suspension of 3.4 g (dℓ)-2-Azido-N-[3-[4-(1-methylethyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide in 50 ml of ethanol, 5 ml of water and 5 ml of acetic acid containing 0.5 g 10% palladium-on-charcoal was stirred as hydrogen was passed into the solution through a dispersion tube. The reaction was continued three hours, the solution was filtered and concentrated, the residue stirred with water and made basic with concentrated ammonium hydroxide to give a gummy solid. This was extracted with ethyl acetate, dried over sodium sulfate and concentrated. The residue was stirred with ether and filtered; yield 1.4 g, m.p. 82-92°C. This was recrystallized from 10 ml of ethyl acetate and a few drops of triethylamine to give 0.84 g, m.p. 105-107°C.

Example 110

Preparation of ℓ-2-Azido-N-[3-(4-Methylsulfonyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide, (I; A=4-$CH_3SO_2$, B=$NHCOCH_2N_3$).

Substituting ℓ-2-chloro-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide in the azide displacement of Example 109, Part A gives the title compound, m.p. 188.8-189.8°C.

Example 111

N-[3-(4-Acetylphenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide Oxime (I;(A=4-$CH_3\overset{NOH}{\overset{\|}{C}}$, B=$NHCOCH_3$)

N-[3-(4-Acetylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (3.16 g) was dissolved in a mixture of 20 ml pyridine and 20 ml ethanol and 5 g hydroxylamine hydrochloride was added. The mixture was heated to reflux under nitrogen for 2 hours. After allowing to cool to room temperature, the solvents were evaporated and the residue was triturated with dilute aqueous hydrochloric acid. The solid was collected and washed with water. Recrystallization from aqueous ethanol gave 1.6 g pure N-[3-(4-acetylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide oxime, m.p. 213-215°C.

Example 112

N-[3-(4-Acetylphenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide Oxime, methyl ether (I; A=$CH_3\overset{NOCH_3}{\overset{\|}{C}}$, B=$NHCOCH_3$)

Substitution of methoxylamine hydrochloride for the hydroxylamine hydrochloride in the procedure of Example 111 gave 1.8 g N-[3-(4-acetylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide oxime methyl ether, m.p. 208-211°C.

Dosage Forms

The antibacterial agents of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 5 to 20 milligrams per kilogram of body weight. Ordinarily, when the more potent compounds of this invention are used, 5 to 15, and preferably 5 to 7.5 milligrams per kilogram per day, given in divided doses 2 to 4 times a day or in sustained release form, is effective to obtain desired results. These drugs may also be administered parenterally.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5 - 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidants such as sodium bisulfate, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 75 milligrams of powdered active ingredient, 150 milligrams of lactose, 24 milligrams of talc and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in soybean oil is prepared and injectd by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 75 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 75 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 250 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 75 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

Utility

Test results indicate that the novel compounds of this invention are biologically active against gram negative and gram positive bacteria including beta-lactamase producing Staphylococcus aureus isolates. These agents are potentially useful for the treatment of both human and animal bacterial infections including diseases of the respiratory, gastrointestinal, genito-urinary and central nervous systems; blood; interstitial fluids, soft tissue; and bone.

As shown in Table 7, compounds of formula I exert an in-vitro antibacterial effect. A standard microdilution method (Conrath, Theodore B., 1972 Handbook of Microtiter Procedures, Dynatech Corporation, Cambridge, Massachusetts) with Mueller-Hinton broth is used to determine the 24-hour minimal inhibitory concentrations (MIC's) for test strains of Staphylococcus epidermidis and Escherichia coli.

In vitro tests conducted with the compound of Example 90 using the same procedures as described above, resulted in no control of Staphylococcus aureus or Escherichia coli. It is believed that the compound of Example 90 would provide control at higher concentrations or under different conditions. It was found to exhibit an antibacterial effect in vivo (see Tables 8 and 9).

The in vivo potency of these compounds is exemplified by the data summarized in Tables 8 and 9.

Determinations of *in vivo* efficacy are performed by inoculating mice intraperitoneally with cultures of the infecting organism diluted to produce 90-100% mortality in control animals within seven days. The diluents used were trypticase soy broth for *E. coli* and 5% aqueous hog gastric mucin for *Staphylococcus aureus* infections. The compounds are dissolved or suspended in 0.25% aqueous Methocel® (Methocel®: Hydroxypropyl Methylcellulose E15 Premium, Dow Chemical Company) for oral administration or sterile distilled water containing 5% dimethylsulfoxide (Fisher Scientific Company, Fairlawn, N.J.) for subcutaneous administration. The mice are dosed at the time of infection and again at four hours post-infection. Mortality is recorded daily until test termination and the 50 percent effective dose, $ED_{50}$, is calculated by the Reed-Muench method (Reed, L. G. and Muench, H., "A simple method of estimating fifty percent end points," *American Journal of Hygiene*, *27*, 493-497 (1938).

Projected therapeutic levels in humans should be attained from the oral administration of 5-20 mg/kg of body weight given in divided doses two to four times daily. The dosages may be increased in severe or life-threatening infections.

Table 7

IN VITRO BROTH DILUTION
MINIMAL INHIBITORY CONCENTRATIONS

Microdilution Broth MIC in µg/ml

| Ex. No. | Staphylococcus epidermidis | Escherichia coli |
|---|---|---|
| 2 | 6.3 | >100.0 |
| 3 | 25.0 | >100.0 |
| 4 | >200.0 | >200.0 |
| 5 | 200.0 | >200.0 |
| 7 | 100.0 | >200.0 |
| 10 | 50.0 | >100.0 |
| 11 | >100.0 | >100.0 |
| 12 | >100.0 | >100.0 |
| 15 | >200.0 | >200.0 |
| 17 | >200.0 | >200.0 |
| 21 | 6.3 | 100.0 |
| 22 | 2.4 | 9.4 |
| 23 | 3.2 | 25.0 |
| 24 | >100.0 | >100.0 |
| 25 | 100.0 | >100.0 |
| 26 | 6.3 | 100.0 |
| 27 | 6.3 | 50.0 |
| 28 | 12.5 | 50.0 |
| 29 | 12.5 | 100.0 |
| 30 | 200.0 | >200.0 |
| 31 | 3.9 | >200.0 |
| 32 | 12.5 | >200.0 |
| 33 | 50.0 | >200.0 |
| 34 | 25.0 | >200.0 |
| 35 | 25.0 | 200.0 |
| 36 | 25.0 | >200.0 |
| 37 | 200.0 | >200.0 |

Table 7 (continued)

IN VITRO BROTH DILUTION
MINIMAL INHIBITORY CONCENTRATIONS

| Ex. No. | Microdilution Broth MIC in µg/ml Staphylococcus epidermidis | Escherichia coli |
|---|---|---|
| 38 | 9.4 | >200.0 |
| 39 | 12.5 | >200.0 |
| 40 | 12.5 | >200.0 |
| 41 | 12.5 | >200.0 |
| 42 | 100.0 | >200.0 |
| 44 | 100.0 | >200.0 |
| 45 | 37.5 | >200.0 |
| 46 | 12.5 | >200.0 |
| 51 | 3.1 | >200.0 |
| 52 | 6.3 | >200.0 |
| 57 | 12.5 | 100.0 |
| 59 | 100.0 | >200.0 |
| 67 | 3.2 | 2.5 |
| 68 | 100.0 | >200.0 |
| 69 | 9.4 | 150.0 |
| 70 | 50.0 | >200.0 |
| 71 | 50.0 | >200.0 |
| 72 | 25.0 | 200.0 |
| 73 | >200.0 | >200.0 |
| 74 | 100.0 | >200.0 |
| 75 | >200.0 | >200.0 |
| 76 | 200.0 | >200.0 |
| 77 | >200.0 | >200.0 |
| 81 | 12.5 | 50.0 |
| 82 | 25.0 | 100.0 |
| 83 | 200.0 | 200.0 |
| 84 | 37.5 | >200.0 |

Table 7 (continued)

IN VITRO BROTH DILUTION
MINIMAL INHIBITORY CONCENTRATIONS

Microdilution Broth MIC in µg/ml

| Ex. No. | Staphylococcus epidermidis | Escherichia coli |
|---|---|---|
| 85 | 12.5 | >200.0 |
| 86 | 200.0 | >200.0 |
| 87 | 9.4 | 166.7 |
| 90 | 18.8 | >200.0 |
| 91 | >200.0 | >200.0 |
| 92 | >200.0 | >200.0 |
| 93 | >200.0 | >200.0 |
| 97 | >200.0 | >200.0 |
| 98 | 2.4 | 200.0 |
| 99 | 200.0 | >200.0 |
| 100 | 200.0 | >200.0 |
| 101 | 100.0 | >200.0 |
| 102 | 200.0 | >200.0 |
| 103 | 200.0 | >200.0 |
| 104 | >200.0 | >200.0 |
| 105 | 32.0 | >32.0 |
| 106 | 3.2 | >200.0 |
| 107 | >200.0 | >200.0 |
| 108 | >200.0 | >200.0 |
| 109 | 50.0 | >200.0 |
| 110 | 6.3 | 50.0 |
| 111 | 50.0 | >200.0 |
| 112 | 50.0 | >200.0 |

Table 8

IN VIVO EFFICACY OF ORALLY ADMINISTERED COMPOUNDS IN MOUSE INTRAPERITONEAL INFECTIONS

| Ex. No. | Infecting Bacterial Organism: Staphylococcus aureus $ED_{50}$ | Infecting Bacterial Organism: Escherichia coli $ED_{50}$ |
|---|---|---|
| 2 | 7.3 | N.T. |
| 3 | 29.3 | >120.0 |
| 4 | 43.3 | N.T. |
| 5 | 172.0 | N.T. |
| 7 | 24.2 | N.T. |
| 11 | 29.9 | 47.4 |
| 12 | 179.0 | N.T. |
| 15 | 40.0 | N.T. |
| 17 | 44.4 | N.T. |
| 21 | 7.3 | 30.3 |
| 22 | 14.2 | 71.1 |
| 23 | 3.3 | 14.0 |
| 24 | 74.3 | N.T. |
| 25 | >360.0 | N.T. |
| 26 | 1.7 | 56.2 |
| 27 | 8.0 | 37.0 |
| 28 | 71.3 | N.T. |
| 29 | 88.7 | N.T. |
| 30 | >120.0 | N.T. |
| 31 | 3.5 | 19.6 |
| 32 | 3.5 | 70.9 |
| 33 | 12.2 | >120.0 |
| 34 | >120 | N.T. |
| 35 | 35.8 | N.T. |
| 36 | 4.7 | 47.2 |
| 37 | 62.9 | N.T. |
| 38 | 9.1 | >120.0 |

Table 8 (continued)

IN VIVO EFFICACY OF ORALLY ADMINISTERED COMPOUNDS IN MOUSE INTRAPERITONEAL INFECTIONS

| Ex. No. | Infecting Bacterial Organism: Staphylococcus aureus $ED_{50}$ | Infecting Bacterial Organism: Escherichia coli $ED_{50}$ |
|---|---|---|
| 39 | 6.1 | >120.0 |
| 40 | 53.1 | N.T. |
| 41 | 5.3 | >120.0 |
| 42 | 45.5 | N.T. |
| 44 | 30.3 | N.T. |
| 45 | >120.0 | N.T. |
| 46 | 15.8 | 62.5 |
| 51 | 6.4 | 62.9 |
| 52 | 4.9 | >120.0 |
| 57 | 10.8 | 39.0 |
| 59 | 4.3 | N.T. |
| 62 | 18.1 | N.T. |
| 67 | 42.5 | >120.0 |
| 68 | 48.0 | N.T. |
| 69 | 12.0 | 85.0 |
| 70 | 51.7 | N.T. |
| 71 | >120.0 | N.T. |
| 72 | >120.0 | N.T. |
| 73 | 59.5 | N.T. |
| 74 | 96.6 | N.T. |
| 75 | 130.9 | N.T. |
| 81 | >360.0 | >360.0 |
| 82 | 17.2 | 29.7 |
| 83 | 15.3 | 10.5 |
| 84 | >120.0 | N.T. |
| 85 | 25.9 | N.T. |
| 86 | 16.1 | >120.0 |

Table 8 (continued)

IN VIVO EFFICACY OF ORALLY ADMINISTERED COMPOUNDS IN MOUSE INTRAPERITONEAL INFECTIONS

| Ex. No. | Infecting Bacterial Organism: Staphylococcus aureus $ED_{50}$ | Infecting Bacterial Organism: Escherichia coli $ED_{50}$ |
|---|---|---|
| 89 | 3.3 | 11.1 |
| 90 | 2.5 | 55.9 |
| 91 | 31.3 | N.T. |
| 92 | 27.6 | N.T. |
| 93 | 48.4 | >120.0 |
| 97 | 62.0 | N.T. |
| 98 | 2.0 | 29.8 |
| 99 | 38.4 | N.T. |
| 100 | 21.0 | >120.0 |
| 101 | 20.2 | >120.0 |
| 102 | 56.9 | N.T. |
| 103 | 62.9 | N.T. |
| 104 | 4.4 | 24.8 |
| 105 | 5.7 | 17.0 |
| 107 | 3.0 | 82.2 |
| 108 | 4.5 | >120.0 |
| 109 | 58.9 | N.T. |
| 110 | 11.4 | 56.5 |
| 111 | 6.5 | 71.5 |
| 112 | 5.1 | 105.3 |

[1] $ED_{50}$ = 50 percent effective dose in mg/kg

[2] N.T. = Not tested.

Table 9



IN VIVO EFFICACY OF COMPOUNDS ADMINISTERED SUBCUTANEOUSLY IN MOUSE INTRAPERITONEAL INFECTIONS

| Ex. No. | Infecting Bacterial Organism: Staphylococcus epidermidis $ED_{50}$ | Infecting Bacterial Organism: Escherichia coli $ED_{50}$ |
|---|---|---|
| 5 | 41.2 | N.T. |
| 7 | 33.7 | N.T. |
| 11 | 16.4 | N.T. |
| 12 | 89.8 | N.T. |
| 15 | 24.9 | N.T. |
| 17 | 24.9 | N.T. |
| 22 | N.T. | 11.8 |
| 23 | N.T. | N.T. |
| 24 | N.T. | N.T. |
| 25 | 83.6 | >100.0 |
| 26 | N.T. | 40.7 |
| 30 | 57.4 | >120.0 |
| 31 | >4.4 | N.T. |
| 32 | >4.4 | N.T. |
| 33 | 8.6 | N.T. |
| 34 | 49.6 | N.T. |
| 36 | 7.4 | >120.0 |
| 38 | 4.8 | 60.4 |
| 39 | 5.5 | >120.0 |
| 41 | 6.1 | N.T. |
| 42 | 20.9 | N.T. |
| 45 | 9.6 | N.T. |
| 46 | >13.0 | 91.0 |
| 57 | N.T. | 12.9. |
| 67 | 18.6 | 99.0 |
| 71 | 69.3 | N.T. |

Table 9 (continued)

IN VIVO EFFICACY OF COMPOUNDS ADMINISTERED SUBCUTANEOUSLY IN MOUSE INTRAPERITONEAL INFECTIONS

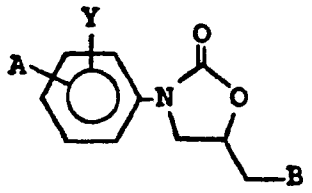
| Ex. No. | Infecting Bacterial Organism: Staphylococcus epidermidis $ED_{50}$ | Infecting Bacterial Organism: Escherichia coli $ED_{50}$ |
|---|---|---|
| 72 | 15.2 | N.T. |
| 76 | 70.9 | N.T. |
| 77 | 67.1 | N.T. |
| 81 | 14.4 | 62.7 |
| 82 | 9.6 | 11.7 |
| 83 | N.T. | 12.5 |
| 84 | 9.6 | N.T. |
| 85 | 14.9 | N.T. |
| 86 | 7.2 | >120.0 |
| 89 | >4.4 | N.T. |
| 91 | 29.3 | N.T. |
| 92 | 46.6 | N.T. |
| 93 | 16.3 | >120.0 |
| 97 | 33.6 | N.T. |
| 98 | >13.0 | 40.0 |
| 100 | 21.5 | N.T. |
| 101 | 10.3 | N.T. |
| 103 | 9.7 | N.T. |
| 104 | >2.5 | N.T. |
| 105 | >13.0 | 57.2 |
| 107 | > 4.4 | N.T. |
| 108 | > 4.4 | N.T. |
| 109 | 19.6 | N.T. |
| 110 | >13.0 | 25.0 |

1 $ED_{50}$ = 50 percent effective dose in mg/kg

2 N.T. = Not tested.

WHAT IS CLAIMED IS: BP-6244-A

1. A compound of the formula



(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

A is $-NO_2$, $-S(O)_nR_1$, $-S(O)_2-N=S(O)_pR_2R_3$, $-SH$, $-S\overset{O}{\overset{\|}{C}}R_4$, $-COR_5$, $-CONR_5R_6$, $-\overset{NR_7}{\overset{\|}{C}}-R_5$, $-CN$, $-OR_5$, $-NR_5R_6$, $-\overset{R_5}{\overset{|}{N}}COR_4$, $-\overset{R_5}{\overset{|}{N}}S(O)_nR_4$, alkyl of 1 to 5 carbons, optionally substituted with one or more halogen atoms, alkenyl of 2-5 carbons or cycloalkyl of 3-8 carbons;

$R_1$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms, CN, $NR_5R_6$ or $CO_2R_8$; $C_2$-$C_4$ alkenyl; $-NR_9R_{10}$; $-N_3$; $-NH\overset{O}{\overset{\|}{C}}R_4$; $-NZ\overset{O}{\overset{\|}{C}}R_4$; $-NX_2$-; $NR_9X$ $-^{-}NXZ^{+}$;

$R_2$ and $R_3$ are independently $C_1$-$C_2$ alkyl or, taken together, are $-(CH_2)_q-$;

$R_4$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

$R_5$ and $R_6$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

$R_7$ is $-NR_5R_6$ or $-OR_5$;

$R_8$ is H or alkyl of 1-4 carbons;

$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11a}$;

$R_{11}$ and $R_{11a}$ are independently H or $C_1$-$C_4$ alkyl, or taken together, are $-(CH_2)_r-$;

X is Cl, Br or I;

Y is H, F, Cl, Br or $NO_2$, or A and Y taken together can be $-O(CH_2)_tO-$;

Z is a physiologically acceptable cation;

n is 0, 1 or 2;

p is 0 or 1;

q is 3, 4 or 5;

r is 4 or 5;

t is 1, 2 or 3;

B is $-NH_2$, $-N(R_{12})-\overset{O}{\overset{\|}{C}}-R_{13}$, $-N(R_{12})-S(O)_uR_{14}$ or $N_3$;

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $\overset{O}{\overset{\|}{C}}R_{15}$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and O-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;

$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;

$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;

$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_4$ alkyl;

$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;

u is 1 or 2;

v is 0, 1 or 2; and

m is 2 or 3;

s is 2, 3, 4 or 5;

or a pharmaceutically suitable salt thereof;

provided that:

1) when A is $CH_3S-$, then B is not $-\overset{CH_3}{\underset{|}{N}}-CO_2CH_3$;

2) when A is $CH_3SO_2-$, then B is not $-\overset{CH_3}{\underset{|}{N}}-COCH_3$ or $-\overset{CH_3}{\underset{|}{N}}-COCF_3$;

3) when A is $H_2NSO_2-$ and B is $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}R_{13}$, then $R_{12}$ is H;

4) when A is -CN, B is not $-N_3$;

5) when A is $(CH_3)_2CH$, B is not $NHCOCH_2Cl$.

2. A compound of Claim 1 wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

Y is H;

A, substituted in the para position is $-NO_2$, $-S(O)_nR_1$ or $-S(O)_2-N=S(O)_pR_2R_3$;

$R_1$ is $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms, $C_2$-$C_4$ alkenyl, $-NR_9R_{10}$, $-N_3$, $-NX_2$, $-NR_9X$ or $-\overset{-}{N}XZ^+$;

$R_2$ and $R_3$ are independently $C_1$-$C_2$ alkyl or, taken together, are $-(CH_2)_q-$;

$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11a}$;

X is Cl, Br or I;

Z is a physiologically acceptable cation;

$R_8$ is H or $C_1$-$C_4$ alkyl;

$R_{11}$ and $R_{11a}$ are independently H or $C_1$-$C_4$ alkyl, or, taken together, are $-(CH_2)_r-$;

n is 0, 1 or 2;

p is 0 or 1;

q is 3, 4 or 5;

r is 4 or 5;

B is $-NH_2$, $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-R_{13}$, $-\overset{R_{12}}{\underset{|}{N}}-S(O)_uR_{14}$ or $N_3$;

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{13})OR_{14}$; $-CH_2S(O)_vR_{14}$; $-OR_{18}$; $-SR_{14}$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; or $-NR_{19}R_{20}$;

$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{15}$ is H or $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms;

$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;

$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;

$R_{19}$ is H or $C_1$-$C_4$ alkyl;

$R_{20}$ is H or $C_1$-$C_4$ alkyl;

u is 1 or 2;

v is 0, 1 or 2; and

m is 2 or 3;

or a pharmaceutically suitable salt thereof;
provided that:

1) when A is $CH_3S$-, then B is not $-\overset{CH_3}{\underset{|}{N}}-CO_2CH_3$;

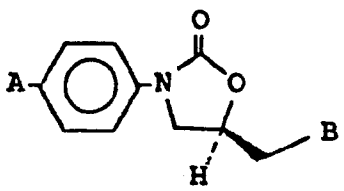
2) when A is $CH_3SO_2$-, then B is not $-\overset{CH_3}{\underset{|}{N}}-COCH_3$ or $-\overset{CH_3}{\underset{|}{N}}-COCF_3$;

3) when A is $H_2NSO_2$- and B is $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}R_{13}$ then $R_{12}$ is H.

3. A compound of Claim 1 wherein
Y is H;
A, substituted in the para position, is
$-S(O)_nR_1$, $NO_2$, $-\overset{O}{\overset{\|}{C}}-CH_3$, or $-CH(CH_3)_2$;
$R_1$ is $C_1$-$C_2$ alkyl optionally substituted with one or more halogen atoms or $NR_5R_6$;
$R_5$ is H or $CH_3$;
$R_6$ is H or $CH_3$;
n is 0, 1 or 2 when $R_1$ is alkyl or substituted alkyl; n is 2 when $R_1$ is $NR_5R_6$.

4. A compound of Claim 1 wherein
B is $-NH-\overset{O}{\overset{\|}{C}}-R_{10}$;
$R_{13}$ is H, $CH_3$, $OR_{18}$, $CHCl_2$, $CH_2Cl$ or $CH_2OR_{15}$;
$R_{15}$ is H or $C_1$-$C_4$ alkyl; and
$R_{18}$ is $C_1$-$C_4$ alkyl.

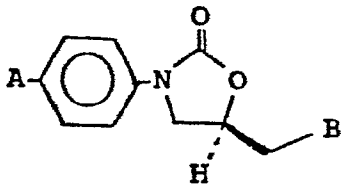
5. A compound of Claim 1 with the stereochemical configuration




wherein

A is $-S(O)CH_3$, $-S-CH_3$, $-S(O)_2CH_3$, $SO_2NH_2$, $-COCH_3$ or $-CH(CH_3)_2$.

6. A compound of Claim 1 with the stereochemical formula



wherein

B is $-N-\overset{\overset{H}{|}}{\underset{\underset{O}{\|}}{C}}-CH_3$, $-N-\overset{\overset{H}{|}}{\underset{\underset{O}{\|}}{C}}-OCH_3$ or $-N-\overset{\overset{H}{|}}{\underset{\underset{O}{\|}}{C}}-CHCl_2$.

7. A compound of Claim 5 wherein

B is $-N-\overset{\overset{H}{|}}{\underset{\underset{O}{\|}}{C}}-CH_3$, $-N-\overset{\overset{H}{|}}{\underset{\underset{O}{\|}}{C}}-OCH_3$ or $-N-\overset{\overset{H}{|}}{\underset{\underset{O}{\|}}{C}}-CHCl_2$.

8. A compound of Claim 1 selected from (ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-carbamic acid, methyl ester,

(ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]carbamic acid, methyl ester,

(ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-formamide,

(ℓ)-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-acetamide,

(ℓ)-N-[3-[4-(methylthio)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

(ℓ)-N-[3-[4-(aminosulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-acetamide,

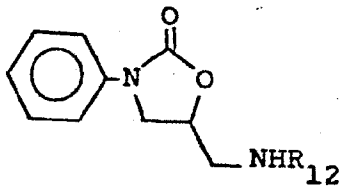
(ℓ)-N-[3-[4-(methylsulfinyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-acetamide,

(ℓ)-2,2-dichloro-N-[3-[4-(methylsulfonyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

(ℓ)-N-[3-(4-isopropylphenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide, and

(ℓ)-N-[3-(4-acetylphenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide.

9. A compound having the formula:

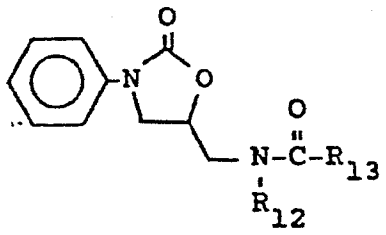


(Ia)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl.

10. A compound of the formula



(Ib)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl;

$-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$;
O
"
$CR_{15}$; $-OR_{18}$; $-SR_{14}$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;

$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;

$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;

$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;

$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_4$ alkyl;

$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl phenyl or, taken together, are $-(CH_2)_s-$;

m is 2 or 3;

v is 0, 1 or 2.

s is 2, 3, 4 or 5.

11. A pharmaceutical composition comprising a suitable pharmaceutical carrier and an antibacterially effective amount of at least one compound of claims 1 to 8.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 316 594**
**A1**

# (12) EUROPEAN PATENT APPLICATION

(21) Application number: 88117304.1

(22) Date of filing: 18.10.88

(51) Int. Cl.4: C07D 263/20 , C07D 413/10 , A61K 31/42

(30) Priority: 21.10.87 US 110837

(43) Date of publication of application: 24.05.89 Bulletin 89/21

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY
1007 Market Street
Wilmington Delaware 19898(US)

(72) Inventor: Brittelli, David Ross
90 Hopewell Road
Nottingham Pennsylvania 19362(US)
Inventor: Gregory, Walter Adelman
104 Rockingham Drive
Wilmington Delaware 19803(US)
Inventor: Corless, Peter Franklin
48 Main Street
Southborough Massachusetts 01772(US)
Inventor: Park, Chung-Ho
5 Woodley Circle
Wilmington Delaware 19803(US)

(74) Representative: von Kreisler, Alek, Dipl.-Chem. et al
Patentanwälte Von Kreisler-Selting-Werner
Deichmannhaus am Hauptbahnhof
D-5000 Köln 1(DE)

## (54) Aminomethyl oxooxazolidinyl ethenylbenzene derivatives useful as antibacterial agents.

(57) Aminomethyl oxooxazolidinyl ethenylbenzene derivatives, including the nitriles, sulfoxides, acetamides and nitro compounds, such as ℓ-N-[3-[4-(E-1-methyl-2-cyanoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide, possess useful antibacterial activity.

EP 0 316 594 A1

# AMINOMETHYL OXOOXAZOLIDINYL ETHENYLBENZENE DERIVATIVES USEFUL AS ANTIBACTERIAL AGENTS

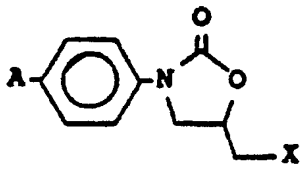
## Technical Field

This invention relates to novel aminomethyl oxooxazolidinyl ethenylbenzene derivatives, their preparation, to pharmaceutical compositions containing them, and to methods of using them to alleviate bacterial infections.

## Background of the Invention

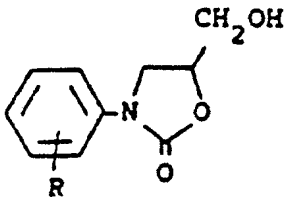
At the present time, no existing antibacterial product provides all features deemed advantageous. There is continual development of resistance by bacterial strains. A reduction of allergic reactions and of irritation at the site of injection, and greater biological half-life (i.e., longer in vivo activity) are currently desirable features for antibacterial products.

U.S. Patent 4,128,654 issued to Fugitt et al. on December 5, 1978, discloses, among others, compounds of the formula:



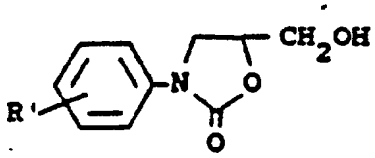
where
A = $RS(O)_n$;
X = Cl, Br or F;
R = $C_1$-$C_3$ alkyl; and
n = 0, 1 or 2.
The compounds are disclosed as being useful in controlling fungal and bacterial diseases of plants.

U.S. Reissue Patent 29,607 reissued April 11, 1978 discloses derivatives of 5-hydroxymethyl-3-substituted-2-oxazolidinones of the formula:



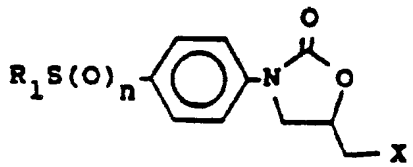
where R is H, F, $CH_3$, or $CF_3$. Such compounds are described as having antidepressive, tranquilizing, sedative, and antiinflammatory properties.

U.S. Patent 4,250,318, which was issued on February 10, 1981, discloses antidepressant compounds of the formula:



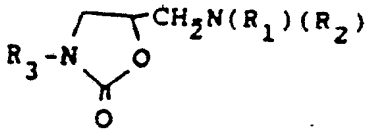
where R' can be, among others, a para-n-pentylamino group, an $SR_1$ group where $R_1$ is $C_1$-$C_5$ alkyl, or an acetylmethylthio group.

U.S. Patent 4,340,606, issued to Fugitt et al. on July 20, 1982, discloses antibacterial agents of the general formula:



where
$R_1$ = $CH_3$, $C_2H_5$, $CF_2H$, $CF_3$ or $CF_2CF_2H$; and
X = $OR_2$($R_2$ = H or various acyl moieties).

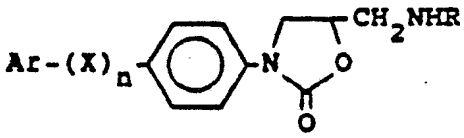
U.S. Patent 3,687,965, issued to Fauran et al. on August 29, 1972, discloses compounds of the formula:



where
$-N(R_1)(R_2)$ represents either dialkylamino radical in which the alkyl portions have one to five carbon atoms, or a heterocyclic amino radical which may be substituted by an alkyl radical having one to five carbon atoms or by a pyrrolidinocarbonylmethyl radical, and
$R_3$ represents a phenyl radical which may be substituted by one or more of the following radicals:
an alkoxy radical having one to five carbon atoms;
a halogen atom;
a trifluoromethyl radical, or
a carboxyl radical which may be esterified.

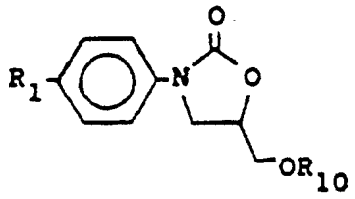
The patent states that these compounds possess hypotensive, vasodilatatory, spasmolytic, sedative, myorelaxant, analgesic and antiinflammatory properties. There is no mention of antibacterial properties.

Belgian Patent 892,270, published August 25, 1982, discloses monoamine oxidase inhibitors of the formula



where
R is H, $C_1$-$C_4$ alkyl or propargyl;
Ar is phenyl, optionally substituted by halo or trifluoromethyl;
n is 0 or 1; and
X is $-CH_2CH_2-$, $-CH=CH-$, an acetylene group or $-CH_2O-$.

U.S. Patent 4,461,773 issued to W. A. Gregory on July 24, 1984 discloses antibacterial agents of the formula



wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

$R_1$ is $R_2SO_2$,

$R_3R_4N\overset{O}{\overset{\|}{C}}$, or $R_3\overset{NR_5}{\overset{\|}{C}}$;

$R_2$ is $-NR_3R_4$, $-N(OR_3)R_4$, $-N_3$, $-NHNH_2$, $-NX_2$, $-NR_6X$, $-NXZ$, $-NH\overset{O}{\overset{\|}{C}}R_7$, $-NZ\overset{O}{\overset{\|}{C}}R_7$

or $-N=S(O)_nR_8R_9$;

$R_3$ and $R_4$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

$R_5$ is $NR_3R_4$ or $OR_3$;

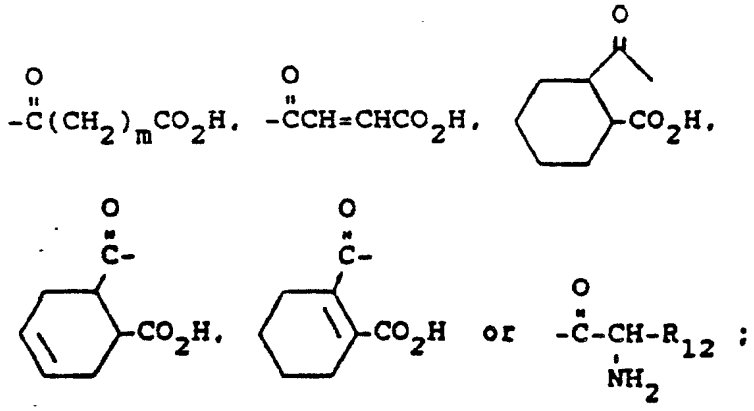
$R_6$ is alkyl of 1-4 carbons;

$R_7$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

$R_8$ and $R_9$ are independently alkyl of 1-4 carbons or, taken together are $-(CH_2)_p-$;

$R_{10}$ is H, alkyl of 1-3 carbons,

$-\overset{O}{\overset{\|}{C}}R_{11}$,



$R_{11}$ is alkyl of 1-12 carbons;

$R_{12}$ is H, alkyl of 1-5 carbons, $CH_2OH$ or $CH_2SH$;

X is Cl, Br or I;

Z is a physiologically acceptable cation;

m is 2 or 3;

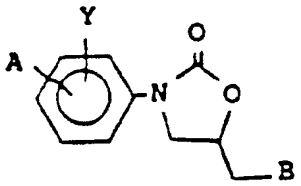
n is 0 or 1; and

p is 3, 4 or 5;

and when $R_{10}$ is alkyl of 1-3 carbons, $R_1$ can also be $CH_3S(O)_q$ where q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

European Patent Application 127,902, published December 12, 1984, and 184,170, published June 11, 1986, disclose antibacterial agents of the formula:



wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,

A is $-NO_2$, $-S(O)_nR_1$, $-S(O)_2-N=S(O)_pR_2R_3$, $-SH$, $-SCR_4$ (O), $-COR_{23}$, $-COR_{25}$, $-CONR_5R_6$, $-C(=NR_7)-R_{23}$,

$-CH(OR_8)-R_{23}$, $-CH(OR_8)-R_{25}$, $-CH(OCR_8=O)-R_{23}$, $-CH(OCR_8=O)-R_{25}$,

$-CN$, $-OR_5$, halogen, $-NR_5R_6$, $-NR_5COR_4$,

$-NR_5S(O)_nR_4$, $CR_{23}(OR_{16})OR_{17}$, $-CR_{23}(NR_5R_6)R_9$, alkyl

of 1 to 8 carbons, optionally substituted with one or more halogen atoms, OH, =O other than at alpha position, $S(O)_nR_{24}$, $NR_5R_6$, alkenyl of 2-5 carbons, alkynyl of 2-5 carbons or cycloalkyl of 3-8 carbons;

$R_1$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms, OH, CN, $NR_5R_6$ or $CO_2R_8$; $C_2$-$C_4$ alkenyl; $-NR_9R_{10}$; $-N_3$;

$-NHC(=O)R_4$; $-NZC(=O)R_4$; $-NX_2$; $NR_9X$ $-{}^{-}NXZ^{+}$;

$R_2$ and $R_3$ are independently $C_1$-$C_2$ alkyl or, taken together are $-(CH_2)_q-$;

$R_4$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

$R_5$ and $R_6$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

$R_7$ is $-NR_5R_5$, $-OR_5$ or $NHC(=O)R_5$;

$R_8$ is H or alkyl of 1-4 carbons;

$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11A}$;

$R_{11}$ and $R_{11A}$ are independently H or $C_1$-$C_4$ alkyl, or taken together, are $-(CH_2)_r-$;

X is Cl, Br or I;

Y is H, F, Cl, Br, alkyl of 1-3 carbons, or $NO_2$, or A and Y taken together can be $-O-(CH_2)_tO-$;

Z is a physiologically acceptable cation;

n is 0, 1 or 2;

p is 0 or 1;

q is 3, 4 or 5;

r is 4 or 5;

t is 1, 2 or 3;

B is $-NH_2$, $-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-R_{13}$, $-\overset{R_{12}}{\underset{|}{N}}-S(O)_uR_{14}$, or $N_3$;

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;
$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-\overset{O}{\overset{\|}{C}}R_{15}$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;
$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;
$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;
$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_2$ alkyl;
$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;
u is 1 or 2;
v is 0, 1 or 2;
m is 2 or 3;
s is 2, 3, 4 or 5; and
$R_{23}$ is H, alkyl of 1-8 carbons optionally substituted with one or more halogens, or cycloalkyl of 3-8 carbons;
$R_{24}$ is alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;
$R_{25}$ is alkyl of 1-4 carbons substituted with one or more of $-S(O)_nR_{24}$, $-OR_8$, $-O\overset{O}{\overset{\|}{C}}R_8$, $-NR_5R_6$, or alkenyl of 2-5 carbons optionally substituted with CHO; or a pharmaceutically suitable salt thereof; provided that;

1) when A is $CH_3S$-, then B is not $-\overset{CH_3}{\underset{|}{N}}-CO_2CH_3$;

2) when A is $CH_3SO_2$-, then B is not

$$-\overset{CH_3}{\underset{|}{N}}-COCH_3 \text{ or } -\overset{CH_3}{\underset{|}{N}}-COCF_3;$$

3) when A is $H_2NSO_2$- and B is

$$-\overset{R_{12}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}R_{13},$$

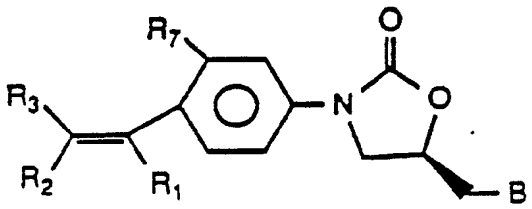
then $R_{12}$ is H;

4) when A is -CN, B is not $-N_3$;
5) when A is $(CH_3)_2CH$, B is not $NHCOCH_2Cl$;
6) when A is $OR_5$, then B is not $NH_2$;
7) when A is F, then B is not $NHCO_2CH_3$.

None of the above-mentioned references suggest the novel antibacterial compounds of this invention.

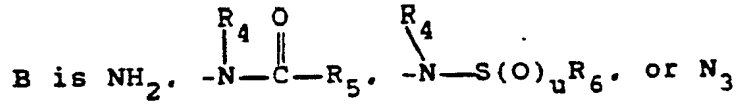
## Summary of the Invention

According to the present invention, there is provided an oxazolidinone of the formula:



(I)

wherein for the ℓ isomer or racemic mixtures containing it



u is 1 or 2:

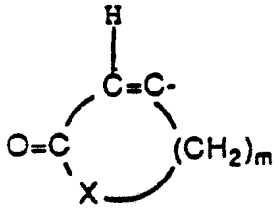
$R_4$ is H, alkyl of 1-10 carbon atoms, or cycloalkyl of 3-8 carbon atoms;

$R_5$ is H, alkyl of 1-4 carbon atoms optionally substituted with one or more halogen atoms, alkenyl of 2-4 carbon atoms, cycloalkyl of 3-4 carbon atoms, phenyl; $OR_6$, or $CH_2OR_4$;

$R_6$ is alkyl of 1-4 carbon atoms optionally substituted with one or more halogen atoms;

$R_7$ is H, $CH_3$, $C_2H_5$, F or OH;

$R_1$ independently is H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, phenyl, or phenyl optionally substituted with one or more halogen atoms, or taken together with $R_2$ forms a 5-, 6-, or 7-membered ring of the formula:

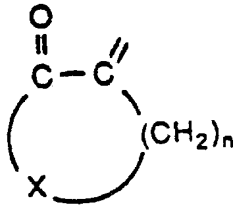


or

$-(CH_2)_p-$, when $R_3$ is an electron-withdrawing group;

$R_2$ and $R_3$ independently are an electron-withdrawing group, H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, or phenyl, provided at least one of $R_2$ or $R_3$ is an electron-withdrawing group, or

$R_2$ and $R_3$ taken together form a 5, 6 or 7-membered ring of the formula:



m is 1, 2 or 3;

n is 2, 3 or 4;

p is 3, 4 or 5; and

X is $CH_2$, O, S, or NR where R is H or alkyl of 1-5 carbon atoms;

or a pharmaceutically suitable salt thereof.

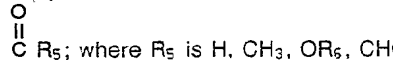
Also provided is a pharmaceutical composition consisting essentially of a suitable pharmaceutical carrier and a compound of Formula (I) and a method of using a compound of Formula (I) to treat bacterial infection in a mammal.

Further provided is a process for preparing compounds of Formula (I), such a process being described in detail hereinafter.

## Preferred Embodiments

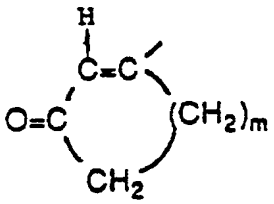
Preferred compounds are the oxazolidinones of Formula (I) where:

(a) B is



-NH C $R_5$; where $R_5$ is H, $CH_3$, $OR_6$, $CHCl_2$, $CH_2Cl$, $CH_2OH$ or $CH_2OCH_3$; or

(b) $R_1$ independently is H or alkyl of 1-3 carbon atoms, or is taken together with $R_2$ to form a 5- or 6-membered ring of the formula:



where m is 1 or 2; or

(c) $R_2$ independently is an electron-withdrawing group; or

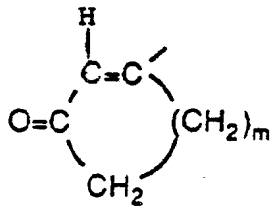
(d) $R_3$ independently is H, alkyl of 1-3 carbon atoms or phenyl.

More preferred compounds are the oxazolidinones of Formula (I) where:

(a) B is

-NH C $CH_3$; or

(b) $R_1$ independently is H, $CH_3$ or $C_2H_5$, or is taken together with $R_2$ to form a 5- or 6-membered ring of the formula:



where m is 1 or 2; or

(c) $R_2$ independently is CN or $NO_2$; or

(d) $R_3$ independently is H, $CH_3$ or $C_2H_5$

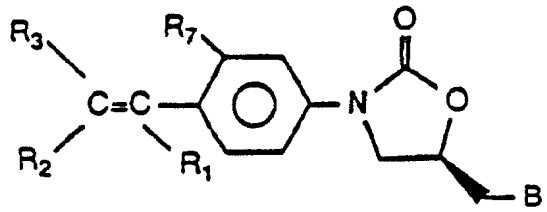
Specifically preferred are the following compounds:

- (ℓ)-N-[3-[4-(E-1-methyl-2-cyanoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(3-oxo-1-cyclohexen-1-yl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(E-2-nitroethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(E-1-methyl-2-nitroethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide

## Detailed Description

The compounds of Formula (I) contain at least one chiral center, and as such exist as two individual isomers or as a mixture of both. This invention relates to the levorotatory isomer (ℓ) which for many of the compounds in this invention can be referred to as the (S) isomer, as well as mixtures containing both the (R) and (S) isomers. Additional chiral centers may be present in any of the R groups and or B and this invention relates to all possible stereoisomers in these groups.

For the purposes of this invention, the ℓ-isomer of compounds of Formula (I) is intended to mean compounds of the configuration depicted; when B is NHAc, and closely related groups, this isomer is described as the (S)-isomer in the Cahn-Ingold-Prelog nomenclature:




(I)

Furthermore, a different type of stereoisomerism exists when the compounds of Formula (I) contain groups $R_1$ and $R_2$ which are different. Such isomers which may be interconverted by torsion around double bonds are classically termed geometric isomers or cis-trans-isomers. The newer method of describing them is based on the Cahn-Ingold-Prelog system by which two groups at each carbon atom of the double bond are ranked by the sequence rules. Then that isomer with two higher ranking groups on the same side of the double bond is called Z (for the German word zusammen meaning together); the other is E (for entgegen meaning opposite). This invention relates to both E- or Z-isomers separately or mixed together.

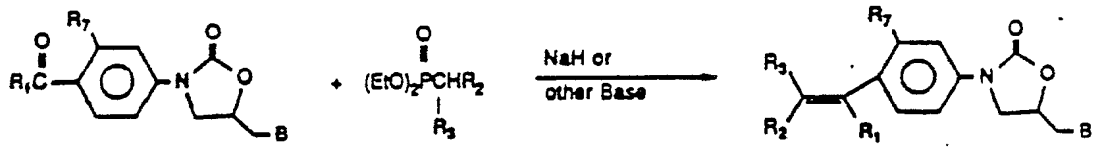
The concept of the electron-withdrawing group derives from consideration of the effect of substituents on the rate of various reactions. Tje constant $\sigma$ may be defined, which is characteristic for a particular group. The $\sigma$ values are numbers which sum up the total electrical effects (field plus resonance) of a group. A positive value of $\sigma$ indicates an electron-withdrawing group. Different $\sigma$ values have been developed for different positions on the benzene ring; we choose $\sigma_p$ as most appropriate for defining the class of substituents operable in this application. (A discussion of the concept of electron-withdrawing groups may be found in: J. March, Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, 2nd Edition, McGraw-Hill, New York, 1977, Chapters 2 and 9, as well as other standard texts on advanced organic chemistry).

The substituents conferring particular antibacterial activity to the subject compounds of this application are unsaturated functional groups having $\sigma_p$ greater than about 0.20. A listing of groups and their $\sigma_p$ constants may be found in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley and Sons, New York, 1979. Some representative examples of electron-withdrawing groups are the nitro ($-NO_2$), cyano (-CN), formyl (-CHO), carboxamido ($-C(=O)NH_2$), N-methyl carboxamido ($-C(=O)NHCH_3$), acetyl ($-C(=O)CH_3$), propionyl ($-C(=O)C_2H_5$), carbomethoxy ($-(C=O)OCH_3$), methylsulfinyl ($-S(O)CH_3$), methylsulfonyl ($-SO_2CH_3$), fluoromethylsulfinyl($-SOCH_2F$), trifluoromethylsulfonyl ($-SO_2CF_3$), and dimethylphosphinyl ($-PO(CH_3)_2$) groups.

## Synthesis

Compounds of Formula (I) can be prepared as follows:

Scheme 1:



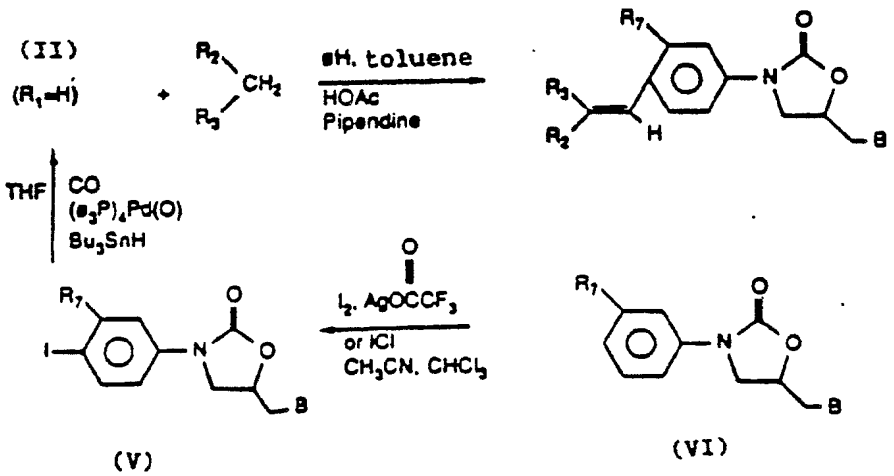

(II) (III) (I)

Wherein $R_1$ independently is H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, or phenyl. $R_2$ and $R_3$ independently are H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, phenyl or CN, provided that only one of $R_2$ and $R_3$ is CN and B is as described previously; provided, $R_5$ in B is not one carbon atom substituted with one or more halogen atoms.

Solvents such as 1,2-dimethoxyethane, dioxane, bis-(2-methoxyethyl)ether, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), acetonitrile, ethanol or other alcohols may be used. Suitable bases include sodium hydride, butyllithium or an alkoxide. The reaction is typically carried out by adding a base to a solution of the phosphonate (III) at 0 to 20 °C followed by addition of the substrate (II). The reaction mixture is stirred from about room temperature to 60 °C for 1 to 2 hours, the solvent is removed under reduced pressure and the residue is triturated with water. The resulting crude product which is usually a mixture of E and Z isomers with E isomer predominant, is separated and purified by conventional means. The starting compound (II) may be dℓ- (the racemate) or the ℓ-isomer.

The compounds of Formula (II) are prepared by the process previously described in published European applications 127,902 and 184,170. Compounds wherein $R_5$ is one carbon atom substituted with one or more halogen atoms can be prepared by reaction of compound (I) (B is $NH_2$) with one or more halogen-substituted acetyl chlorides or acetic anhydrides in the presence of a base. Solvents such as 1,2-dimethoxyethane, dioxane, acetonitrile, tetrahydrofuran, or DMF may be used. Suitable bases include triethylamine or pyridine.

Scheme 2:



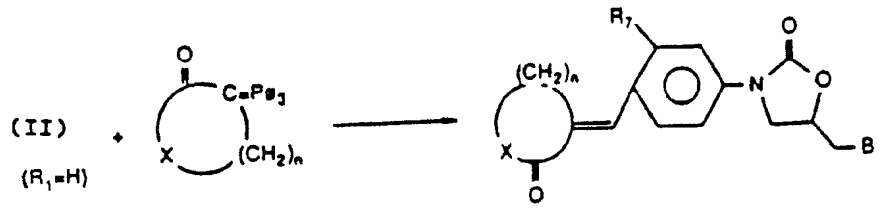

(V) (VI)

Compounds of Formula (I) which may be prepared using the procedures of Scheme 2 are those where $R_1$ is H, and $R_2$ and $R_3$ independently are both electron-withdrawing groups previously defined except that when one of $R_2$ or $R_3$ is $NO_2$, the remaining $R_2$ or $R_3$ group can be an electron-withdrawing group including another $NO_2$ group or H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one or more halogen atoms, or phenyl. The reaction is typically carried out in an aprotic solvent such as benzene or toluene under reflux in the presence of catalytic amounts of a carboxylic acid such as acetic acid and an amine such as piperidine with azeotropic removal of water. The solvent is then removed under reduced pressure

and the desired product is isolated as previously described.

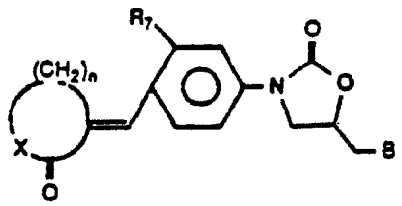
Compounds of Formula (VI) are iodinated using iodine and silver trifluoroacetate or iodine monochloride in solvents such as chloroform, acetonitrile, acetic acid or mixtures of solvents thereof at 0° to 60° C. After the reaction mixture is stirred for 1 to 24 hours, the resulting silver halide was filtered off, the solvent was removed under reduced pressure and the residue was triturated with distilled water. The crude product obtained by filtration is purified by recrystallization from suitable solvents such as acetonitrile with the aid of activated charcoal. The iodocompounds (V) are then converted to the aldehydes (II) by addition of carbon monoxide in suitable solvents such as toluene, THF, glyme and DMF or mixtures thereof at 10° to 70° C in the presence of tributyltin hydride and tetrakis(triphenylphosphine)palladium(O).

Scheme 3:




(VII)

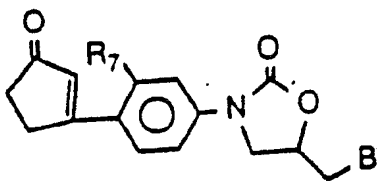
Compounds of Formula (I) where $R_1$ is H and $R_2$ and $R_3$ are taken together to form a 5, 6 or 7-membered ring of formula:




where n is 2, 3, or 4;
X is $CH_2$, O, S, or NR where R is H or alkyl of 1-5 carbon atoms, or a pharmaceutically suitable salt thereof,

may be prepared by reaction of the cyclic ylides of Formula (VII) with compounds of Formula (II) in Scheme 3. The cyclic ylides of Formula (VII) can be prepared by procedures describe in H. O. House and H. Barad, J. Org. Chem., 28, 90 (1963).

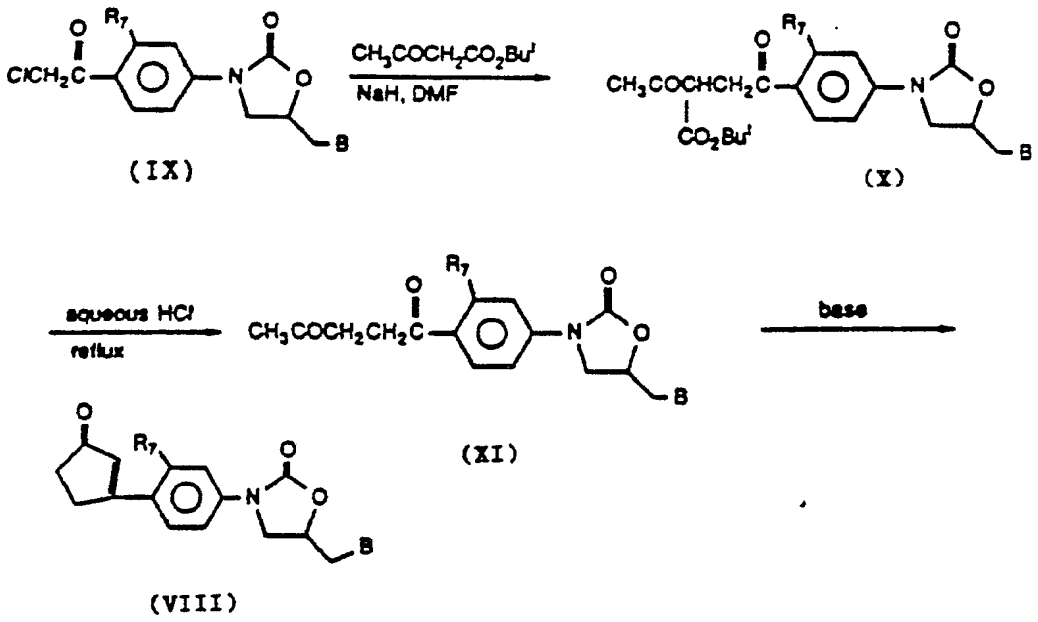
Compounds of Formula (I) where $R_1$ is taken together with $R_2$ to form a 5-membered ring of Formula (VIII)




(VIII)

may be prepared according to synthetic Scheme 4.

Scheme 4:

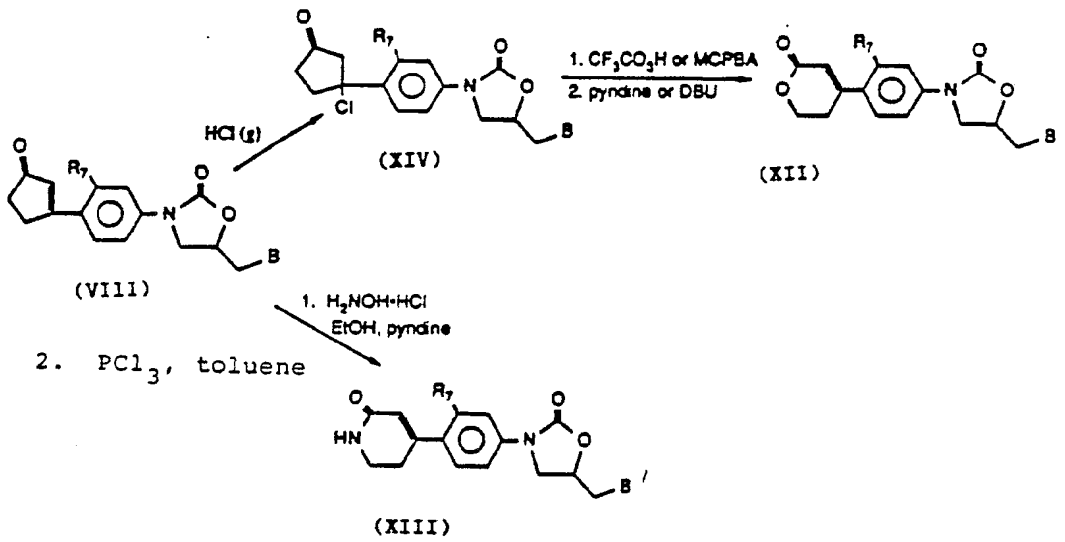



Compounds of Formula (IX) which are prepared by the process described in published European Patent Applications 127,902 and 184,170 can be converted into diketoester (X) by reaction with the anion of t-butyl acetoacetate in an aprotic solvent such as THF or DMF. Suitable bases to generate the anion include sodium hydride, potassium hydride, or potassium t-butoxide. The reaction is carried out from 0° to room temperature. Compounds (X) can be decarboxylated upon treatment with refluxing aqueous hydrochloric acid.

Finally a suitable base such as proline, morpholine, pyrrolidine, or potassium t-butoxide can be used to convert diketone (XI) into (VIII). Solvents such as benzene, toluene, or t-butanol can be used. The reaction temperature may be from room temperature to 130° C.

Compounds of Formula (VIII) can be used to prepare lactones (XII) or lactams (XIII) (Scheme 5).

Scheme 5:

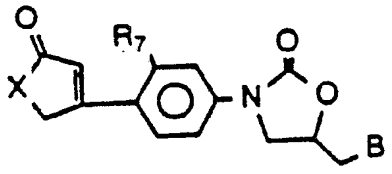



Compounds of Formula (XIV) may be derived from reaction of gaseous hydrogen chloride with (VIII). Methylene chloride, dioxane, chloroform, or THF may be used as solvents and the reaction temperature can be from 0° to 80° C. Bayer-Villiger oxidation of (XIV) with either trifluoroperacetic acid or m-chloroperbenzoic acid (MCPBA) in solvents such as methylene chloride, benzene, or THF at temperatures from 0° to 80° C followed by treatment of the resulting oxidation products with a base such as pyridine, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in solvents such as methylene chloride, benzene, toluene, or THF at room temperature to 110° C may convert (XIV) into the desired lactones (XII).

Treatment of (VIII) with hydroxyamine hydrochloride in the presence of a base such as pyridine or triethylamine in an alcoholic solvent such as methanol or ethanol at room temperature to 100° C gives the corresponding oxime which undergoes a Beckmann rearrangement upon treatment with phosphorous pentachloride in a solvent such as benzene or toluene at room temperature to 110° C to afford the desired lactams (XIII).

By using the same procedures shown in Scheme 5, 7-membered ring lactones and lactams can be obtained from 6-membered enones which are prepared by the procedure described in Example 68 which follows.

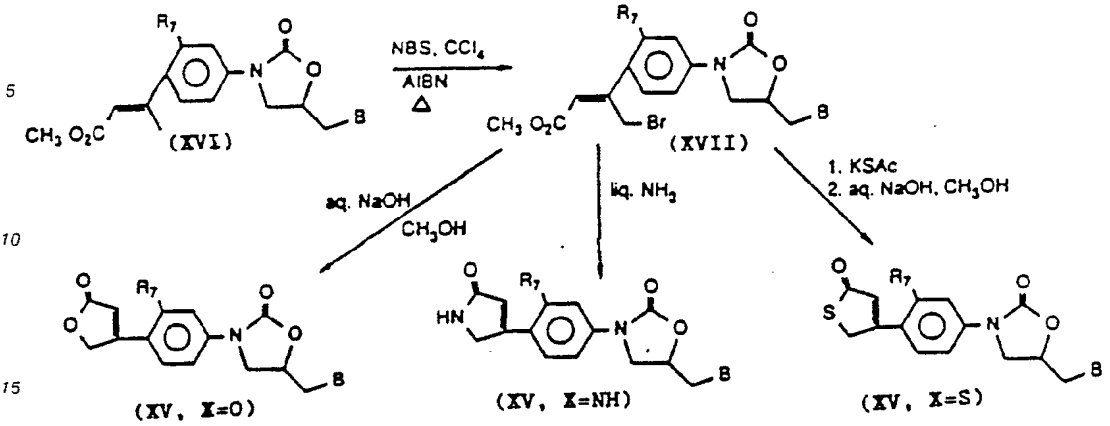
Compounds of Formula (I) where $R_1$ is taken together with $R_2$ to form a 5-membered ring of formula (XV) may be prepared according to



(XV, wherein X=O, S, or NH)

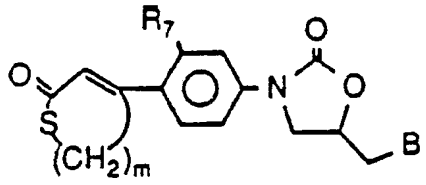
synthetic Scheme 6.

Scheme 6:



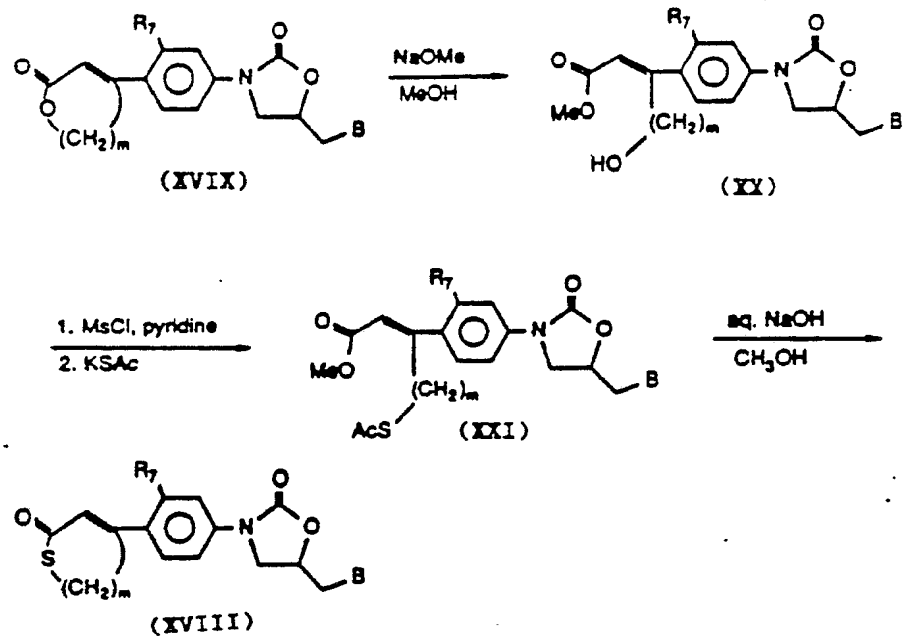

Compounds of Formula (XVI) are prepared according to the procedure described in Example 58 which follows. Treatment of (XVI) with N-bromosuccinimide (NBS) in refluxing carbon tetrachloride in the presence of a radical initiator such as azobisisobutyronitrile (AIBN) or benzoyl peroxide yields the bromide (XVII). Hydrolysis of (XVII) with aqueous sodium hydroxide or potassium hydroxide in an alcoholic solvent such as methanol or ethanol at room temperature gives lactones (XV, X=O). Liquid ammonia converts (XVII) into lactams (XV, X=NH). The reaction temperature may be from 0° to 100°C. Treatment of (XVII) with potassium thioacetate (KSAc) or thioacetic acid in the presence of triethylamine in a solvent such as acetonitrile, THF, or DMF at 0°C to room temperature followed by hydrolysis of the resulting products with aqueous base such as sodium hydroxide or potassium hydroxide in an alcoholic solvent such as methanol or ethanol at 0° to room temperature gives thiolactones (XV, X=S).

Compounds of Formula (I) where $R_1$ is taken together with $R_2$ to form a 6 or 7-membered ring of formula (XVIII) may be prepared according to Scheme 7.



(XVIII, m=2 or 3)

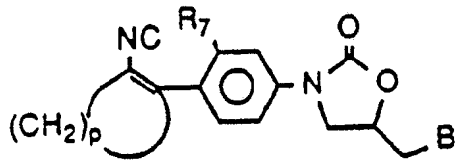
Scheme 7:




(XVIX) (XX) (XXI) (XVIII)

Treatment of lactones (XVIX) with sodium methoxide in methanol at room temperature to 80 °C gives the hydroxy esters (XX). The hydroxy group in (XX) is converted into mesylate or tosylate with mesyl chloride (MsCl) or tosyl chloride in pyridine at room temperature. The mesylate or tosylate is then displaced with potassium thioacetate (KSAc) or thioacetic acid in the presence of triethylamine in a solvent such as acetonitrile, THF, or DMF at 0 ° to 50 °C to give (XXI). Hydrolysis of (XXI) with aqueous sodium hydroxide or potassium hydroxide in an alcoholic solvent such as methanol or ethanol at 0 °C to room temperature yields the desired compound (XVIII, m = 2 or 3).

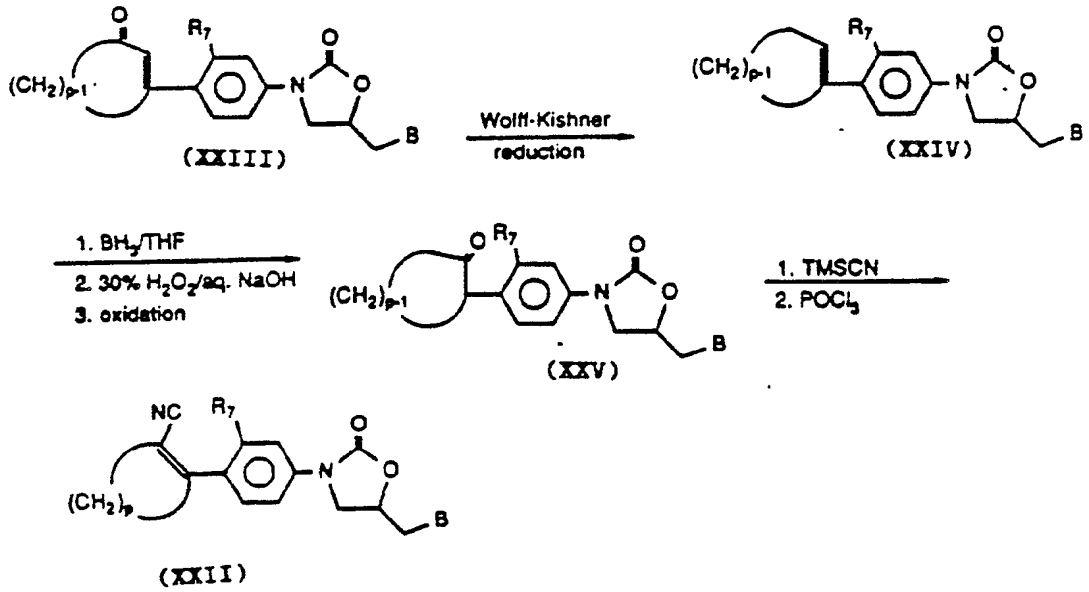
Compounds of Formula (I) where $R_1$ is taken together with $R_2$ to form a 5, 6 or 7-membered ring and $R_3$ is a cyano group of formula (XXII):



(XXII, p=3, 4 or 5)

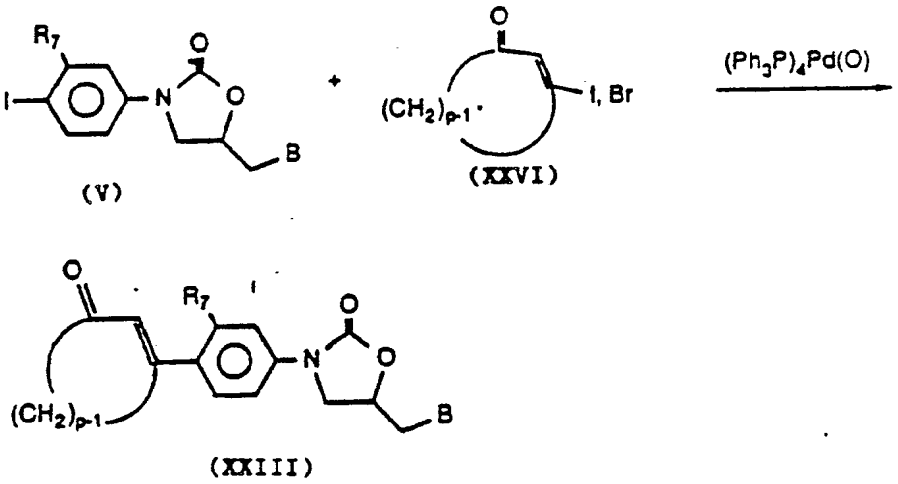
may be prepared by the synthetic transformations shown in Scheme 8.

Scheme 8:




Compounds of Formula (XXIII) where p is 3 and 4 are prepared by the process described in Scheme 4 previously and Example 68 which follows. Alternatively, compounds (XXIII, p = 3, 4 or 5) may be prepared according to Scheme 9. Thus, compounds (V) may react with

Scheme 9:




iodoenones or bromoenones (XXVI) in the presence of tetrakis(triphenylphosphine)palladium(O) or bis-(triphenylphosphine)palladium(II) chloride in a solvent such as THF, benzene, toluene, or DMF at room temperature to 60 °C to give (XXIII).

Wolff-Kishner reduction of (XXIII) using hydrazine hydrate and potassium hydroxide in diethylene glycol at 150° to 200 °C gives (XXIV). Hydroboration of (XXIV) with diborane in THF or ether at 0 °C to room temperature followed by treatment with hydrogen peroxide in the presence of aqueous sodium hydroxide at room temperature to 70 °C and the resulting alcohols oxidized with a suitable oxidizing agent such as pyridinium chlorochromate, pyridinium dichlorochromate, or chromium trioxide in methyl chloride, DMF, or pyridine yields (XXV). Treatment of (XXV) with trimethylsilyl cyanide (TMSCN) in THF, acetonitrile or

methylene chloride at 0° to 50° C followed by dehydration with phosphorus oxychloride at 0° C to room temperature gives (XXII).

Pharmaceutically suitable salts of compounds of Formula (I) can be prepared in a number of ways known in the art. Where B is $NH_2$, pharmaceutically suitable salts include those resulting from treatment with acetic, hydrochloric, sulfuric, phosphoric, succinic, fumaric, ascorbic, and glutaric acid.

Example 1

Preparation of (ℓ)-N-[3-[4-(E-1-Methyl-2-cyanoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = CH_3$, $R_2 = CN$, $R_3 = R_7 = H$, $B = NHCOCH_3$)

A 100 mL 3-necked flask under nitrogen was charged with 0.452 g (11.3 mmol) of sodium hydride (60% dispersion in mineral oil) and 10 mL of dry DMF. The flask was cooled to 5° C and 2.0 g (11.3 mmol) of diethyl cyanomethylphosphonate was added dropwise over 15 minutes. The solution was stirred for 30 minutes after hydrogen evolution was complete and then 2.5 g (9.05 mmol) of a (ℓ)-N-[3-(4-acetylphenyl-2-oxooxazolidin-5-ylmethyl]acetamide was added as a solid. The reaction was allowed to warm to room temperature and stirred overnight. It was then poured onto 40 g of ice and the mixture was extracted with chloroform and the chloroform solution was dried over magnesium sulfate. The solvent was removed under reduced pressure and the solid residue was recrystallized from acetonitrile to give 1.6 g (59%) of (ℓ)-N-[3-[4-(E-1-methyl-2-cyanoethenyl)phenyl-2-oxooxazolidin-5-ylmethyl]acetamide as a colorless crystalline solid, m.p. 176.0-177.0° C. The geometry of the product was shown to be E by nmr analyses. The Z-isomer was isolated from the mother liquor of recrystallization and purified by liquid chromatography.

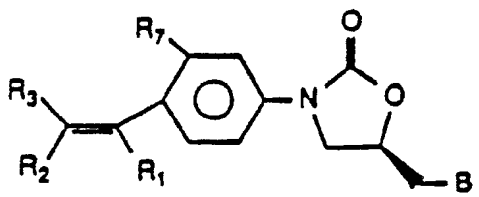
Example 2

Preparation of (ℓ)-N-[3-[4-(E-2-Cyanoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = R_3 = R_7 = H$, $R_2 = CN$, $B = NHCOCH_3$)

To a solution of 0.742 g (4.2 mmol; 10% excess) of diethyl cyanophosphonate in 30 mL of THF was added 2.6 mL of n-butyllithium solution (1.6M in hexane) dropwise at below 5° C, and then it was allowed to stir at room temperature for 10 minutes. The mixture was cooled to 0° C and 1 g (3.81 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide was added in one portion. After the mixture was allowed to warm to room temperature and stirred for 1 hour, 5 g of ice was added and the volatile solvents were removed under reduced pressure. The resulting residue was triturated in water to give 0.9 g of solid which was filtered and recrystallized from 40 mL of ethanol with the help of activated charcoal to give 0.6 g (55%) of (ℓ)-N-[3-[4-(E-2-cyanoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide as a colorless crystalline solid, m.p. 189-190° C.

By using the procedures described in Examples 1 and 2, additional cyano compounds which were prepared or can be prepared are illustrated in Table I.

Table I



| EX. | $R_1$ | $R_2$ | $R_3$ | $R_7$ | B | isomer | m.p.(°C) |
|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | NC- | H | H | $NHCOCH_3$ | ℓ | 176-177 |
| 2 | H | NC- | H | H | $NHCOCH_3$ | ℓ | 189-190 |
| 3 | $CH_3$ | NC- | H | $CH_3$ | $NHCOCH_3$ | ℓ | 150-151 |
| 4 | $CH_3$ | NC- | H | H | $NHCOCH_3$ | dℓ | |
| 5 | $C_6H_5$ | NC- | H | H | $NHCOCH_3$ | dℓ | |
| 6 | p-$FC_6H_4$ | NC- | H | H | $NHCOCH_3$ | ℓ | 217-219 |
| 7 | $C_2H_5$ | NC- | H | H | $NHCOCH_3$ | ℓ | |
| 8 | n-$C_3H_7$ | NC- | H | H | $NHCOCH_3$ | ℓ | |
| 9 | $CH_3$ | NC- | $CH_3$ | H | $NHCOCH_3$ | ℓ | 52-59 |
| 10 | $CH_3$ | NC- | $CH_3$ | H | $NHCOCH_3$ | dℓ | |
| 11 | $CH_3$ | $CH_3$ | NC- | H | $NHCOCH_3$ | ℓ | 146-149 |
| 12 | H | NC- | $CH_3$ | H | $NHCOCH_3$ | ℓ | |
| 13 | $CH_3$ | H | NC- | H | $NHCOCH_3$ | ℓ | |
| 14 | $CF_3$ | NC- | H | F | $NHCO_2CH_3$ | ℓ | |
| 15 | $CH_3$ | NC- | H | OH | $NHCO_2CH_3$ | ℓ | |
| 16 | $CH_3$ | H | NC- | $C_2H_5$ | NHCO-  | ℓ | |
| 17 | H | NC- | H | H | $N_3$ | ℓ | |
| 18 | $CH_3$ | NC- | H | H | $NH_2$ | ℓ | |

Example 19

Preparation of (ℓ)-N-[3-[4-(E-Nitroethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I, $R_1 = R_3 = R_7 = H$, $R_2 = NO_2$, $B = NHCOCH_3$)

PART A: Preparation of (ℓ)-N-[3-(4-Iodophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

To a mixture containing 23.4 g (0.1 mol) of (ℓ)-N-(3-phenyl-2-oxooxazolidin-5-ylmethyl)acetamide and 29 g (0.13 mol) of silver trifluoroacetate, 300 mL of acetonitrile and 200 mL of chloroform was added 27 g of iodine in one portion and allowed to stir at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a brown solid which was triturated with distilled water, filtered and washed thoroughly with distilled water. The resulting solid was recrystallized from 200 mL of acetonitrile (activated charcoal used) to give 27.5 g (77%) of the desired product as a colorless crystalline solid, m.p. 194.5-195.5° C.

Part B: Preparation of (ℓ)-N-[3-(4-Formylphenyl-2-oxooxazolidin-5-ylmethyl]acetamide

A mixture containing 31 g (96 mmol) of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and 10 g of tetrakis(triphenylphosphine)]palladium(0) in 400 mL of dry degassed THF was heated to 50-55° C under a slight positive pressure of carbon monoxide (using balloon filled with CO). While the temperature and positive pressure of carbon monoxide were being maintained, a solution of 30 mL (25% excess) of tributyltin hydride dissolved in 65 mL of dry toluene, which had previously been flushed with carbon monoxide, was added dropwise over a period of 4 hours. When the addition was complete, 8 mL more of tributyltin hydride dissolved in 65 mL of toluene was added rapidly followed by 35 mL of toluene, and the mixture was stirred at room temperature overnight. The resulting precipitate was filtered, washed three times with toluene to give 19.1 g (85%) of the desired aldehyde, m.p. 171-172° C.

PART C:

A mixture containing 0.5 g (1.9 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide, 0.25 mL of nitromethane, 2 drops of piperidine and 5 drops of acetic acid in absolute ethanol was heated under reflux for 5 hours. The clear mixture was then allowed to stir at room temperature overnight to give deep yellow precipitate which was collected by filtration. The solid was recrystallized once from ethanol to give 0.19 g (33%) of (ℓ)-N-[3-[4-(E-2-nitroethenyl)phenyl]-2-oxooxazolidin-5-yl-methyl]-acetamide as a bright yellow solid, m.p. 216-218° C.

Example 20

Preparation of (ℓ)-N-[3-[4-(E-2-Nitro-2-methylethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide ($R_1 = R_7 = H$, $R_2 = NO_2$, $R_3 = CH_3$, $B = NHCOCH_3$)

A mixture of 3 g (11.4 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 2 mL (27.8 mmol) of nitroethane, 9 drops of piperidine and 30 drops of acetic acid in 125 mL of dry benzene was heated under reflux overnight while water formed from the reaction was removed using a Dean-Stark trap. When the clear reaction mixture was allowed to cool to room temperature, fine yellow precipitate formed. The mixture was diluted with 150 mL of ether, and the solid was collected and recrystallized from a chloroform/n-butyl chloride mixture to give 2.7 g (74%) of the desired product as a bright yellow crystalline

solid, m.p. 151.5-152.5° C.

Example 21

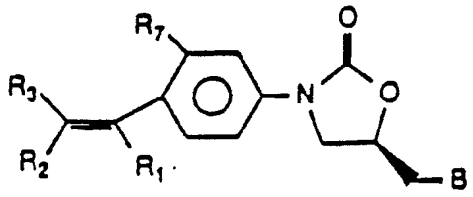
Preparation of (ℓ)-N-[3-(4-(2-Cyano-2-methylsulfenylethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = R_7 = H$, $R_2 = CN$, $R_3 = CH_3SO$, $B = NHCOCH_3$)

Methylsulfenylacetonitrile was prepared by adding in small portions 4.6 g (23 mmol) of m-chloroperbenzoic acid to a stirred solution of 2 g (23 mmol) of methylthioacetonitrile in 50 mL of methylene chloride at -20° C. When the oxidation was complete as shown by starch-iodide paper test, the solvent was removed under reduced pressure, and the solid residue was triturated with 18 mL of water. The mixture was filtered and water from the aqueous filtrate was removed under reduced pressure to give 2.19 g of the sulfoxide as a colorless solid. When the reaction was carried out at room temperature using an excess of m-chloroperbenzoic acid, methylsulfonylacetonitrile was obtained.

A mixture containing 1 g (3.8 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 0.4 g (3.8 mmol) of methylsulfenylacetonitrile, 3 drops of piperidine and 10 drops of acetic acid in 50 mL of dry benzene was heated under reflux overnight and the water formed during the reaction was removed using a Dean-Stark trap. Solid precipitate obtained on cooling was collected by filtration and recrystallized once from a n-butyl chloride/acetonitrile mixture (activated charcoal) to give 0.74 g (83%) of the desired product as a pale yellowish solid, m.p. 158.5-160° C.

By using the procedures of Examples 19-25, the following compounds in Table II were prepared or can be prepared.

Table II



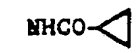
| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_7$ | B | iso-mer | m.p.(°C) |
|---|---|---|---|---|---|---|---|
| 19 | H | $-NO_2$ | H | H | $NHCOCH_3$ | ℓ | 216-218 |
| 20 | H | $-NO_2$ | $CH_3$ | H | $NHCOCH_3$ | ℓ | 151.5-152.5 |
| 21 | H | NC- | $CH_3SO$ | H | $NHCOCH_3$ | ℓ | 158.5-160 |
| 22 | H | $-CO_2C_2H_5$ | H | H | $NHCOCH_3$ | ℓ | 135-136 |
| 23 | $CH_3$ | $-CONH_2$ | H | H | $NHCOCH_3$ | ℓ | 203-204 |
| 24 | H | $-SOCH_3$ | H | H | $NHCOCH_3$ | ℓ | 62-69 |
| 25 | J | -CHO | H | H | $NHCOCH_3$ | ℓ | 203-204 |
| 26 | H | NC- | NC- | H | $NHCOCH_3$ | ℓ | 188.5-190.0 |
| 27 | H | NC- | $-SO_2CH_3$ | H | $NHCOCH_3$ | ℓ | 222-223 |
| 28 | H | Ac | Ac | H | $NHCOCH_3$ | ℓ | 151-152 |
| 29 | H | $-NO_2$ | $C_2H_5$ | H | $NHCOCH_3$ | ℓ | 155-156 |
| 30 | H | $-NO_2$ | n-$C_3H_7$ | H | $NHCOCH_3$ | ℓ | 132.5-133.5 |
| 31 | H | $-SO_2CH_3$ | $-CO_2C_2H_5$ | H | $NHCOCH_3$ | ℓ | 151.5-152.5 |
| 32 | H | $-SOCH_3$ | $-CO_2C_2H_5$ | H | $NHCOCH_3$ | ℓ | 95-99 |
| 33 | H | $-NO_2$ | $CF_3$ | $CH_3$ | NHCO-  | ℓ | |
| 34 | H | NC- | $-SO_2CH_3$ | F | $NHCO_2CH_3$ | ℓ | |

Table II

| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_7$ | B | isomer | m.p.(°C) |
|---|---|---|---|---|---|---|---|
| 35 | H | Ac | Ac | OH | $NHSOCH_3$ | ℓ | |
| 36 | H | $-NO_2$ | $C_2H_5$ | $C_2H_5$ | $N_3$ | ℓ | |
| 37 | H | NC- | NC- | H | $NCH_3COCH_3$ | ℓ | |

Example 22

Preparation of (ℓ)-N-[3-[4-(E-2-Carboethoxyethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = R_3 = R_7 = H$, $R_2 = -CO_2C_2H_5$, $B = NHCOCH_3$)

To a slurry of 0.175 g (4.38 mmol) of sodium hydride (60% dispersion in mineral oil) in 10 mL of DMF was added 0.984 g (4.38 mmol) of triethyl phosphonoacetate dropwise at 0 to 5 °C over a period of 15 minutes. The mixture was stirred for 30 minutes after the evolution of hydrogen subsided, and 1 g (3.8 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide was added in one portion. The reaction was allowed to warm to room temperature and stirred overnight. About 5 mL of ice water was added, the mixture was concentrated under reduced pressure and the residue was recrystallized from an isopropanol-methylene chloride mixture to give 0.25 g (22%) of (ℓ)-N-[3-[4-(E-2-carboethoxyethenyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide as a colorless solid, m.p. 135.0-136.0 °C.

Example 23

Preparation of (ℓ)-N-[3-[4-(E-1-Methyl-2-carbamidoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = CH_3$, $R_2 = -CONH_2$, $R_3 = R_7 = H$, $B = NHCOCH_3$)

The copper (O) catalyst was prepared by the procedure described in Ravindranathan et. al., J. Org. Chem., 47, 4812 (1982). A mixture containing 6.0 g of the copper (O) catalyst, 4.8 g (16 mmol) of (ℓ)-N-[3-[4-(E-1-methyl-2-cyanoethenyl)phenyl-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = CH_3$, $R_2 = CN$, $R_3 = R_7 = H$, $B = NHCOCH_3$), 100 mL of water and 100 mL of glyme was heated under reflux under nitrogen atmosphere for 8 hours. The catalyst was removed by filtration while still hot, and the filtrate was concentrated under reduced pressure to give a white solid which was purified by flash column chromatography on silica gel to give 3.98 g (78%) of (ℓ)-N-[3-[4-(E-1-methyl-2-carbamidoethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-acetamide, m.p. 203.0-204.0 °C.

Example 24

Preparation of (ℓ)-N-[3-[4-(2-Methylsulfenylethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = R_3 = R_7 = H$, $R_2 = -SOCH_3$, $B = NHCOCH_3$)

To a solution of 1.22 g (5.72 mmol) of methylsulfenylmethyldiethylphosphonate [prepared by the procedure in M. Nikolajczyk and A. Zaotorski, Synthesis, 669 (1973)] in 10 mL of THF cooled at -78° C was added 3.57 mL (5.72 mmol) of n-butyllithium (1.6 M in hexane). After stirring for 2 hours, 1.5 g (5.72 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide dissolved in THF was added dropwise and stirred for 3 hours after the addition was complete. The mixture was then allowed to warm to room temperature and stirred for several more hours. The solvent was removed under reduced pressure and the resulting residue was dissolved in water and extracted thoroughly with methylene chloride. After drying, the solvent was removed and the crude residue was purified by flash column chromatography on silica gel to give 275 mg (15%) of (ℓ)-N-[3-[4-(2-methylsulfenylethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide as a colorless solid, m.p. 62-69° C.

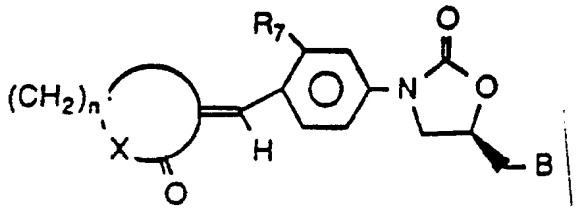
Example 25

Preparation of (ℓ)-N-[3-[4-(E-2-Formylethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; $R_1 = R_3 = R_7 = H$, $R_2 = CHO$, $B = NHCOCH_3$)

To 5 g (11.6 mmol) of (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide in 200 mL of glyme was added 7.5 mL of 1.55 M n-BuLi at 0° C, then the mixture was stirred at room temperature for 1 hour. To the mixture was added 3 g (11.4 mmol) of (ℓ)-N-[3-(4-formylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide in one portion at 0° C, slowly heated to reflux for 1 hour and stirred at room temperature overnight. The resulting dark brown, almost clear solution with small amount of brown gum at the bottom was stripped, triturated with ether followed by water and dissolved in 100 mL of acetone. Ten drops of 6 M HCl was added to the solution and stirred at room temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure, triturated with water to give a tan/brown solid which was treated with 10 mL of acetonitrile (not very soluble) and diluted with 100 mL of ether to give 0.99 g of a tan solid. It was recrystallized once from 20 mL of acetonitrile (with activated charcoal) to give 0.71g (22%) of (ℓ)-N-[3-[4-(E-2-formylethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide as light tan needles, m.p. 203-204° C.

By using the procedure of Example 25, the following compounds shown in Table III can be prepared.

Table III



| Ex. | $R_7$ | B | n, X | isomer | m.p.(°C) |
|---|---|---|---|---|---|
| 38 | H | $NHCOCH_3$ | 2, $CH_2$ | E, ℓ | 207-208 |
| 39 | $CH_3$ | $NHCOCH_3$ | 3, $CH_2$ | E, ℓ | |
| 40 | H | $NHCOCH_3$ | 3, $CH_2$ | E, ℓ | 118-121 |
| 41 | H | $NHCOCH_3$ | 2, O | E, ℓ | 119-122 |
| 42 | OH | $NHCOCH_3$ | 3, O | E, ℓ | |
| 43 | H | $NHCOCH_3$ | 4, O | E, ℓ | |
| 44 | H | $NHCOCH_3$ | 2, S | E, ℓ | |
| 45 | $CH_3$ | $NH_2$ | 3, S | E, ℓ | |
| 46 | F | $NHCOCH_3$ | 4, S | E, ℓ | |
| 47 | H | $NHCOCH_3$ | 2, NH | E, ℓ | |
| 48 | $CH_3$ | $NHCOCH_3$ | 3, NH | E, ℓ | |
| 49 | OH | $NHCOCH_3$ | 4, NH | E, ℓ | |
| 50 | H | NHCO- | 2, $CH_2$ | E, ℓ | |
| 51 | $CH_3$ | $NHCO_2CH_3$ | 3, O | E, ℓ | |
| 52 | $C_2H_5$ | $NHSOCH_3$ | 2, $CH_2$ | E, ℓ | |
| 53 | F | $NHSOCH_3$ | 3, O | E, ℓ | |
| 54 | OH | $N_3$ | 2, S | E, ℓ | |
| 55 | H | $N_3$ | 3, $NCH_3$ | E, ℓ | |
| 56 | H | $N_3$ | 4, $CH_2$ | E, ℓ | |
| 57 | H | $N_3$ | 4, O | E, ℓ | |

Example 58

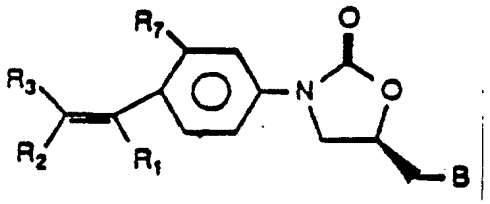
Preparation of (ℓ)-N-[3-[4-E-1-Methyl-2-carbomethoxyethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I, $R_1 = CH_3$, $R_2 = CO_2CH_3$, $R_3 = R_7 = H$, $B = NHCOCH_3$)

To a mixture containing 3g (11.4 mmol) of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide, 10 mL of triethylamine and 30 mL of THF under reflux was added 4 mL of methyl crotonate and

0.86 g of diacetobis(triphenyl-phosphine)palladium(II). After stirring overnight, the mixture was cooled to room temperature, diluted with ether, filtered through a bed of celite. The filtrate was concentrated under reduced pressure, the residue was taken up into methylene chloride and diluted with hexane to precipitate the crude product. The crude product was recrystallized from a methylene chloride-hexane mixture to give 1.0 g (26%) of (ℓ)-N-[3-[4-E-1-methyl-2-carbomethoxyethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide as a white solid, m.p. 173-178° C.

By using the procedure described in Example 58, the following compounds in Table IV were prepared or can be prepared.

Table IV



| Ex. | $R_1$ | $R_2$ | $R_3$ | $R_7$ | B | isomer | m.p.(°C) |
|---|---|---|---|---|---|---|---|
| 58 | $CH_3$ | $CO_2CH_3$ | H | N | $NHCOCH_3$ | ℓ | 173-178 |
| 59 | H | $CO_2CH_3$ | H | H | $NHCOCH_3$ | ℓ | 183-185 |
| 60 | H | $COCH_3$ | H | H | $NHCOCH_3$ | ℓ | 175-178 |
| 61 | H | $CON(CH_3)_2$ | H | H | $NHCOCH_3$ | ℓ | 228 dec |
| 62 | H | $CONH_2$ | H | H | $NHCOCH_3$ | ℓ | 249-250 dec |
| 63 | $CH_3$ | $CO_2CH_3$ | H | $CH_3$ | $NH_2$ | ℓ | |
| 64 | $CH_3$ | $CONH_2$ | H | $C_2H_5$ | $NHCO_2CH_3$ | ℓ | |
| 65 | $CH_3$ | $COCH_3$ | H | F | $NHSOCH_3$ | ℓ | |
| 66 | $CH_3$ | $CO_2CH_3$ | H | OH | $NCH_3COCH_3$ | ℓ | |
| 67 | $CH_3$ | $CO_2CH_3$ | H | H | $N_3$ | ℓ | |

Example 68

Preparation of (ℓ)-N-[3-[4-(3-oxo-1-cyclohexen-1-yl)phenyl)]-2-oxooxazolidin-5-ylmethyl]acetamide (I, $R_1$-$R_2 = (CH_2)_3CO$, $R_3 = R_7 = H$, $B = NHCOCH_3$)

Part A: Preparation of (ℓ)-N-[3-[4-(3-Dimethylamino-1-oxopropyl)phenyl]-2-oxooxazolidin-5-yl-methyl]-acetamide

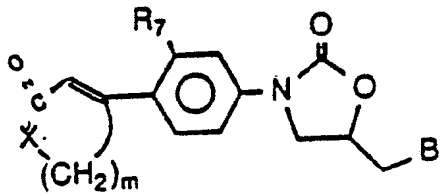
To 20 mL of trifluoroacetic acid at 0-5° C under nitrogen in an ice-bath was added 2.70 mL of N,N,N′,N′-tetramethyldiaminomethane and then 5.0 g of (ℓ)-N-[3-[4-(1-oxoethyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide. The mixture was allowed to warm to room temperature, then heated at 50° C for 24 hours. The mixture was cooled to room temperature and diluted with water and adjusted to pH 7 by addition of 5% $NaHCO_3$ solution. The product was extracted into ethyl acetate which was dried($MgSO_4$) and evaporated in vacuo to give 3.30 g (55%) of the product.

PART B

To 0.48 g of 50% sodium hydride in mineral oil (washed free of the oil by decantation with petroleum ether) under nitrogen was added 10 mL of glyme and then by pipette 1.10 mL of methyl acetoacetate. The mixture was stirred until hydrogen evolution ceased and all the sodium hydride had reacted, and then treated with a solution of 3.33 g of the product from Part A in 15 mL of glyme and the mixture was heated under reflux; after about 15 minutes, a bright yellow precipitate formed. The mixture was diluted with an equal volume of dry acetonitrile and heated under reflux overnight. The mixture was acidified with acetic acid and then the glyme was removed in vacuo. The residue was dissolved in ethyl acetate, filtered to remove insoluble material, which was washed with water, dried and purified by recrystallization from ethanol to give 0.15 g (5%) of (ℓ)-N-[3-[4-(3-oxo-1-cyclohexen-1-yl)phenyl-2-oxooxazolidin-5-ylmethyl]acetamide, m.p. 205.5-207° C, d.

By using the procedure described in Example 68 and synthesis Schemes 4-7, the following compounds can be prepared.

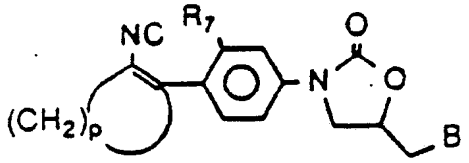
Table V




| Ex. | $R_7$ | B | X, m | isomer | m.p.(°C) |
|---|---|---|---|---|---|
| 68 | H | $NHCOCH_3$ | $CH_2$, 2 | ℓ | 205.5-207 |
| 69 | H | $NHCOCH_3$ | $CH_2$, 1 | ℓ | |
| 70 | OH | $NHCOCH_3$ | $CH_2$, 1 | ℓ | |
| 71 | F | $NHCOCH_3$ | $CH_2$, 1 | ℓ | |
| 72 | H | $NHCOCH_3$ | O, 1 | ℓ | |
| 73 | H | $NHCOCH_3$ | O, 2 | ℓ | |
| 74 | H | $NHCOCH_3$ | O, 3 | ℓ | |
| 75 | $CH_3$ | $NHSOCH_3$ | S, 1 | ℓ | |
| 76 | $C_2H_5$ | $NHCO_2CH_3$ | S, 2 | ℓ | |
| 77 | OH | $N_3$ | S, 3 | ℓ | |
| 78 | H | NHCO-◁ | NH, 1 | ℓ | |
| 79 | H | $NCH_3COCH_3$ | NH, 2 | ℓ | |
| 80 | H | $NHCOCH_3$ | NH, 3 | ℓ | |
| 81 | F | $NH_2$ | NH, 1 | ℓ | |
| 82 | OH | $NHCOCH_3$ | NH, 2 | ℓ | |

By using the procedure described in synthesis discussion Scheme 8, the following compounds can be prepared.

Table VI



(XXII, p=3, 4 or 5)

| Ex. | $R_7$ | B | p | isomer | m.p.(°C) |
|---|---|---|---|---|---|
| 83 | H | $NHCOCH_3$ | 3 | ℓ | |
| 84 | H | $NHCOCH_3$ | 4 | ℓ | |
| 85 | H | $NHCOCH_3$ | 5 | ℓ | |
| 86 | $CH_3$ | $NHCO_2CH_3$ | 3 | ℓ | |
| 87 | OH | $NHSOCH_3$ | 4 | ℓ | |
| 88 | F | $N_3$ | 5 | ℓ | |
| 89 | $C_2H_5$ | $NH_2$ | 3 | ℓ | |
| 90 | H | $NCH_3COCH_3$ | 4 | ℓ | |

Dosage Forms

The antibacterial agents of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carried selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and the effect desired. Usually a daily dosage of active ingredient can be about 5 to 20 milligrams per kilogram of body weight. Ordinarily, when the more potent compounds of this invention are used, 5 to 15, and preferably 5 to 7.5 milligrams per kilogram per day, given in divided doses 2 to 4 times a day or in sustained release form, is effective to obtain desired results. These drugs may also be administered parenterally.

Projected therapeutic levels in humans should be attained by the oral administration of 5-20 mg/kg of body weight given in divided doses two to four times daily. The dosages may be increased in severe or life-threatening infections.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, manitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to

make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidants such as sodium bisulfate, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

## Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 75 milligrams of powdered active ingredient, 150 milligrams of lactose, 24 milligrams of talc, and 6 milligrams of magnesium stearate.

## Soft Gelatin Capsules

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 75 milligrams of the active ingredient. The capsules are washed and dried.

## Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 75 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 250 milligrams for microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

## Injectables

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

## Suspensions

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 75 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

Utility

Test results indicate that the novel compounds of this invention are biologically active against gram positive bacteria including multiply antibiotic resistant strains of staphylococci and streptococci. These agents are potentially useful for the treatment of both human and animal bacterial infections including diseases of the respiratory, gastrointestinal genito-urinary systems; blood; interstitial fluids; and soft tissues.

As shown in Table VII compounds of formula I exert an in vitro antibacterial effect. A standard microdilution method (National Committee for Clinical Standards. Tentative standard M7-T. Standard methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, PA. 1982) with Mueller-Hinton broth is used to determine the 24-hour minimal inhibitory concentrations (MIC's) for test strains of Staphylococcus aureus and Escherichia coli.

The in vivo potency of these compounds is exemplified by the data summarized in Table VIII. Determinations of in vivo efficacy are performed by inoculating mice intraperitoneally with cultures of the infecting organism diluted to produce 100% mortality in control animals within twenty-four hours. The culture of S. aureus used to infect the animals was diluted to the required bacterial density using 5% aqueous hog gastric mucin. The compounds are dissolved or suspended in 0.25 % aqueous Methocel® (Methocel®: Hydroxypropyl Methylcellulose, E15 Premium, Dow Chemical Company) for oral administration or sterile distilled water containing 5% dimethylsulfoxide (Fisher Scientific Company, Fairlawn, NJ) for subcutaneous administration. The mice are dosed at one hour and at four hours post-infection. Mortality is recorded daily until test termination seven days post infection. The number of survivors in each treatment group on the seventh day after infection is used in the calculation of the $ED_{50}$, the dose of compound that protects 50% of the mice (Litchfield, J.T. and Wildoxon. A simplified method for evaluating dose-effect experiments. J. Pharmacol Exp. Ther., 96:99-113, 1949).

Table VII

In Vitro Broth Microdilution Minimal Inhibitory Concentrations (MIC's)

| Ex. No. | Minimum Inhibitory Concentration (µg/mL) | |
|---|---|---|
| | Staphylococcus aureus | Escherichia coli |
| 1 | 1 | >128 |
| 2 | 4 | >128 |
| 3 | 2 | >128 |
| 5 | 32 | >128 |
| 6 | >128 | >128 |
| 7 | 1 | >128 |
| 8 | 2 | >128 |
| 9 | 2 | >128 |
| 11 | 8 | >128 |
| 12 | 1 | >128 |
| 13 | 8 | >128 |
| 19 | 8 | >128 |
| 20 | 0.1 | >128 |
| 21 | 4 | >128 |
| 22 | 8 | >128 |
| 23 | 4 | >128 |
| 24 | 8 | >128 |
| 25 | 0.5 | >128 |
| 26 | 16 | >128 |
| 27 | 16 | >128 |
| 28 | 16 | >128 |
| 29 | 1 | >128 |
| 30 | 4 | >128 |
| 31 | 16 | >128 |
| 32 | 16 | >128 |

Table VII continued)

| Ex. No. | Minimum Inhibitory Concentration (µg/mL) | |
|---|---|---|
| | Staphylococcus aureus | Escherichia coli |
| 58 | 2 | >128 |
| 59 | 8 | >128 |
| 60 | 4 | >128 |
| 61 | 32 | >128 |
| 62 | 32 | >128 |
| 68 | 0.5 | >128 |

Table VIII

In Vivo Activity of Compounds Against Staphylococcus Aureus in an Acute Lethal Mouse Model

| Ex. No. | $ED_{50}$ (mg/kg) | |
|---|---|---|
| | Oral Administration | Subcutaneous Administration |
| 1 | 1.3 | 0.8 |
| 2 | 3.5 | 2.8 |
| 3 | 6.4 | 5.1 |
| 5 | >90 | >90 |
| 6 | NT | NT |
| 7 | 3.1 | 2.1 |
| 8 | >90 | >90 |
| 9 | 3.8 | 2.5 |
| 11 | NT | NT |
| 12 | 2.9 | 1.9 |
| 13 | NT | NT |
| 19 | >90 | >90 |
| 20 | 14.1 | 9.1 |
| 21 | >90 | 11.8 |
| 22 | >90 | >90 |
| 23 | 26.4 | 36.2 |
| 24 | 33.3 | 14.6 |
| 25 | >80 | >80 |
| 26 | >90 | >90 |
| 27 | >90 | >90 |
| 28 | >90 | >90 |
| 29 | >90 | >90 |
| 30 | >90 | >90 |
| 31 | >90 | >90 |
| 32 | >90 | >90 |
| 58 | NT | 46.2 |
| 59 | NT | >90 |

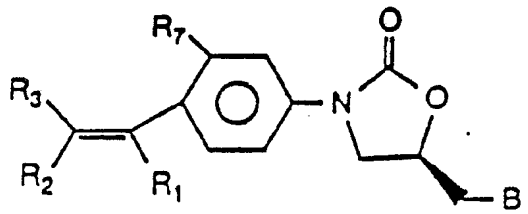
Table VIII (continued)

| Ex. No. | $ED_{50}$ (mg/kg) | |
|---|---|---|
| | Oral Administration | Subcutaneous Administration |
| 60 | NT | 51.9 |
| 61 | NT | 39.5 |
| 62 | NT | 20.4 |
| 68 | 2.4 | 1.7 |

NT = Not Tested

## Claims

1. A compound having the formula:

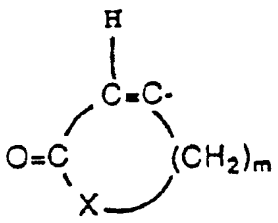


(I)

wherein for the ℓ isomer or racemic mixtures containing it

B is $NH_2$, $-N(R_4)-C(=O)-R_5$, $-N(R_4)-S(O)_uR_6$, or $N_3$

u is 1 or 2;
$R_4$ is H, alkyl of 1-10 carbon atoms, or cycloalkyl of 3-8 carbon atoms;
$R_5$ is H, alkyl of 1-4 carbon atoms optionally substituted with one or more halogen atoms, alkenyl of 2-4 carbon atoms, cycloalkyl of 3-4 carbon atoms, phenyl; $OR_5$, or $CH_2OR_4$;
$R_6$ is alkyl of 1-4 carbon atoms optionally substituted with one or more halogen atoms:
$R_7$ is H, $CH_3$, $C_2H_5$, F or OH;
$R_1$ independently is H, $CF_3$ alkyl of 1-3 carbon atoms optionally substituted with one halogen, phenyl, or phenyl optionally substituted with one or more halogen atoms, or taken together with $R_2$ forms a 5-, 6-, or 7-membered ring of the formula:

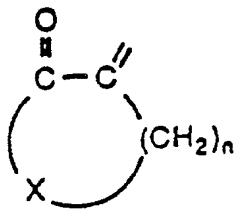


or

$-(CH_2)_p-$ when $R_3$ is an electron-withdrawing group;

$R_2$ and $R_3$ independently are an electron-withdrawing group, H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, or phenyl, provided at least one of $R_2$ or $R_3$ is an electron-withdrawing group, or

$R_2$and $R_3$ taken together form a 5, 6 or 7-membered ring of the formula:



m is 1, 2 or 3;

n is 2, 3 or 4;

p is 3, 4 or 5; and

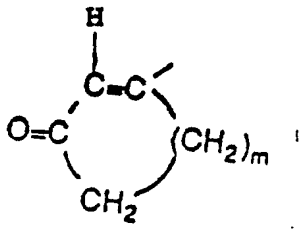
X is $CH_2$, O, S, or NR where R is H or alkyl of 1-5 carbon atoms;

or a pharmaceutically suitable salt thereof.

2. A compound of Claim 1 wherein B is

$-NHCR_5$ where $R_5$ is H, $CH_3$, $OR_6$, $CHCl_2$, $CH_2Cl$, $CH_2OH$ or $CH_2OCH_3$ where $R_6$ is defined in Claim 1.

3. A compound of Claim 1 wherein $R_1$ independently is H or alkyl of 1-3 carbon atoms, or is taken together with $R_2$ to form a 5- or 6-membered ring of the formula:



where m is 1 or 2.

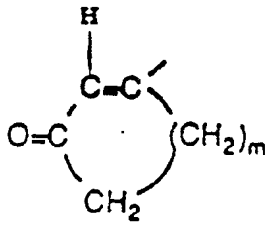
4. A compound of Claim 1 wherein $R_2$ independently is an electron-withdrawing group.

5. A compound of Claim 1 wherein $R_3$ independently is H, alkyl of 1-3 carbon atoms, or phenyl.

6. A compound of Claim 1 wherein:

(a) B is $-NHCR_5$ where $R_5$ is H, $CH_3$, $OR_6$, $CHCl_2$, $CH_2Cl$, $CH_2OH$ or $CH_2OCH_3$ where $R_6$ is defined in Claim 1.

(b) $R_1$ independently is is H or alkyl of 1-3 carbon atoms, or is taken together with $R_2$ to form a 5- or 6-membered ring of the formula:



where m is 1 or 2.

(c) $R_2$ independently is an electron-withdrawing group.

(d) $R_3$ independently is H, alkyl of 1-3 carbon atoms, or phenyl.

7. A compound of Claim 1 wherein B is

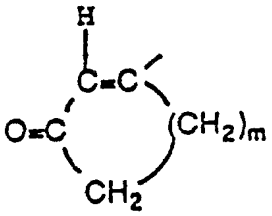
8. A compound of Claim 1 wherein $R_2$ independently is CN or $NO_2$.

9. A compound of Claim 1 wherein $R_3$ independently is H, $CH_3$ or $C_2H_5$.

10. A compound of Claim 1 wherein:

(a) B is

(b) $R_1$ independently is H, $CH_3$ or $C_2H_5$, or is taken together with $R_2$ to form a 5- or 6-membered ring of the formula:



where m is 1 or 2;

(c) $R_2$ independently is CN or $NO_2$; and

(d) $R_3$ independently is H, $CH_3$ or $C_2H_5$.

11. Compounds of Claims 1 to 10 selected from:

(ℓ)-N-[3-[4-(E-1-methyl-2-cyanoethenyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;

(ℓ)-N-[3-[4-(3-oxo-1-cyclohexen-1-yl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;

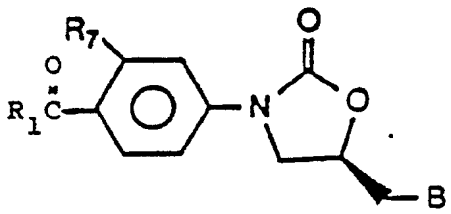
(ℓ)-N-[3-[4-(E-2-nitroethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide; and

(ℓ)-N-[3-[4-(E-1-methyl-2-nitroethenyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

12. A pharmaceutical composition containing essentially of a pharmaceutically suitable carrier and an antibacterial effective amount of a compound of any one of claims 1 to 11.

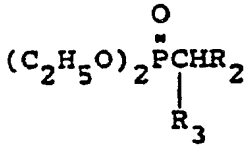
13. A process for preparing a compound of Claim 1 comprising:

(a) reacting a compound of the formula:

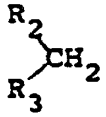


(II)

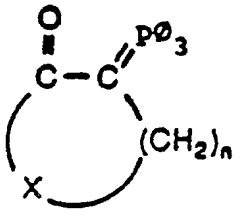
wherein B is as described in Claim 1 provided $R_5$ is not one carbon atom substituted with one or more halogen atoms; and
$R_7$ is H, $CH_3$, $C_2H_5$, F or OH;
with (1) when $R_1$ in (II) independently is H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, or phenyl, phosphonate of the formula:



wherein $R_2$ and $R_3$ independently are H, $CF_3$, alkyl of 1-3 carbon atoms optionally substituted with one halogen, phenyl, or CN, provided that only one of $R_2$ and $R_3$ is CN; or
(2) when $R_1$ in (II) is H, a compound of the formula:



where $R_2$ and $R_3$ independently are both electron-withdrawing groups except that when one of $R_2$ or $R_3$ is $NO_2$, the other group can be an electron-withdrawing group, including another $NO_2$ group, or H, $CF_3$, alkyl optionally substituted with one or more halogen atoms, or phenyl; or
(3) when $R_1$ in (II) is H, a cyclic ylide of the formula:



where x and n are as defined in Claim 1.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 88 11 7304

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.4) |
|---|---|---|---|
| D,X | EP-A-0 127 902 (DU PONT DE NEMOURS) * Claims * --- | 1-13 | C 07 D 263/20<br>C 07 D 413/10<br>A 61 K 31/42 |
| D,X | EP-A-0 184 170 (DU PONT DE NEMOURS) * Claims * --- | 1-13 | |
| D,A | US-A-3 687 965 (C.P. FAURAN) * Whole document * --- | 1,12 | |
| D,A | FR-A-2 500 450 (DELALANDE) * Claims * ----- | 1,12 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 263/00
C 07 D 413/00

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 08-12-1988 | HENRY J.C. |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 350 002 A1**

(12) # EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: 89112263.2

(22) Anmeldetag: 05.07.89

(51) Int. Cl.4: C07F 9/38 , A61K 31/66 , C07F 9/60 , C07F 9/572 , C07F 9/650 , C07F 9/59 , C07F 9/650 , C07F 9/654 , C07F 9/653

(30) Priorität: 05.07.88 DE 3822650

(43) Veröffentlichungstag der Anmeldung: 10.01.90 Patentblatt 90/02

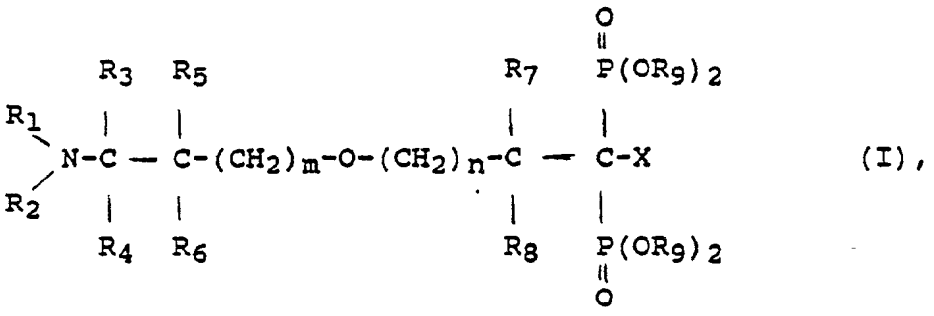
(84) Benannte Vertragsstaaten: AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Anmelder: BOEHRINGER MANNHEIM GMBH
Sandhofer Strasse 116
D-6800 Mannheim 31(DE)

(72) Erfinder: Bosies, Elmar, Dr. phil.nat.
Delpstrasse 11
D-6940 Weinheim(DE)
Erfinder: Zilch, Harald, Dr. rer.nat.
Alsenweg 2 A
D-6800 Mannheim 31(DE)

(54) **Neue Diphosphonsäurederivate, Verfahren zu deren Herstellung und diese Verbindungen enthaltende Arzneimittel.**

(57) Verbindungen der Formel I



(I),

in der $R_1$-$R_9$, m, n und X die in den Ansprüchen angegebene Bedeutung haben,
Verfahren zu ihrer Herstellung sowie Arzneimittel, die diese Verbindungen enthalten, zur Behandlung von Calciumstoffwechselstörungen.

EP 0 350 002 A1

# Neue Diphosphonsäurederivate, Verfahren zu deren Herstellung und diese Verbindungen enthaltende Arzneimittel

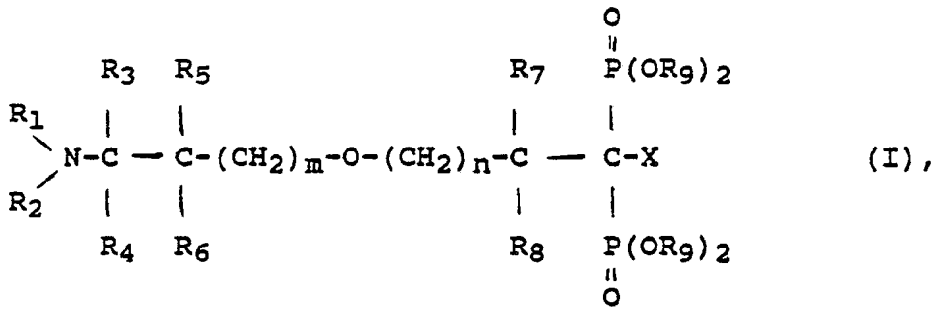
Die vorliegende Erfindung betrifft neue Diphosphonsäurederivate, Verfahren zu deren Herstellung sowie Arzneimittel, die diese Substanzen enthalten.

In der DE-PS 18 13 659 sind Diphosphonsäurederivate beschrieben, von denen die 1-Hydroxyethan-1,1-diphosphonsäure als Mittel zur Behandlung von Morbus Paget Bedeutung erlangt hat.

In der DE-PS 25 34 391 sind Aminoalkan-1,1-diphosphonsäuren, die am Stickstoffatom mit $C_1$-$C_3$-Alkylgruppen substituiert sein können, mit einer Wirkung auf den Calciumstoffwechsel beschrieben.

Überraschenderweise wurde nun gefunden, daß Aminoalkan-1,1-diphosphonsäuren, bei denen die Alkylkette durch ein Sauerstoffatom unterbrochen ist, eine deutlich ausgeprägtere Wirkung auf den Calciumstoffwechsel zeigen als die bisher bekannten Verbindungen. Diese Substanzen sind somit besonders zu einer breiten Behandlung von Calciumstoffwechselstörungen geeignet. Sie lassen sich vor allem sehr gut dort einsetzen, wo der Knochenauf- und -abbau gestört ist, d.h. sie sind geeignet zur Behandlung von Erkrankungen des Skelettsystems wie z.B. Osteoporose, Morbus Paget, Morbus Bechterew u.a.. Aufgrund dieser Eigenschaften finden sie aber auch Verwendung in der Therapie von Knochenmetastasen, der Urolithiasis und zur Verhinderung heterotoper Ossifikationen. Durch ihre Beeinflussung des Calciumstoffwechsels bilden sie weiterhin eine Grundlage für die Behandlung der rheumatoiden Arthritis, der Osteoarthritis und der degenerativen Arthrose.

Gegenstand der vorliegenden Erfindung sind demnach Diphosphonate der allgemeinen Formel I



(I),

in der

$R_1$ und $R_2$ jeweils unabhängig voneinander Wasserstoff, eine geradkettige oder verzweigte, gesättigte oder ungesättigte Alkylkette mit 1-9 Kohlenstoffatomen, die gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkoxy oder $C_1$-$C_5$ Alkylthio, einen Phenyl- oder einen $C_5$-$C_7$ Cycloalkylring substituiert sein kann, wobei der Phenylring gegebenenfalls durch $C_1$-$C_5$ Alkyl, $C_1$-$C_5$ Alkoxy, Hydroxy oder Halogen substituiert sein kann, einen $C_5$-$C_7$ Cycloalkyl-oder den Phenylrest,

$R_3$ = Wasserstoff, niederes geradkettiges oder verzweigtes $C_1$-$C_5$ Alkyl, das gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkoxy, $C_1$-$C_5$ Alkylthio, Mercapto, Phenyl, 3-Indolyl oder 4-Imidazolyl substituiert sein kann, oder gebenenfalls durch Hydroxy oder $C_1$-$C_5$ Alkoxy substituiertes Phenyl,

$R_4$, $R_6$, $R_8$ und $R_9$ jeweils unabhängig voneinander Wasserstoff oder $C_1$-$C_5$ Alkyl,

$R_5$ und $R_7$ jeweils unabhängig voneinander Wasserstoff, $C_1$-$C_5$ Alkyl oder gegebenenfalls durch Hydroxy oder $C_1$-$C_5$ Alkoxy substituiertes Phenyl,

X = Wasserstoff, OH oder die Gruppe $-NR_{10}$, $R_{11}$, wobei $R_{10}$ und $R_{11}$ jeweils unabhängig voneinander Wasserstoff oder $C_1$-$C_5$ Alkyl sein soll,

m bzw. n = 0 oder 1

bedeuten, wobei

$R_1$ und $R_2$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, ein mono- oder bicyclisches Ringsystem mit 4-9 Kohlenstoffatom, das teilweise oder ganz hydriert ist und gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkyl oder $C_1$-$C_5$ Alkoxy substituiert und/oder im Falle eines Monocyclus durch ein Sauerstoff-, Stickstoff- oder Schwefelatom unterbrochen sein kann,

$R_1$ und $R_3$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, einen Fünf- oder Sechsring, der gegebenenfalls mit einem weiteren Sechsring kondensiert sein kann,

$R_1$ und $R_5$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, sowie dem

dazwischenliegenden Kohlenstoffatom einen Fünf-oder Sechsring,
$R_3$ und $R_4$ zusammen mit dem Kohlenstoffatom, and das sie gebunden sind, einen Fünf- oder Sechsring,
$R_4$ und $R_6$ zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Fünf- oder Sechsring,
$R_5$ und $R_6$ zusammen mit dem Kohlenstoff, an das sie gebunden sind, einen Fünf- oder Sechsring,
$R_7$ und $R_8$ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen Fünf- oder Sechsring bilden können,
sowie deren pharmakologisch unbedenkliche Salze.

Unter $C_1$-$C_5$ Alkyl sind vorzugsweise die Methyl-, Ethyl-, Isopropyl und Isobutylgruppe zu verstehen. $C_1$-$C_5$ Alkoxy- bzw. Alkylthio sollen bevorzugt die Methoxy-bzw. Methylthiogruppe sein.

Bei dem $C_5$-$C_7$ Cycloalkylrest handelt es sich bevorzugt um den Cyclohexylrest.

Halogen soll insbesondere Chlor oder Brom darstellen.

Bei der bei $R_1$ und $R_2$ angeführten Alkylkette mit 1-9 Kohlenstoffatomen handelt es sich vorzugsweise um die Metyl-, Ethyl-, Isopropyl-, Isobutyl-, sec-Butyl-, n-Pentyl-, n-Nonyl, Allyl- und Methallylgruppe.

Unter der durch einen gegebenenfalls subtituierten Phenylring substituierten Alkylgruppe versteht man insbesondere eine Benzylgruppe.

Bei Gruppe $-NR_{10}R_{11}$ handelt es sich bevorzugt um die Amino-, Dimethylamino- bzw. Diethylaminogruppe.

Falls $R_1$ und $R_2$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Ring bilden, versteht man hierunter bevorzugt einen Pyrrolidin-, Piperidin-, Di- bzw. Octahydroisoindolin- oder Decahydrochinolinring. Ein durch ein Heteroatom unterbrochener Ring stellt insbesondere einen Piperazin-, Morpholin-, bzw. Thiamorpholinring dar.

Im Falle, daß $R_1$ und $R_3$ zusammen mit dem Kohlenstoff-bzw. Stickstoffatom, an das sie gebunden sind, einen Ring bilden, ist hierunter ein in 2-Stellung substituierter Pyrrolidin-, Piperidin- oder Octahydroindolring zu verstehen.

Wenn $R_1$ und $R_5$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, sowie dem dazwischenliegenden Kohlenstoffatom einen Ring bilden, stellt dieser Ring vorzugsweise einen in 3-Stellung substituierten Pyrrolidin- oder Piperidinring dar.

Für den Fall, daß $R_3$ und $R_4$ bzw. $R_5$ und $R_6$ bzw. $R_7$ und $R_8$ mit dem Kohlenstoffatom, an das sie gebunden sind einen Ring bilden, ist dies bevorzugt der Spiro-Cyclopenhylring.

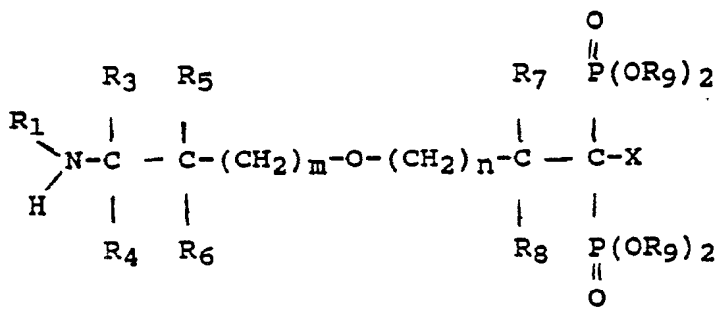
Bilden $R_4$ und $R_6$ zusammen mit den C-Atomen an die sie gebunden sind, einen Ring, so handelt es sich um den Cyclohexyl- oder Cyclopentylring.
X stellt bevorzugt Wasserstoff oder Hydroxyl dar.

Bevorzugte Verbindungen der Formel I sind Verbindungen, in denen $R_1$ Wasserstoff oder Methyl, $R_2$ Wasserstoff oder Methyl, $R_3$ Wasserstoff oder $C_1$ - $C_5$ Alkyl, $R_4$ Wasserstoff oder Methyl, $R_5$ Wasserstoff oder Methyl, $R_6$ Wasserstoff, $R_7$ Wasserstoff, $R_8$ Wasserstoff, $R_9$ Wasserstoff, m die Zahl 0 oder 1, n die Zahl O und X eine Hydroxylgruppe bedeuten,
wobei $R_1$ und $R_2$ zusammen mit dem Stickstoffatom einen Morpholin-Ring, $R_1$ und $R_3$ zusammen mit dem Stickstoffatom und dem Kohlenstoffatom, an das sie gebunden sind, einen Pyrrolidin- oder Piperidin-Ring, $R_1$ und $R_5$ zusammen mit dem Kohlenstoffatom und dem Stickstoffatom, an das sie gebunden sind, einen Piperidin-Ring, $R_4$ und $R_6$ zusammen mit den C-Atomen an das sie gebunden sind, einen Cyclohexyl-Ring und $R_5$ und $R_6$ zusammen mit dem C-Atom , an das sie gebunden sind, einen Spiro-cyclopentan-Ring darstellen.

Asymmetrische Kohlenstoffatome können die R- oder S-Konfiguration besitzen und die Verbindungen können in optisch aktiver Form oder als racemisches Gemisch vorliegen. Sie sind ebenfalls Gegenstand der Erfindung.

Verbindungen der allgemeinen Formel I werden nach an sich bekannten Verfahren dargestellt, vorzugsweise, indem man

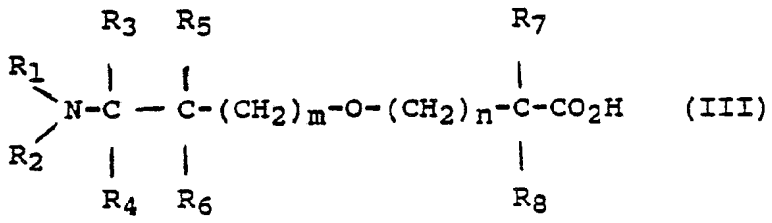
I. eine Verbindung der allgemeinen Formel II



(II),

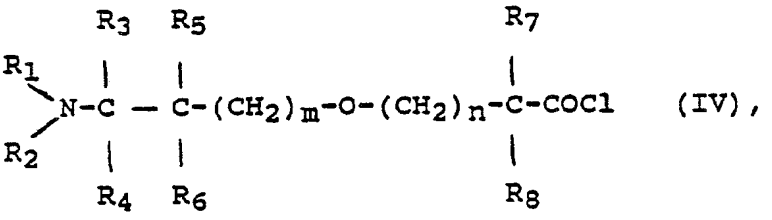
in der $R_1$, $R_3$-$R_9$, X, m und n die oben angegebenen Bedeutungen haben, mono- oder dialkyliert und gegebenenfalls die entstandenen Tetraester zu Diestern oder Säuren der allgemeinen Formel I verseift, oder

II. für den Fall, daß X in der allgemeinen Formel I OH bedeutet,
a) eine Carbonsäure der allgemeinen Formel III



(III)

in der $R_1$-$R_8$, m und n die oben angegebenen Bedeutungen haben, mit einem Gemisch aus phosphoriger Säure oder Phosphorsäure und einem Phosphorhalogenid bzw. Phosphoroxyhalogenid umsetzt und anschließend zur freien Diphosphonsäure verseift,
oder
b) ein Carbonsäurechlorid der allgemeinen Formel IV

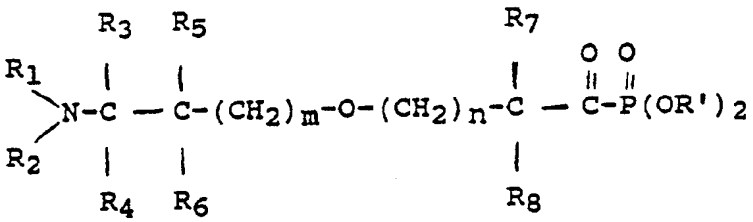


(IV),

in der $R_1$-$R_8$, m und n die oben genannten Bedeutungen haben, wobei $R_1$ auch eine Acylgruppe oder mit $R_2$ zusammen auch als Schutzgruppe den Phthaloylrest darstellen kann, mit einem Trialkylphosphit der allgemeinen Formel V

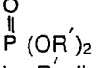
$P(OR')_3$ (V),

in der R' für Alkylreste mit 1-4 Kohlenstoffatomen, vorzugsweise Methyl, Ethyl, Isopropyl und Isobutyl steht, zu einem Acylphosphonat der allgemeinen Formel VI



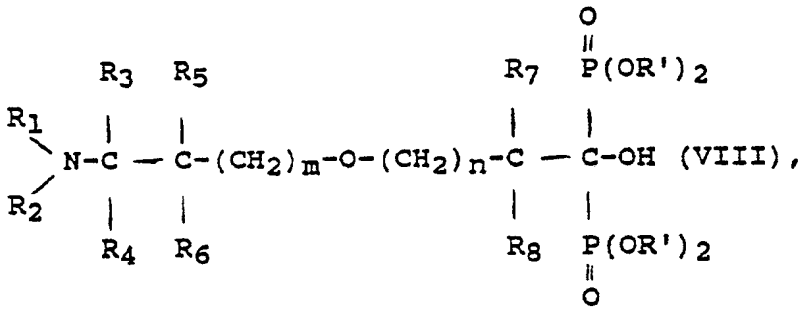
(VI),

in der $R_1$-$R_8$, m, n und $R'$ die oben genannten Bedeutungen haben, $R_1$ auch eine Acylgruppe oder mit $R_2$ zusammen auch den Phthaloylrest darstellen kann, umsetzt, anschließend mit einem Dialkylphosphit der allgemeinen Formel VII



(VII),

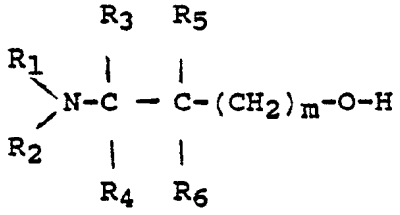
in der $R'$ die oben angegebene Bedeutung hat, zu einem Diphosphonat der allgemeinen Formel VIII



(VIII),

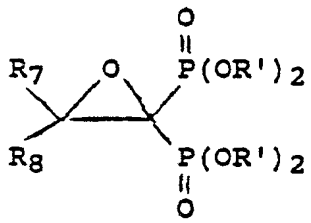
in der $R_1$-$R_8$, m, n, und $R'$ die oben angebenen Bedeutungen haben, $R_1$ auch eine Acylgruppe oder mit $R_2$ zusammen auch den Phthaloylrest darstellen kann, reagieren läßt und gegebenenfalls die Phthaloylgruppe durch Hydrazinoylse entfernt und die entstandenen Tetraester zu Diestern oder Säuren der allgemeinen Formel I verseift, wobei unter diesen Bedingungen die als Schutzgruppe verwendete Acyl- bzw. Phthaloylgruppe gleichzeitig abgespalten wird,
oder

c) für den fall, daß n = O bedeutet, eine Verbindung der allgemeinen Formel IX



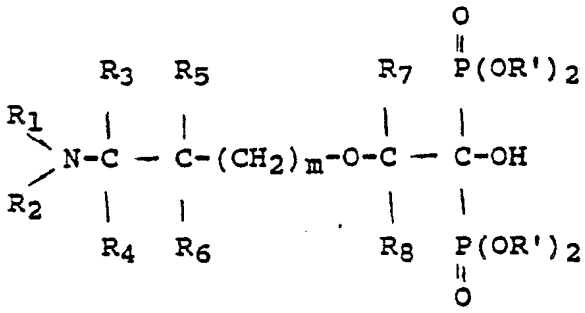
(IX),

in der $R_1$-$R_6$ und m die oben angegebenen Bedeutungen haben mit einem Epoxid der allgemeinen Formel X



(X),

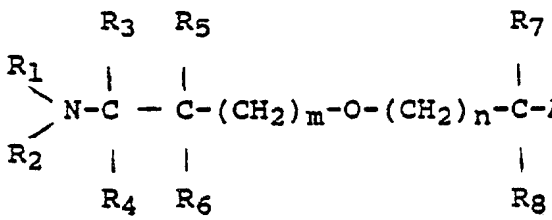
in der $R_7$, $R_8$ und $R'$ die oben angegebenen Bedeutungen haben, reagieren läßt und das entstandene. Diphosphonsäurederivat der allgemeinen Formel XI



(XI),

gewünschtenfalls zu Diestern oder Säuren verseift,
oder

III. für den Fall, daß X in der allgemeinen Formel I die Gruppe $-NR_{10}R_{11}$ bedeutet, ein Carbonsäurederivat der allgemeinen Formel XII



(XII),

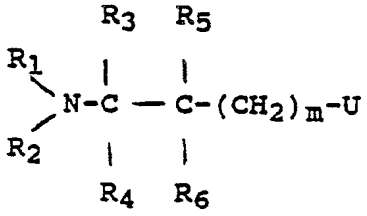
in der $R_1$-$R_8$, m und n die oben angegebenen Bedeutungen haben und A eine Nitril-, Iminoether- oder eine $-CONR_{10}R_{11}$-Gruppe, wobei $R_{10}$ und $R_{11}$ die oben angegebenen Bedeutungen haben, darstellt, mit einer Phosphorverbindung der allgemeinen Formel XIII

$PT_3$ (XIII),

in der T = Halogen, OH oder OR' bedeutet, wobei R' die oben angegebene Bedeutung hat, umsetzt und gegebenenfalls anschließend verseift,
oder

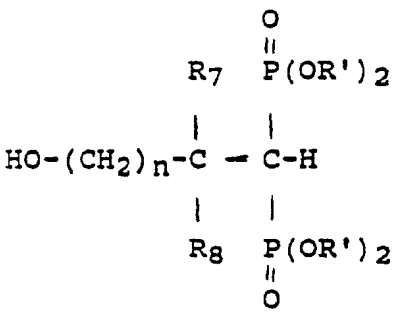
IV. für den Fall, daß X in der allgemeinen Formel I Wasserstoff bedeutet,

a) eine Verbindung der allgemeinen Formel XIV



(XIV),

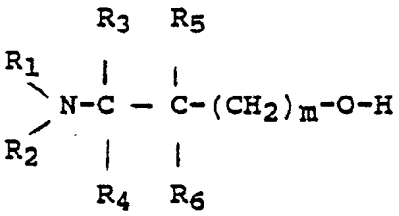
in der $R_1$-$R_6$ und m die oben angegebenen Bedeutungen haben, wobei $R_1$ auch ein Acyl- oder mit $R_2$ zusammen der Phthaloylrest sein kann, und U eine reaktive Gruppe wie z.B. Halogen oder ein Sulfonat darstellt, mit einem Diphosphonsäurederivat der allgemeinen Formel XV,



(XV),

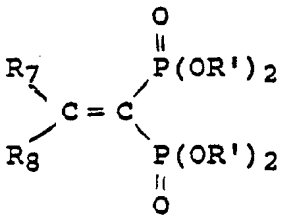
in der $R_7$, $R_8$, $R'$ und n die oben angegebenen Bedeutungen haben, reagieren läßt, und die Phthaloylgruppe gewünschtenfalls durch Hydrazinolyse entfernt und die gebildeten Tetraester gegebenenfalls zu Diestern oder Säuren verseift, wobei unter diesen Bedingungen die als Schutzgruppe verwendete Acyl- oder Phthaloylgruppe gleichzeitig abgespalten wird,
oder

b) eine Verbindung der allgemeinen Formel IX



(IX),

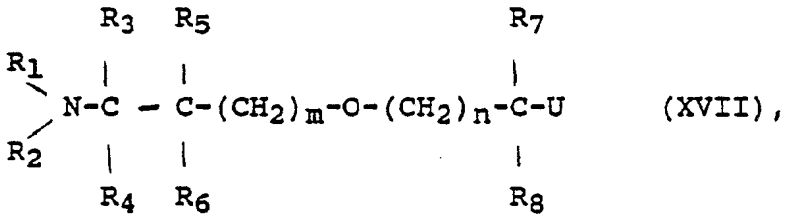
in der $R_1$-$R_6$, und m die oben angegebenen Bedeutungen haben, an eine Verbindung der allgemeinen Formel XVI



(XVI),

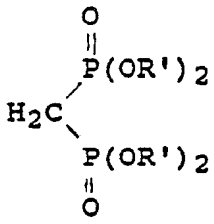
in der $R_7$, $R_8$ und $R'$ die oben angegebenen Bedeutungen haben, addiert und die entstehenden Tetraester gegebenenfalls zu Diestern oder Säuren verseift,
oder

c) eine Verbindung der allgemeinen Formel XVII



(XVII),

in der $R_1$-$R_8$, U, m und n die oben angegebenen Bedeutungen haben, wobei $R_1$ auch ein Acyl- oder mit $R_2$ zusammen der Phthaloylrest sein kann, mit einem Diphosphonsäurederivat der allgemeinen Formel XVIII



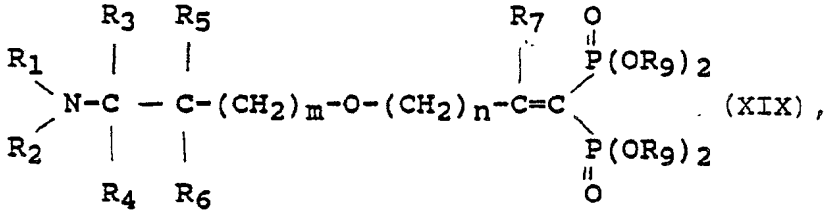
(XVIII),

in der R' die oben angegebene Bedeutung hat, umsetzt, die Phthaloylgruppe gewünschtenfalls durch Hydrazinolyse entfernt und die entstandenen Tetraester gegebenenfalls zu Diestern oder Säuren verseift, wobei unter diesen Bedingungen die als Schutzgruppe verwendete Acyl- oder Phthaloylgruppe gleichzeitig abgespalten wird

oder

für den Fall, daß $R_8$ Wasserstoff bedeutet,

d) eine Verbindung der allgemeinen Formel XIX



(XIX),

in der $R_1$-$R_7$, $R_9$, m und n die oben angegebenen Bedeutungen haben, wobei $R_1$ auch eine Acylgruppe darstellen kann, katalytisch hydriert und anschließend gegebenenfalls die entstandenen Tetraester zu Diester oder Säuren verseift, wobei dabei auch eine evtl. vorhandene Acylgruppe mit abgespalten werden kann und die freien Säuren in pharmakologisch unbedenkliche Salze überführt.

Bei der reduktiven Alkylierung (Verfahren I) behandelt man ein Gemisch aus primärem oder sekundärem Amin der allgemeinen Formel II und einer Carbonylverbindung oder deren Acetal in Gegenwart eines Hydrierungskatalysators, wie Palladium auf Kohle, oder Nickel, mit Wasserstoff unter Atmosphären- oder erhöhtem Druck oder man setzt als Reduktionsmittel Ameisensäure zu. Schließlich lassen sich Alkylierungen eines sekundären Amins der allgemeinen Formel II besonders vorteilhaft nach dem Phasentransferverfahren mit Dialkylsulfaten durchführen.

Die bei Verfahren II a) eingesetzten Carbonsäuren der allgemeinen Formel III werden mit 1-2, vorzugsweise 1.5 mol phosphoriger Säure oder Phosphorsäure und 1-2, vorzugsweise 1.5 mol Phosphortrihalogenid oder Phosphoroxyhalogenid bei Temperaturen von 80°-130°C, vorzugsweise 100-110°C umgesetzt. Man kann die Reaktion auch in Gegenwart von Verdünnungsmitteln wie Halogenkohlenwasserstoffen, insbesondere Chlorbenzol, Tetrachlorethan oder auch Sulfolan bzw. Dioxan durchführen. Die anschließende Hydrolyse erfolgt durch Kochen mit Wasser, zweckmäßigerweise jedoch mit halbkonzentrierter Salz- oder Bromwasserstoffsäure. Als Phosphortrihalogenide kommen in dem genannten Verfahren beispielsweise Phosphortrichlorid oder Phosphortribromid, als Phosphoroxyhalogenid vor allem Phosphoroxychlorid infrage.

Bei Verfahren II b) läßt man das Säurechlorid der allgemeinen Formel IV mit dem Trialkylphosphit der

allgemeinen Formel V bei Temperaturen zwischen 0 und 60 °C, vorzugsweise bei 20-40 °C zur Reaktion kommen. Man kann ohne Lösungsmittel oder auch in Gegenwart von inerten Lösungsmitteln wie Diethylether, Tetrahydrofuran, Dioxan oder auch halogenierten Kohlenwasserstoffen, wie z.B. Methylenchlorid arbeiten. Das als Zwischenprodukt entstehende Acylphosphonat der allgemeinen Formel VI kann isoliert oder direkt weiter umgesetzt werden. Die anschließende Reaktion führt man in Gegenwart einer schwachen Base, vorzugsweise einen sec. Amin wie z.B. Dibutylamin bei einer Temperatur von 0-60 °C, vorzugsweise bei 10-30 °C durch. Für den Fall, daß $R_1$ und $R_2$ zusammen als Schutzgruppe den Phthaloylrest bilden, wird dieser Rest durch Hydrazinolyse bzw. saure Hydrolyse abgespalten. Bei der Hydrazinolyse setzt man Hydrazin in Essigsäure oder auch Ethanol bei Temperaturen zwischen 20 und 80 ° ein. Die saure Hydrolyse kann sehr gut durch Kochen mit halbkonzentrierter Salzsäure durchgeführt werden. Auf diese Weise wird auch eine als Schutzgruppe verwendete Acylgruppe - vorzugsweise die Acetylgruppe - abgespalten.

Bei Verfahren II c werden die Alkohole der allgemeinen Formel IX in der Regel in Form ihrer Alkalisalze, vorzugsweise als Natriumsalze eingesetzt. Als Lösungsmittel verwendet man bevorzugt Toluol, Dioxan, Tetrahydrofuran oder auch Dimethylformamid; die Reaktionen werden zwischen 20 und 80 ° C durchgeführt.

Bei Verfahren III setzt man die Nitrile der allgemeinen Formal XII mit phosphoriger Säure bei Temperaturen von 110-180 ° C um. Die Reaktion kann ohne oder in Gegenwart von aprotischen Lösungsmitteln wie z.B. Diethylenglykoldimethylether oder Diethylenglykoldiethylether durchgeführt werden. Man kann die Nitrile jedoch auch mit einem Phosphortrihalogenid, z.B. Phosphortribromid oder Phosphortrichlorid in einem inerten Lösungsmittel wie z.B. Dioxan oder Tetrahydrofuran gegebenenfalls unter Zusatz von Wasser bei Temperaturen von 20-80 ° C zur Reaktion bringen. Iminoether der allgemeinen Formel XII läßt man mit Dialkylphosphiten vorzugsweise in Gegenwart äquimolarer Mengen Natrium in inerten Lösungsmitteln wie Diethylether, Dioxan oder auch Benzol reagieren, wobei die Umsetzungen in der Regel bei der Rückflußtemperatur des entsprechenden Lösungsmittels stattfindet. Säureamide der allgemeinen Formel XII kann man in inerten Lösungsmitteln wie z.B. halogenierten Kohlenwasserstoffen oder Ethern wie z.B. Diethylether mit einem Gemisch aus Phosphorpentahalogenid/phosphoriger Säure oder auch Oxalylchlorid/Trialkylphosphit umsetzen.

Bei Verfahren IV a) setzt man das Diphosphonsäurederivat der allgemeinen Formel XV in Form eines Natrium- oder Kaliumsalzes ein. Hierzu wird es mit Natrium, Kalium oder dem entsprechenden Hydrid in einem inerten Lösungsmittel wie z.B. Benzol, Toluol oder Dimethylformamid bei einer Temperatur von 0 bis 40 ° C, vorzugsweise bei 25 ° C umgesetzt. Das Alkalisalz wird ohne Isolierung mit dem entsprechenden Halogenid bzw. Sulfonat zur Reatkion gebracht. Die Temperatur liegt hierbei bei 20-110 ° C.

Falls $R_1$ und $R_2$ zusammen als Schutzgruppe den Phthaloylrest bilden oder $R_1$ eine Acylgruppe, vorzugsweise die Acetylgruppe darstellt, werden diese Reste wie in Verfahren II b beschrieben abgespalten.

Bei Verfahren IV b werden die Alkohole der allgemeinen Formel IX in Form ihrer Alkalisalze, vorzugsweise der Natriumsalze eingesetzt. Hierzu werden sie mit Natrium bzw. Natriumhydrid in einem inerten Lösungsmittel wie Benzol, Toluol, Dioxan oder Dimethylformamid bei einer Temperatur von 0-60 ° C, vorzugsweise bei 25 ° C umgesetzt. Das Alkalisalz wird in der Regel ohne Isolierung mit dem entsprechenden Diphosphonat der allgemeinen Formel XVI zur Reaktion gebracht. Die Temperatur liegt bei 20-80 ° C.

Bei Verfahren IV c) setzt man den Methylendiphosphonsäureester der allgemeinen Formel XVIII in Form seines Natrium-oder Kaliumsalzes ein. Hierzu wird er mit Natrium, Kalium oder dem entsprechenden Hydrid in einem inerten Lösungsmittel wie z.B. Benzol, Toluol oder Dimethylformamid bei einer Temperatur von 0 bis 40 ° C, vorzugsweise bei 25 ° C umgesetzt. Das Alkalisalz wird ohne Isolierung mit dem entsprechenden Halogenid bzw. Sulfonat zur Reaktion gebracht. Die Temperatur liegt hierbei bei 20-110°C.

Die Hydrierung bei Verfahren IV d wird in Gegenwart eines Edelmetallkatalysators wie z.B. Palladium auf Kohle oder Platin in einem Alkohol wie Methanol oder Ethanol als Lösungsmittel oder auch in Wasser durchgeführt. Man kann jedoch auch Nickel in alkalischem Medium verwenden. Die Abspaltung der N-Acylgruppe kann alkalisch, vorzugsweise jedoch sauer mit z.B. 6N Salzsäure vorgenommen werden.

Optisch aktive Verbindungen der Formel I werden in der Regel in der Weise hergestellt, daß man optisch aktive Ausgangsverbindungen einsetzt.

Die bei Verfahren II a eingesetzten Amino-oxa-alkancarbonsäuren werden in der Regel auf folgende Weise hergestellt.

Das entsprechende Aminoalkanol wird z.B. mit einem Halogenessigsäureester zu einem Amino-oxa-alkancarbonsäureester umgesetzt, der abhängig von der Kettenlänge und der Substitution am Stickstoffatom zu einem Oxalactam cyclisieren kann. Der entstandene Carbonsäureester wird nach üblichen Methoden sauer oder alkalisch verseift. Im Falle der Ringbildung wird das Lactam durch Kochen mit Bariumhydroxidlösung geöffnet und das Bariumsalz der Amino-oxa-alkancarbonsäure mit Schwefelsäure in die freie Säure überführt.

Die bei diesem Verfahren sowie auch Verfahren II c und IV b eingesetzten Aminoalkanole sind in der

Regel literaturbekannt oder lassen sich aus den entsprechenden Aminosäuren bzw. deren Ester leicht durch Reduktion mit z.B. Lithiumaluminiumhydrid herstellen.

Die bei Verfahren III verwendeten Amino-oxa-alkancarbonsäurenitrile oder Amide der Formel XII lassen sich aus den entsprechenden Aminoalkanolen der Formel IX durch Umsetzung mit Halogenessigsäurenitrilen bzw. Halogenessigsäureamiden synthetisieren. Aus den so gewonnen Nitrilen kann man nach üblichen Verfahren, z.B. durch Reaktion mit einem niederen Alkohol in Gegenwart von gasförmigem Chlorwasserstoff die entsprechenden Iminoether erhalten.

Durch Reaktion eines Aminoalkanols mit einem Phosphorhalogenid wie z.B. Phosphortrichlorid oder Phosphortribromid bzw. mit einem aliphatischen oder aromatischen Sulfochlorid, wie z.B. Methansulfochlorid oder Benzolsulfochlorid erhält man die bei Verfahren IV a eingesetzten Verbindungen der allgemeinen Formel XIV.

Die bei Verfahren IV b eingesetzten Verbindungen der allgemeinen Formel XIX können z.B. aus einer Verbindung der Formel I durch Eliminierung einer H-X-Gruppe hergestellt werden, wobei z.B. ein Halogen, vorzugsweise Brom oder Chlor, oder eine Acyloxygruppe, insbesondere die Acetoxy-oder Propionyloxygruppe, darstellt. Die Eliminierung kann durch Basen wie z.B. tert.-Amine, insbesondere Triethylamin, Pyridin oder Diazabicycloundecen, in inerten Lösungsmitteln wie Alkoholen, Ethern (z.B. Dioxan oder Tetrahydrofuran) erfolgen. Bei der Abspaltung von Essigsäure bzw. Propionsäure setzt man vorzugsweise das Tetranatrium- oder Tetrakaliumsalz der entsprechenden Diphosphonsäure ein und führt die Abspaltung durch Erhitzen auf 180-300° C, vorzugsweise 180-240° C durch. Aus dem Tetraalkalisalz kann man die freien Säuren dann z.B. durch Behandlung mit einem sauren Ionenaustauscher (z.B. Amberlite-IR 120, $H^+$-Form) freisetzen.

Die oben angeführten Ausgangsverbindungen können als Racemate oder als Enaniomere eingesetzt werden, wobei die optisch aktiven Verbindungen üblicherweise aus entsprechend optisch aktiven Aminosäuren erhalten werden.

Die bei den Verfahren gegebenenfalls anfallenden Tetraalkylester können zu Diestern oder den freien Tetrasäuren verseift werden. Die Verseifung zu Diestern geschieht in der Regel dadurch, daß man den Tetraalkylester mit einem Alkalihalogenid, vorzugsweise Natriumjodid in einem geeigneten Lösungsmittel wie z.B. Aceton bei Zimmertemperatur behandelt.

Hierbei entsteht das symmetrische Diester/Dinatriumsalz, das gegebenenfalls durch einen sauren Ionenaustauscher in die Diester/Disäure umgewandelt werden kann. Die Verseifung zu freien Diphosphonsäuren geschieht in der Regel durch Kochen mit halbkonzentrierter Salz- oder Bromwasserstoffsäure. Man kann jedoch auch eine Spaltung mit Trimethylsilylhalogenid, vorzugsweise dem Bromid oder Jodid vornehmen. Die freien Diphosphonsäuren können umgekehrt durch Kochen mit Orthoameisensäurealkylestern wieder in die Tetraalkylester überführt werden. Die freien Diphosphonsäuren der allgemeinen Formel I können als freie Säuren oder in Form ihrer Mono- oder Dialkalisalze isoliert werden. Die Alkalisalze lassen sich in der Regel durch Umfällen aus Wasser/Methanol oder Wasser/Aceton gut reinigen.
Als pharmakologisch verträgliche Salze werden vor allem Alkali- oder Ammoniumsalze verwendet, die man in üblicher Weise z. B. durch Titrieren der Verbindungen mit anorganischen oder organischen Basen wie z.B. Natrium- oder Kaliumhydrogencarbonat, Natronlauge, Kalilauge, wässrigem Ammoniak oder Aminen wie z.B. Trimethyl- oder Triethylamin herstellt.

Die erfindungsgemäßen neuen Substanzen der Formel I und ihre Salze können in flüssiger oder fester Form enteral oder parenteral appliziert werden. Hierbei kommen alle üblichen Applikationsformen infrage, beispielsweise Tabletten, Kapseln, Dragees, Sirupe, Lösungen, Suspensionen etc.. Als Injektionsmedium kommt vorzugsweise Wasser zur Anwendung, welches die bei Injektionslösungen üblichen Zusätze wie Stabilisierungsmittel, Lösungsvermittler und Puffer enthält. Derartige Zusätze sind z.B. Tartrat- und Citrat-Puffer, Ethanol, Komplexbildner (wie Ethylendiamintetraessigsäure und deren nichttoxische Salze), hochmolekulare Polymere (wie flüssiges Polyethylenoxid) zur Viskositätsregelung. Flüssige Trägerstoffe für Injektionslösungen müssen steril sein und werden vorzugsweise in Ampullen abgefüllt. Feste Trägerstoffe sind z.B. Stärke, Lactose, Mannit, Methylcellulose, Talkum, hochdisperse Kieselsäuren, höhermolekulare Fettsäuren (wie Stearinsäure), Gelatine, Agar-Agar, Calciumphosphat, Magnesiumstearat, tierische und pflanzliche Fette, feste hochmolekulare Polymere (wie Polyethylenglykole); für orale Applikation geeignete Zubereitungen können gewünschtenfalls Geschmacks- und Süßstoffe enthalten. Die Dosierung kann von verschiedenen Faktoren, wie Applikationsweise, Spezies, Alter und/oder individuellem Zustand abhängen. Die tägliche zu verabreichenden Dosen liegen bei etwa 0.1-100 mg/Mensch, vorzugsweise bei 1-20 mg/Mensch und können auf einmal oder mehrere Male verteilt eingenommen werden.

Bevorzugt im Sinne der vorliegenden Erfindung sind außer den in den Beispielen genannten Verbindungen und durch Kombination aller in den Ansprüchen genannten Bedeutungen der Substituenten ableitbaren Verbindungen die folgenden Diphosphonate, sowie deren Natriumsalze, Methyl-, Ethyl-oder Isopropylester:

5-N,N-Dimethylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-Methyl-N-propylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-Methyl-N-nonylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-Benzylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-Isobutyl-N-methylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-Methallyl-N-methylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-(2-Methoxyethyl)-N-methylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-(2-Hydroxyethyl)-N-methylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-(2-Methylmercaptoethyl)-N-methylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-(4-Methylbenzyl)amino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-(2-Chlorbenzyl)amino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N-Cyclohexyl-N-methylamino-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-Amino-7-methyl-3-oxa-octan-1-hydroxy-1,1-diphosphonsäure
5-Amino-6-phenyl-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-Amino-6-(3-indolyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-Amino-6-(4-imidazolyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-Amino-6-hydroxy-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-Amino-7-methylmercapto-3-oxa-heptan-1-hydroxy-1,1-diphosphonsäure
5-N-Methyl-N-propylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-N-Methyl-N-pentylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-N-Allyl-N-methylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-Amino-6-(4-hydroxyphenyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-Amino-4,4-dimethyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-Amino-4-phenyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-Amino-2-methyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure-
5-Amino-2,2-dimethyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-Amino-2-phenyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(1-Pyrrolidinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(1-Piperidinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(3-Hydroxy-1-pyrrolidinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(3,4,-Dimethoxy-1-pyrrolidinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(2,3-Dihydro-isoindolin-1-yl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(Octahydro-isoindolin-1-yl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(Decahydro-chinolin-1-yl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(1-Piperazinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(4-Methyl-1-piperazinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(4-Thiamorpholinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-(4-Hydroxy-1-piperidinyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-4-(2-Pyrrolindinyl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
4-(2-Piperidinyl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
4-(1-Methyl-2-piperidinyl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
5-(1-Methyl-2-piperidinyl)-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
4-(Octahydro-indolin-2-yl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
4-(1-Ethyl-2-pyrrolindinyl-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
3-(3-Pyrrolindinyl)-3-oxa-propan-1-hydroxy-1,1-diphosphonsäure
5-Amino-5,5-butylen-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-N,N-Dimethylamino-5,5-pentylen-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
4-(2-Aminocyclohexyl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
3-(2-Aminocyclopentyl)-3-oxa-propan-1-hydroxy-1,1-diphosphonsäure
4-(2-Aminocyclopentyl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
4-(2-N,N-Dimethylamino-cyclohexyl)-3-oxa-butan-1-hydroxy-1,1-diphosphonsäure
5-Amino-4,4-butylen-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
6-Amino-2,2-butylen-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
5-N,N-Dimethylamino-2,2-pentylen-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
1,5-Diamino-3-oxa-pentan-1,1-diphosphonsäure
5-Amino-1-N,N-diethylamino-3-oxa-hexan-1,1-diphosphonsäure
5-Amino-3-oxa-hexan-1,1-diphosphonsäure
R-5-Amino-3-oxa-hexan-1,1-diphosphonsäure

S-5-Amino-3-oxa-hexan-1,1-diphosphonsäure
5-N,N-Dimethylamino-3-oxa-pentan-1,1-diphosphonsäure
R-5-Amino-7-methyl-3-oxa-octan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-6-phenyl-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-6-phenyl-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-6-(3-indolyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-6-(3-indolyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-6-(4-imidazolyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-6-(4-imidazolyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-1.6-dihydroxy-3-oxa-hexan-1,1-diphosphonsäure
S-5-Amino-1.6-dihydroxy-3-oxa-hexan-1,1-diphosphonsäure
R-5-Amino-7-methylmercapto-3-oxa-heptan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-7-methylmercapto-3-oxa-heptan-1-hydroxy-1,1-diphosphonsäure
R-5-N-Methyl-N-propylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-N-Methyl-N-propylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-N-Methyl-N-pentylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-N-Methyl-N-pentylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-N-Allyl-N-methylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-N-Allyl-N-methylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-6-(4-hydroxyphenyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-6-(4-hydroxyphenyl)-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-4-phenyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-4-phenyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-2-methyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-2-methyl-3-oxa-heptan-1-hydroxy-1,1-diphosphonsäure
R-5-Amino-2-phenyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
S-5-Amino-2-phenyl-3-oxa-pentan-1-hydroxy-1,1-diphosphonsäure
5-Amino-2-methyl-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
6-Amino-3-oxa-heptan-1-hydroxy-1,1-diphosphonsäure
6-Amino-5-methyl-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure
6-Amino-4-methyl-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure

Die nachfolgenden Beispiele zeigen einige der Verfahrensvarianten, die zur Synthese der erfindungsgemäßen Verbindungen verwendet werden können. Sie sollen jedoch nicht eine Einschränkung des Erfindungsgegenstandes darstellen. Die Verbindungen fallen in der Regel als hochschmelzende Festprodukte an (Mono- oder Dinatriumsalz), deren Struktur durch H-, P- und gegebenenfalls durch $^{13}C$ NMR-Spektroskopie gesichert wurde. Die Reinheit der Substanzen wurde mittels C,H,N,P,S, Na-Analyse sowie durch Dünnschichtelektrophorese (Cellulose, Oxalat-Puffer von pH = 4.0) bestimmt. Zur Charakterisierung der einzelnen Verbindungen werden die $M_{rel}$-Werte (= relative Mobilität) bezogen auf Pyrophosphat ($M_{rel}$ = 1) angegeben.

Beispiel 1

**R,S-5-Amino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure**

0.67 g (5 mmol) R,S-5-Amino-3-oxa-hexansäure werden mit 0.82 g (10 mmol) phosphoriger Säure bei 100 °C geschmolzen. Man entfernt das Ölbad, tropft 1 ml (11 mmol) Phosphortrichlorid zu und erhitzt weitere 24 h auf 100 °C Außentemperatur. Nach dem Abkühlen versetzt man mit 10 ml Wasser, kocht 45 min unter Rückfluß, saugt ab, engt das Filtrat auf die Hälfte ein, stellt die Lösung mit 10 N Natronlauge auf pH = 5, versetzt mit 20 ml Methanol und kühlt die Lösung im Eisbad. Der ausgefallene Niederschlag wird abgesaugt, mit Methanol gewaschen und getrocknet. Der Rückstand wird in wenig Wasser gelöst und über eine Ionenaustauschersäule (35 gAmberlite-IR 120; $H^+$-Form) gereinigt. Man erhält 0.49 g = 34 % der gewünschten Verbindung, die 0.5 mol Wasser enthält; Fp: 240-260 °C; $M_{rel}$: 0.40.

Die als Ausgangsmaterial verwendete R,S-5-Amino-3-oxahexansäure wurde auf folgende Weise hergestellt: R,S-5-Methyl-morpholin-3-on (Fp: 62-64 °C) wird mit Bariumhydroxid gekocht und aus dem Bariumsalz mit Schwefelsäure bei pH = 5 die freie Säure (Fp: 190-193 °C) hergestellt.

In analoger Weise erhält man durch Umsetzung von phosphoriger Säure und Phosphortrichlorid mit

a) R,S-5-N,N-Dimethylamino-3-oxa-hexansäure (Fp: 108-110 °C) (hergestellt durch reduktive Methylierung von R,S-5-Amino-3-oxa-hexansäure mittels Ameisensäure/Formaldehyd) die R,S-5-N,N-Dimethylamino-3-oxa-hexan-1-hydroxy-1,1-diphosphonsäure als freie Säure mit 1 mol Wasser in einer Ausbeute von 36 %; Fp: ca. 270 °C $M_{rel}$: 0.40.

## Beispiel 2

Analog wie im Beispiel 1 beschrieben erhält man durch Verwendung von

a) 5-Amino-3-oxa-pentansäure (Fp: 188-190 °C) die 5-Amino-3-oxa-pentan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 31 %; Fp: 255-260 °C; $M_{rel}$: 0.30.

b) 6-(N-Acetyl-amino)-3-oxa-hexansäure (Öl) die 6-Amino-3-oxa-hexan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 23 %; Fp: 125-130 °C; $M_{rel}$: 0.30.

c) 5-N-Methylamino-3-oxa-pentansäure (Fp: 242-245 °C) die 5-N-Methylamino-3-oxa-pentan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 28 %; Fp: 155-160 °C; $M_{rel}$: 0.35

d) 6-N,N-Dimethylamino-3-oxa-hexansäure-hydrochlorid (Öl) die 6-N,N-Dimethylamino-3-oxa-hexan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 22 %; Fp: 115-120 °C; $M_{rel}$: 0.30

e) R-5-Amino-3-oxa-hexansäure (Fp: 182-185 °C; $[\alpha]_D^{20}$ : -30.5°, c = 1.5 in Wasser) die R-5-Amino-3-oxa-hexan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 30 %, Fp: 118-123 °C; $[\alpha]_D^{20}$ : -22.6°, c = 0.8 in Wasser; $M_{rel}$: 0.30.

f) S-5-Amino-3-oxa-hexansäure (Fp: 180-182 °C; $[\alpha]_D^{20}$ : -28.5°, c = 1.4 in Wasser) die S-5-Amino-3-oxa-hexan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 34 %, Fp: 115-120 °C; $[\alpha]_D^{20}$ : +21.2°, c = 0.8 in Wasser; $M_{rel}$: 0.30.

g) 5-Amino-6-methyl-3-oxa-heptansäure (Öl) die 5-Amino-6-methyl-3-oxa-heptan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 22 %, Fp: 135-140 °C; $M_{rel}$: 0.35.

h) S-5-Amino-6-methyl-3-oxa-heptansäure (Fp: 140-145 °C; $[\alpha]_D^{20}$ : +23.9°, c = 1 in Wasser) die S-5-Amino-6-methyl-3-oxa-heptan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 27 %, Fp: 245-250 °C; $[\alpha]_D^{20}$ : +19.3°, c = 1.0 in Wasser; $M_{rel}$: 0.30.

i) R-5-Amino-6-methyl-3-oxa-heptansäure (Fp: 143-147 °C; $[\alpha]_D^{20}$ : -24.3°, c = 1.1 in Wasser) die R-5-Amino-6-methyl-3-oxa-heptan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 26 %, Fp: 245-250 °C; $[\alpha]_D^{20}$ : -18.9°, c = 1.0 in Wasser; $M_{rel}$ 0.30.

j) S-5-Amino-7-methyl-3-oxa-octansäure (Fp: 148-150 °C; $[\alpha]_D^{20}$ : +17.7°, c = 1.2 in Wasser) die S-5-Amino-7-methyl-3-oxa-octan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 31 %, Fp: 250-255 °C; $[\alpha]_D^{20}$ : +14.8°, c = 1.2 in Wasser; $M_{rel}$: 0.30.

k) 5-Amino-5-methyl-3-oxa-hexansäure (Fp: 243-245 °C) die 5-Amino-5-methyl-3-oxa-hexan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 27 %, Fp: 155-160 °C; $M_{rel}$: 0.40.

l) 5-Amino-4-methyl-3-oxa-pentansäure (Fp: 213-215 °C;) die 5-Amino-4-methyl-3-oxa-pentan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 33 %, Fp: 145-150 °C; $M_{rel}$: 0.30.

m) 5-(4-Morpholinyl)-3-oxa-pentansäure-hydrochlorid (Öl) die 1-Hydroxy-5-(4-morpholinyl)-3-oxa-pentan-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 28 %, Fp: 135-140 °C; $M_{rel}$: 0.35.

n) 3-(N-Acetyl-3-piperidinyl)-3-oxa-propionsäure (Öl) die 1-Hydroxy--(3-piperidinyl)-3-oxa-propan-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 15 %, Fp: 185-190 °C; $M_{rel}$: 0.30.

o) 3-(2-Aminocyclohexyl)-3-oxa-propionsäure (Fp: 218-220 °C;) die 3-(2-Aminocyclohexyl)-3-oxa-propan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 19 %, Fp: 215-220 °C; $M_{rel}$ 0.25.

p) 5-Amino-4.4-pentylen-3-oxa-pentansäure (Fp: 203-205 °C;) die 5-Amino-4.4-pentylen-3-oxa-pentan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 29 %, Fp: 235-240 °C; $M_{rel}$: 0.30.

q) S-4-(2-Pyrrolidinyl)-3-oxa-buttersäure (Fp: 152-155 °C;$[\alpha]_D^{20}$ : +20.3°, c = 1.3 in Wasser) die S-1-Hydroxy-4-(2-pyrrolidinyl)-3-oxa-butan-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 26 %, Fp: 120-125 °C, $[\alpha]_D^{20}$ : +18.0°, c = 0.9 in Wasser; $M_{rel}$: 0.30.

r) R-5-Amino-4-methyl-3-oxa-pentansäure (Fp: 210-212 °C; $[\alpha]_D^{20}$ : -97.0°, c = 1 in Wasser) die R-5-Amino-4-methyl-3-oxa-pentan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 23 %, Fp: 140-145 °C; $[\alpha]_D^{20}$ : -22.5°, c = 1 in Wasser; $M_{rel}$: 0.30.

s) S-5-Amino-4-methyl-3-oxa-pentansäure (Fp: 212-214 °C; $[\alpha]_D^{20}$ : +97.8°, c = 1 in Wasser) die S-5-Amino-4-methyl-3-oxa-pentan-1-hydroxy-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 15 %, Fp: 145-150 °C; $[\alpha]_D^{20}$ : +22.9°, c = 1 in Wasser; $M_{rel}$: 0.30.

t) 4-(2-Piperidinyl)-3-oxa-buttersäure (Fp: 158-160 °C) die 1-Hydroxy-4-(2-piperidinyl)-3-oxa-butan-1.1-diphosphonsäure mit 1 mol Wasser in einer Ausbeute von 24 %, Fp: 175-180 °C; $M_{rel}$: 0.30.

Die im Beispiel 2 a eingesetzte 5-Amino-3-oxa-pentansäure wird auf folgende Weise hergestellt: Ethanolamin wird in Gegenwart von Natriumhydrid mit Chloressigsäureethylester zum Morpholin-3-on (Fp: 100-102 °C) umgesetzt und daraus durch Erhitzen mit Bariumhydroxid und anschließender Behandlung mit Schwefelsäure die gewünschte Säure erhalten.

In gleicher Weise wurden die in der folgenden Tabelle aufgeführten Zwischenprodukte hergestellt und umgesetzt.

| Beisp.Nr. | Morpholinon | Fp. °C | $[\alpha]_D^{20}$ in Methanol |
|---|---|---|---|
| 2 c | N-Methyl-morpholin-3-on | Öl | - |
| 2 e | R-5-Methyl-morpholin-3-on | 60-62 | -3.7° |
| 2 f | S-5-Methyl-morpholin-3-on | 59-61 | +3.1° |
| 2 g | 5-Isopropyl-morpholin-3-on | 86-88 | - |
| 2 h | S-5-Isopropyl-morpholin-3-on | 86-88 | +3.9° |
| 2 i | R-5-Isobutyl-morpholin-3-on | 87-89 | -4,3° |
| 2 j | S-5-Isobutyl-morpholin-3-on | 70-72 | -4.° |
| 2 k | 5,5-Dimethyl-morpholin-3-on | 133-35 | - |
| 2 l | 6-Methyl-morpholin-3-on | 96-98 | - |
| 2 o | 2-Oxa-5-aza-bicyclo[4.4.0]decan-4-on | 174-76 | - |
| 2 p | 1-Oxa-4-aza-bicyclospiro[5.5]undecan-3-on | 93-95 | - |
| 2 q | S-3-Oxa-6-aza-bicyclo[4.3.0] nonan-5-on | 64-66 | - |
| 2 r | R-6-Methyl-morpholin-3-on | 96-98 | -134.1° |
| 2 s | S-6-Methyl-morpholin-3-on | 95-97 | +131.1° |
| 2 t | 3-Oxa-6-aza-bicyclo[4.4.0] decan-5-on | Öl | - |

Im Falle der Beispiele 2 b und 2 n wurden die Ausgangsaminoalkohole erst am Stickstoff acetyliert, anschließend in Gegenwart von Natriumhydrid mit Bromessigsäureethylester zum entsprechenden Alkoxiessigsäureethylester umgesetzt und dann mit Natronlauge verseift. Alle Zwischenprodukte fielen als Öle an.

Im Falle der Beispiele 2 d und 2 m wurden die tert.-Aminoalkohole in Gegenwart von Natriumhydrid mit Bromessigsäureethylester (2 m) bzw. dem Natriumsalz der Chloressigsäure (2 d) umgesetzt, im letzteren Fall mit Ethanol-Schwefelsäure zum entsprechenden Ethylester verestert und in beiden Fällen anschließend mit 2 N Salzsäure verseift. Alle Zwischenprodukte fielen auch hier als Öle an.

## Beispiel 3

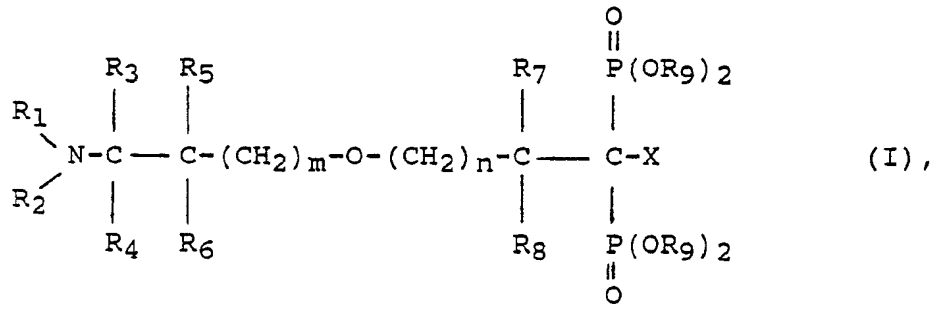
5-Amino-3-oxa-pentan-1.1-diphosphonsäure

Zu 144 mg (6 mmol) Natriumhydrid in 5 ml abs. Toluol tropft man 1.73 g (6mmol) Methandiphosphonsäuretetraethylester. Man läßt nach Beendigung der Wasserstoffentwicklung noch 30 min nachrühren und tropft dann 1.7 g (6 mmol) N-(2-Brommethoxy-ethyl)phthalimid (Fp: 83-85 °C) zu. Man läßt 24 h bei Raumtemperatur rühren, versetzt die Mischung mit Wasser, stellt die wässrige Phase mit 2 N Salzsäure auf pH = 5 ein, trennt die organische Phase ab, trocknet und engt ein. Den Rückstand reinigt man über 250 g Kieselgel (Elutionsmittel: Methylenchlorid/Methanol i.V. 4/1) und erhält 0.35 g = 12 % des 5-Phthalimido-3-oxa-pentan-1.1-diphosphonsäure-tetraethylester als ölige Substanz. Der Ester wird anschließend mit 10 ml 6 N Salzsäure 12 h unter Rückfluß gekocht, nach dem Abkühlen wird ausgefallene Phthalsäure abgesaugt, das Filtrat mit Kohle behandelt, filtriert und eingeengt. Den Rückstand nimmt man in Wasser auf, stellt die Lösung mit 2 N Natronlauge auf $P_H$ = 5 und versetzt unter Eiskühlung mit einem großen Überschuß an Methanol. Der Niederschlag wird abgesaugt und getrocknet. Man erhält 0.125 g = 7.2 % der gewünschten

Verbindung in Form des Mononatriumsalzes mit 1 mol Wasser, Fp: >300 °C; $M_{rel}$: 0.30.

**Ansprüche**

1. Verbindungen der allgemeinen Formel I



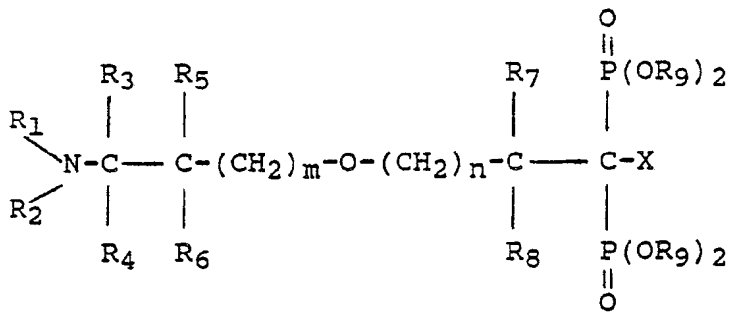
(I),

in der
$R_1$ und $R_2$ jeweils unabhängig voneinander Wasserstoff, einegeradkettige oder verzweigte, gesättigte oder ungesättigte Alkylkette mit 1-9 Kohlenstoffatomen, die gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkoxy oder $C_1$-$C_5$ Alkylthio, einen Phenyl- oder einen $C_5$-$C_7$ Cycloalkylring substituiert sein kann, wobei der Phenylring gegebenenfalls durch $C_1$-$C_5$ Alkyl, $C_1$-$C_5$ Alkoxy, Hydroxy oder Halogen substituiert sein kann, einen $C_5$-$C_7$ Cycloalkyl- oder den Phenylrest,
$R_3$ = Wasserstoff, niederes geradkettiges oder verzweigtes $C_1$-$C_5$ Alkyl, das gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkoxy, $C_1$-$C_5$ Alkylthio, Mercapto, Phenyl,3-Indolyl oder 4-Imidazolyl substituiert sein kann, oder gebenenfalls durch Hydroxy oder $C_1$-$C_5$ Alkoxy substituiertes Phenyl,
$R_4$, $R_6$, $R_8$ und $R_9$ jeweils unabhängig voneinander Wasserstoff oder $C_1$-$C_5$ Alkyl,
$R_5$ und $R_7$ jeweils unabhängig voneinander Wasserstoff, $C_1$-$C_5$ Alkyl oder gegebenenfalls durch Hydroxy oder $C_1$-$C_5$ Alkoxy substituiertes Phenyl,
X = Wasserstoff, OH oder die Gruppe $-NR_{10}$, $R_{11}$, wobei $R_{10}$ und $R_{11}$ jeweils unabhängig voneinander Wasserstoff oder $C_1$-$C_5$ Alkyl sein soll,
m bzw. n = 0 oder 1
bedeuten, wobei
$R_1$ und $R_2$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, ein mono- oder bicyclisches Ringsystem mit 4-9 Kohlenstoffatomen, das teilweise oder ganz hydriert ist und gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkyl oder $C_1$-$C_5$ Alkoxy substi-tuiert und/oder im Falle eines Monocyclus durch ein Sauerstoff-, Stickstoff- oder Schwefelatom unterbrochen sein kann,
$R_1$ und $R_3$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, einen Fünf- oder Sechsring, der gegebenenfalls mit einem weiteren Sechsring kondensiert sein kann,
$R_1$ und $R_5$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, sowie dem dazwischenliegenden Kohlenstoffatom einen Fünf- oder Sechsring,
$R_3$ und $R_4$ zusammen mit dem Kohlenstoffatom, and das sie gebunden sind, eine Fünf- oder Sechsring,
$R_4$ und $R_6$ zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Fünf- oder Sechsring,
$R_5$ und $R_6$ zusammen mit dem Kohlenstoff, an das sie gebunden sind, einen Fünf- oder Sechsring,
$R_7$ und $R_8$ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen Fünf- oder Sechsring
bilden können,
sowie deren pharmakologisch unbedenkliche Salze und optische Isomere.

2. Verbundungen der Formel I gemäß Anspruch 1, in denen $R_1$ Wasserstoff oder Methyl, $R_2$ Wasserstoff oder Methyl, $R_3$ Wasserstoff oder $C_1$-$C_5$ Alkyl, $R_4$ Wasserstoff oder Methyl, $R_5$ Wasserstoff oder Methyl, $R_6$ Wasserstoff, $R_7$ Wasserstoff, $R_8$ Wasserstoff, $R_9$ Wasserstoff, m die Zahl 0 oder 1, n die Zahl 0 und X eine Hydroxylgruppe bedeuten, wobei $R_1$ und $R_2$ zusammen mit dem Stickstoffatom einen Morpholin-Ring, $R_1$ und $R_3$ zusammen mit dem Stickstoffatom und dem Kohlenstoffatom, an das sie gebunden sind, einen Pyrrolidin- oder Piperidin-Ring, $R_1$ und $R_5$ zusammen mit dem Kohlenstoffatom und dem Stickstoffatom, an das sie gebunden sind, einen Piperidin-Ring, $R_4$ und $R_6$ zusammen mit den C-Atomen an das sie gebunden sind, einen Cyclohexyl-Ring und $R_5$ und $R_6$ zusammen mit dem C-Atom, an

das sie gebunden sind, einen Spirocyclo-pentan-Ring darstellen.

3. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel I



(I),

in der

$R_1$ und $R_2$ jeweils unabhängig voneinander Wasserstoff, einegeradkettige oder verzweigte, gesättigte oder ungesättigte Alkylkette mit 1-9 Kohlenstoffatomen, die gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkoxy oder $C_1$-$C_5$ Alkylthio, einen Phenyl- oder einen $C_5$-$C_7$ Cycloalkylring substituiert sein kann, wobei der Phenylring gegebenenfalls durch $C_1$-$C_5$ Alkyl, $C_1$-$C_5$ Alkoxy, Hydroxy oder Halogen substituiert sein kann, einen $C_5$-$C_7$ Cycloalkyl- oder den Phenylrest,

$R_3$ = Wasserstoff, niederes geradkettiges oder verzweigtes $C_1$-$C_5$ Alkyl, das gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkoxy, $C_1$-$C_5$ Alkylthio, Mercapto, Phenyl,3-Indolyl oder 4-Imidazolyl substituiert sein kann, oder gebenenfalls durch Hydroxy oder $C_1$-$C_5$ Alkoxy substuiertes Phenyl,

$R_4$, $R_6$, $R_8$ und $R_9$ jeweils unabhängig voneinander Wasserstoff oder $C_1$-$C_5$ Alkyl,

$R_5$ und $R_7$ jeweils unabhängig voneinander Wasserstoff, $C_1$-$C_5$ Alkyl oder gegebenenfalls durch Hydroxy oder $C_1$-$C_5$ Alkoxy substituiertes Phenyl,

X = Wasserstoff, OH oder die Gruppe $-NR_{10}$, $R_{11}$, wobei $R_{10}$ und $R_{11}$ jeweils unabhängig voneinander Wasserstoff oder $C_1$-$C_5$ Alkyl sein soll,

m bzw. n = 0 oder 1

bedeuten, wobei

$R_1$ und $R_2$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, ein mono- oder bicyclisches Ringsystem mit 4-9 Kohlenstoffatomen, das teilweise oder ganz hydriert ist und gegebenenfalls durch Hydroxy, $C_1$-$C_5$ Alkyl oder $C_1$-$C_5$ Alkoxy substituiert und/oder im Falle eines Monocyclus durch ein Sauerstoff-, Stickstoff- oder Schwefelatom unterbrochen sein kann,

$R_1$ und $R_3$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, einen Fünf- oder Sechsring, der gegebenenfalls mit einem weiteren Sechsring kondensiert sein kann,

$R_1$ und $R_5$ zusammen mit dem Kohlenstoff- bzw. Stickstoffatom, an das sie gebunden sind, sowie dem dazwischenliegenden Kohlenstoffatom einen Fünf- oder Sechsring,

$R_3$ und $R_4$ zusammen mit dem Kohlenstoffatom, and das sie gebunden sind, einen Fünf- oder Sechsring,

$R_4$ und $R_5$ zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Fünf- oder Sechsring,

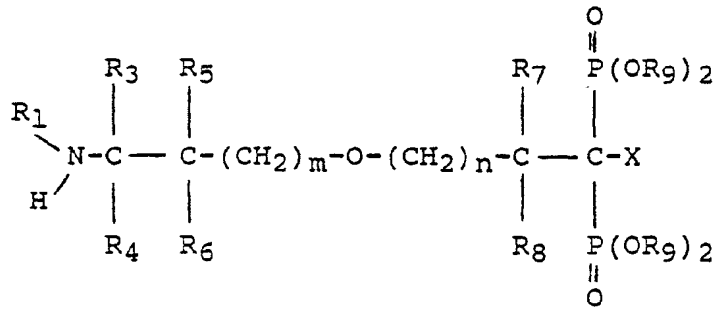
$R_5$ und $R_6$ zusammen mit dem Kohlenstoff, an das sie gebunden sind, einen Fünf- oder Sechsring,

$R_7$ und $R_8$ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen Fünf- oder Sechsring bilden können,

sowie deren pharmakologisch unbedenkliche Salze und optische Isomere,

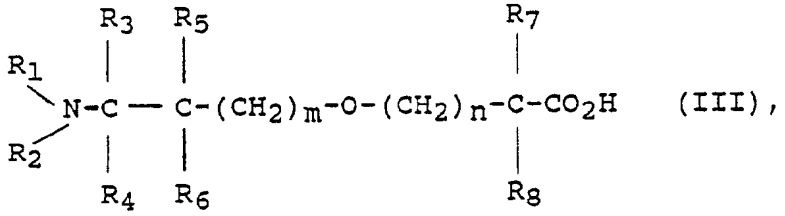
dadurch gekennzeichnet, daß man in an sich bekannter Weise

I. eine Verbindung der allgemeinen Formel II



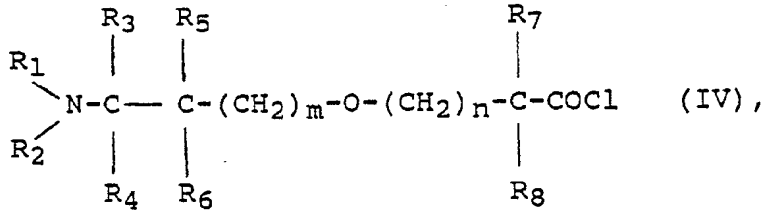
(II),

in der $R_1$ $R_3$-$R_9$, X, m und n die oben angegebenen Bedeutungen haben, mono- oder dialkyliert und gegebenenfalls die entstandenen Tetraester zu Diestern oder Säuren der allgemeinen Formel I verseift,
oder
II. für den Fall, daß X in der allgemeinen Formel I OH bedeutet,
a) eine Carbonsäure der allgemeinen Formel III



(III),

in der $R_1$-$R_8$, m und n die oben angegebenen Bedeutungen haben, mit einem Gemisch aus phosphoriger Säure oder Phosphorsäure und einem Phosphorhalogenid bzw. Phosphoroxyhalogenid umsetzt und anschließend zur freien Diphosphonsäure verseift,
oder
b) ein Carbonsäurechlorid der allgemeinen Formel IV

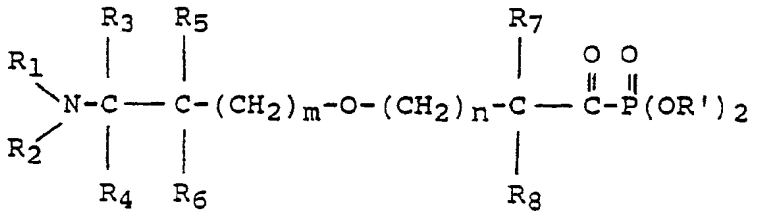


(IV),

in der $R_1$-$R_8$, m und n die oben genannten Bedeutungen haben, wobei $R_1$ auch eine Acylgruppe oder mit $R_2$ zusammen auch als Schutzgruppe den Phthaloylrest darstellen kann, mit einem Trialkylphosphit der allgemeinen Formel V

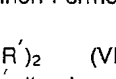
$P(OR')_3$ (V),

in der R' für Alkylreste mit 1-4 Kohlenstoffatomen, vorzugsweise Methyl, Ethyl, Isopropyl und Isobutyl steht, zu einem Acylphosphonat der allgemeinen Formel VI



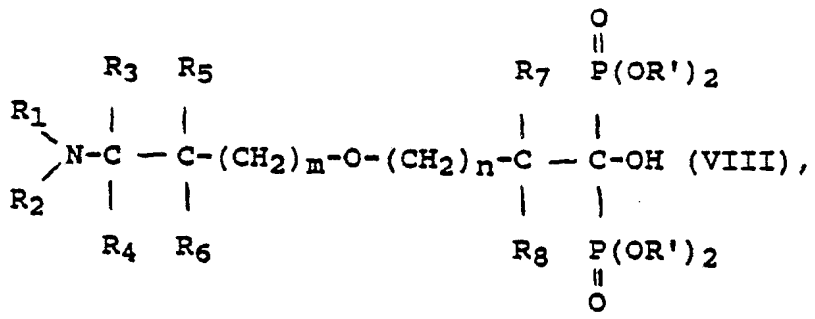
(VI),

in der $R_1$-$R_8$, m, n und R' die oben genannten Bedeutungen haben, $R_1$ auch eine Acylgruppe oder mit $R_2$ zusammen auch den Phthaloylrest darstellen kann, umsetzt, anschließend mit einem Dialkylphosphit der allgemeinen Formel VII



(VII),

in der R' die oben angegebene Bedeutung hat, zu einem Diphosphonat der allgemeinen Formel VIII

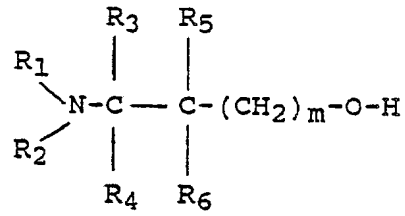


(VIII),

in der $R_1$-$R_8$, m, n, und R' die oben angebenen Bedeutungen haben, $R_1$ auch eine Acylgruppe oder mit $R_2$ zusammen auch den Phthaloylrest darstellen kann, reagieren läßt und gegebenenfalls die Phathaloylgruppe durch Hydrazinoylse entfernt und die entstandenen Tetraester zu Diestern oder Säuren der allgemeinen Formel I verseift, wobei unter diesen Bedingungen die als Schutzgruppe verwendete Acetyl- bzw. Phthaloylgruppe gleichzeitig abgespalten wird,

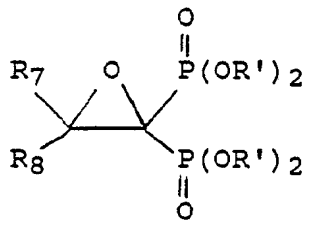
oder

c) für den Fall, daß n = O bedeutet, eine Verbindung der allgemeinen Formel IX



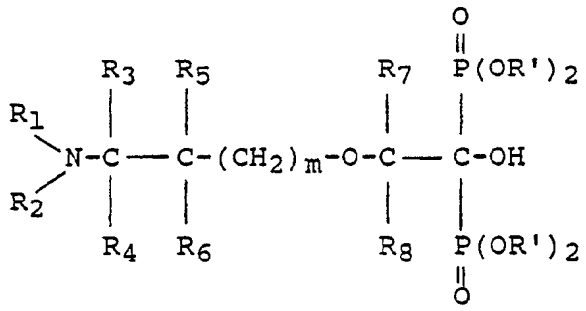
(IX),

in der $R_1$-$R_6$ und m die oben angegebenen Bedeutungen haben mit einem Epoxid der allgemeinen Formel X



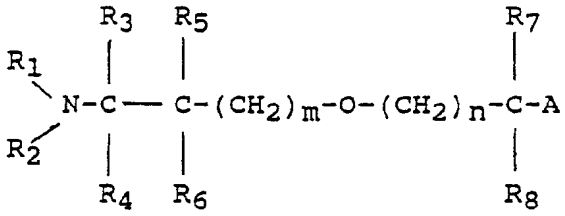
(X),

in der $R_7$, $R_8$ und R' die oben angegebenen Bedeutung haben, reagieren läßt und das entstandene Diphosphonsäurederivat der allgemeinen Formel XI



(XI),

gewünschtenfalls zu Diestern oder Säuren verseift,
oder
III. für den Fall, daß X in der allgemeinen Formel I die Gruppe $-NR_{10}R_{11}$ bedeutet,
ein Carbonsäurederivat der allgemeinen Formel XII

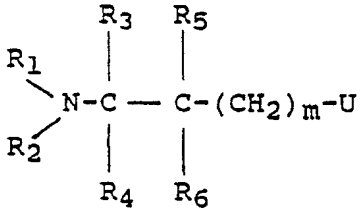


(XII),

in der $R_1$-$R_8$, m und n die oben angegebenen Bedeutungen haben und A eine Nitril-, Iminoether-oder eine $-CONR_{10}R_{11}$-Gruppe, wobei $R_{10}$ und $R_{11}$ die oben angegebenen Bedeutungen haben, darstellt, mit einer Phosphorverbindung der allgemeinen Formel XIII

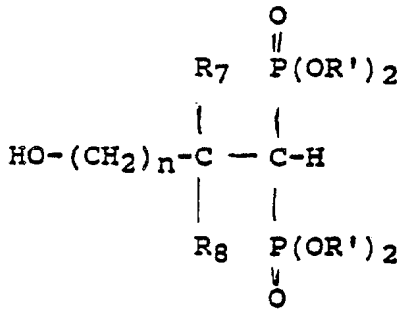
$PT_3$ (XIII),

in der T = Halogen, OH oder OR' bedeutet, wobei R' die oben angegebene Bedeutung hat, umsetzt und gegebenenfalls anschließend verseift,
oder
IV. für den Fall, daß X in der allgemeinen Formel I Wasserstoff bedeutet,
a) eine Verbindung der allgemeinen Formel XIV



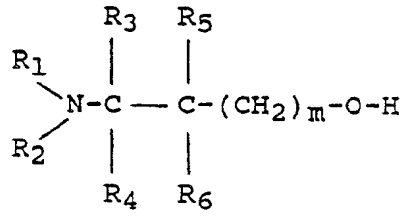
(XIV),

in der $R_1$-$R_6$ und m die oben angegebenen Bedeutungen haben, wobei $R_1$ auch ein Acyl- oder mit $R_2$ zusammen der Phthaloylrest sein kann, und U eine reaktive Gruppe wie z.B. Halogen oder ein Sulfonat darstellt, mit einem Diphosphonsäurederivat der allgemeinen Formel XV,



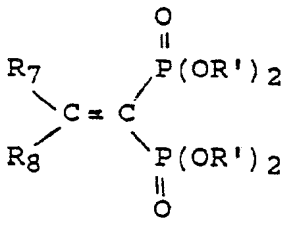
(XV),

in der $R_7$, $R_8$, $R'$ und n die oben angegebenen Bedeutungen haben, reagieren läßt, und die Phthaloylgruppe gewünschtenfalls durch Hydrazinolyse entfernt und die gebildeten Tetraester gegebenenfalls zu Diestern oder Säuren verseift, wobei unter diesen Bedingungen die als Schutzgruppe verwendete Acyl- oder Phthaloylgruppe gleichzeitig abgespalten wird,
oder
b) eine Verbindung der allgemeinen Formel IX



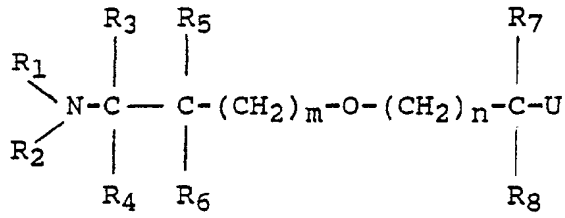
(IX),

in der $R_1$-$R_6$, und m die oben angegebenen Bedeutungen haben, an eine Verbindung der allgemeinen Formel XVI



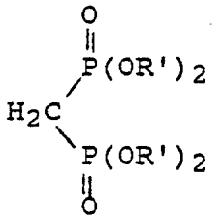
(XVI),

in der $R_7$, $R_8$ und $R'$ die oben angegebenen Bedeutungen haben, addiert und die entstehenden Tetraester gegebenenfalls zu Diestern oder Säuren verseift,
oder
c) eine Verbindung der allgemeinen Formel XVII



(XVII),

in der $R_1$-$R_8$, U, m und n die oben angegebenen Bedeutungen haben, wobei $R_1$ auch ein Acyl- oder mit $R_2$ zusammen der Phthaloylrest sein kann, mit einem Diphosphonsäurederivat der allgemeinen Formel XVIII



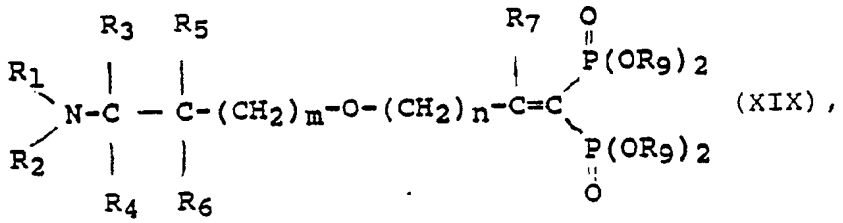
(XVIII),

in der $R'$ die oben angegebene Bedeutung hat, umsetzt, die Phthaloylgruppe gewünschtenfalls durch Hydrazinolyse entfernt und die entstandenen Tetraester gegebenenfalls zu Diestern oder Säuren verseift, wobei unter diesen Bedingungen die als Schutzgruppe verwendete Acyl- oder Phthaloylgruppe gleichzeitig abgespalten wird

oder

für den Fall, daß $R_8$ Wasserstoff bedeutet,

d) eine Verbindung der allgemeinen Formel IXX



(XIX),

in der $R_1$-$R_7$, $R_9$, m und n die oben angegebenen Bedeutungen haben, wobei $R_1$ auch eine Acylgruppe darstellen kann, katalytisch hydriert

und anschließend gegebenenfalls die entstandenen Tetraester zu Diester oder Säuren verseift, wobei dabei auch eine evtl. vorhandene Acylgruppe mit abgespalten werden kann und die freien Säuren in pharmakologisch unbedenkliche Salze überführt.

4. Verfahren zur Herstellung von Verbindungen gemäß Anspruch 3, in denen $R_1$ Wasserstoff oder Methyl, $R_2$ Wasserstoff oder Methyl, $R_3$ Wasserstoff oder $C_1$-$C_5$ Alkyl, $R_4$ Wasserstoff oder Methyl, $R_5$ Wasserstoff oder Metyl, $R_6$ Wasserstoff, $R_7$ Wasserstoff, $R_8$ Wasserstoff, $R_9$ Wasserstoff, m die Zahl 0 oder 1, n die Zahl 0 und X eine Hydroxylgruppe bedeuten, wobei $R_1$ und $R_2$ zusammen mit dem Stickstoffatom einen Morpholin-Ring, $R_1$ und $R_3$ zusammen mit dem Stickstoffatom und dem Kohlenstoffatom, an das sie gebunden sind, einen Pyrrolidin- oder Piperidin-Ring, $R_1$ und $R_5$ zusammen mit dem Kohlenstoffatom und dem Stickstoffatom, an das sie gebunden sind, einen Piperidin-Ring, $R_4$ und $R_6$ zusammen mit den C-Atomen an das sie gebunden sind, einen Cyclohexyl-Ring und $R_5$ und $R_6$ zusammen mit dem C-Atom, an das sie gebunden sind, einen Spirocyclo-pentan-Ring darstellen.

5. Arzneimittel, enthaltend eine Verbindung gemäß Anspruch 1 oder 2 neben üblichen Träger- und Hilfsstoffen.

6. Verwendung von Verbindungen gemäß Anspruch 1 oder 2 zur Behandlung von Calciumstoffwechselstörungen.

Europäisches Patentamt

# EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 89 11 2263

## EINSCHLÄGIGE DOKUMENTE

| Kategorie | Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile | Betrifft Anspruch | KLASSIFIKATION DER ANMELDUNG (Int. Cl.5) |
|---|---|---|---|
| X,Y | ZA-A- 879 454 (NORWICH EATON PHARMACEUTICALS)<br>* Insgesamt * & EP-A-274 158 (Kat. P,X)<br>--- | 1-6 | C 07 F 9/38<br>A 61 K 31/66<br>C 07 F 9/60<br>C 07 F 9/572<br>C 07 F 9/650<br>C 07 F 9/59<br>C 07 F 9/650<br>C 07 F 9/654<br>C 07 F 9/653 |
| Y | EP-A-0 186 405 (THE PROCTER & GAMBLE CO.)<br>* Ansprüche *<br>----- | 1-6 | |

RECHERCHIERTE SACHGEBIETE (Int. Cl.5)

C 07 F 9/00

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

| Recherchenort | Abschlußdatum der Recherche | Prüfer |
|---|---|---|
| DEN HAAG | 04-10-1989 | BESLIER L.M. |

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur

T : der Erfindung zugrunde liegende Theorien oder Grundsätze
E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

EPO FORM 1503 03.82 (P0403)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 352 781**
**A2**

# (12) EUROPEAN PATENT APPLICATION

(21) Application number: **89113837.2**

(22) Date of filing: **27.07.89**

(51) Int. Cl.[4]: **C07D 263/20 , C07D 413/10 , A61K 31/42 , C07D 413/14 , C07D 417/10**

(30) Priority: **29.07.88 US 225809**

(43) Date of publication of application:
**31.01.90 Bulletin 90/05**

(84) Designated Contracting States:
**AT BE CH DE ES FR GB GR IT LI LU NL SE**

(71) Applicant: **E.I. DU PONT DE NEMOURS AND COMPANY**
**1007 Market Street**
**Wilmington Delaware 19898(US)**

(72) Inventor: **Carlson, Randall Kent**
**121 Scarborough Park Drive**
**Wilmington Delaware 19804(US)**
Inventor: **Gregory, Walter Adelman**
**104 Rockingham Drive**
**Wilmington Delaware 19803(US)**
Inventor: **Park, Chung-ho**
**5 Woodley Circle**
**Wilmington Delaware 19803(US)**

(74) Representative: **von Kreisler, Alek,**
**Dipl.-Chem. et al**
**Patentanwälte Von Kreisler-Selting-Werner**
**Deichmannhaus am Hauptbahnhof**
**D-5000 Köln 1(DE)**

## (54) Aminomethyloxooxazolidinyl arylbenzene derivatives useful as antibacterial agents.

(57) Novel aminomethyloxooxazolidinyl arylbenzene derivatives, wherein the aryl includes the phenyl, substituted phenyl, pyridyl, and substituted pyridyl groups, such as (ℓ)-N-{3-[4-(4′-pyridyl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide, possess useful antibacterial activity.

EP 0 352 781 A2

# AMINOMETHYLOXOOXAZOLIDINYL ARYLBENZENE DERIVATIVES USEFUL AS ANTIBACTERIAL AGENTS

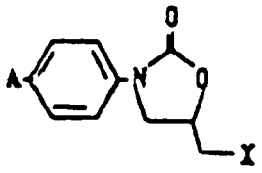
## Technical Field

This invention relates to aminomethyloxooxazolidinyl arylbenzene derivatives, their preparation, to pharmaceutical compositions containing them, and to methods of using them to alleviate bacterial infections.

## Background of the Invention

At the present time, no existing antibacterial product provides all features deemed advantageous for such a product. There is continual development of resistance by bacterial strains. A reduction of allergic reactions and of irritation at the site of injection, and greater biological half-life (i.e., longer in vivo activity) are currently desirable features for antibacterial products.

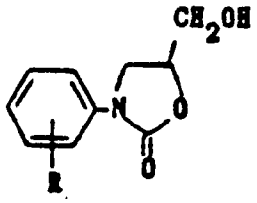
U.S. Patent 4,128,654 issued to Fugitt et al. on December 5, 1978, discloses, among others, compounds of the formula:



where
A = $RS(O)_n$;
X = Cl, Br or F;
R = $C_1$-$C_3$ alkyl; and
n = 0, 1 or 2.

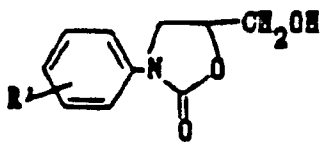
The compounds are disclosed as being useful in controlling fungal and bacterial diseases of plants.

U.S. Reissue Patent 29,607 reissued April 11, 1978 discloses derivatives of 5-hydroxymethyl-3-substituted-2-oxazolidinones of the formula:



where R is H, F, $CH_3$, or $CF_3$. Such compounds are described as having antidepressive, tranquilizing, sedative, and antiinflammatory properties.

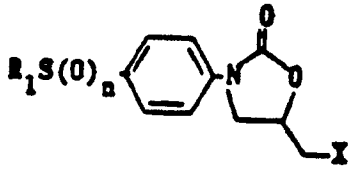
U.S. Patent 4,250,318, which was issued on February 10, 1981, discloses antidepressant compounds of the formula:



where R′ can be, among others, a para-n-pentylamino group, an $SR_1$ group where $R_1$ is $C_1$-$C_5$ alkyl, or an

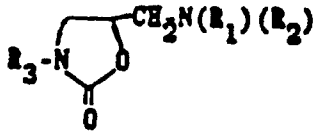
acetylmethylthio group.

U.S. Patent 4,340,606, issued to Fugitt et al. on July 20, 1982, discloses antibacterial agents of the general formula:



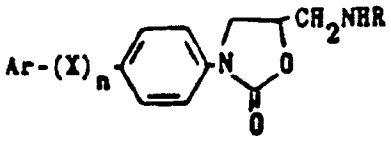
where
$R_1$ = $CH_3$, $C_2H_5$, $CF_2H$, $CF_3$ or $CF_2CF_2H$; and
X = $OR_2$ ($R_2$ = H or various acyl moieties).

U.S. Patent 3,687,965, issued to Fauran et al. on August 29, 1972, discloses compounds of the formula:



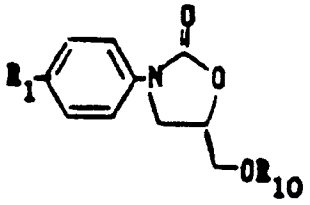
where
$-N(R_1)(R_2)$ represents either dialkylamino radical in which the alkyl portions have one to five carbon atoms, or a heterocyclic amino radical which may be substituted by an alkyl radical having one to five carbon atoms or by a pyrrolidinocarbonylmethyl radical, and
$R_3$ represents a phenyl radical which may be substituted by one or more of the following radicals:
an alkoxy radical having one to five carbon atoms;
a halogen atom;
a trifluoromethyl radical, or
a carboxyl radical which may be esterified.
The patent states that these compounds possess hypotensive, vasodilatatory, spasmolytic, sedative, myorelaxant, analgesic and antiinflammatory properties. There is no mention of antibacterial properties.

Belgian Patent 892,270, published August 25, 1982, discloses monoamine oxidase inhibitors of the formula



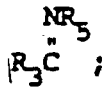
where
R is H, $C_1$-$C_4$ alkyl or propargyl;
Ar is phenyl, optionally substituted by halo or trifluoromethyl;
n is 0 or 1; and
X is $-CH_2CH_2-$, $-CH=CH-$, an acetylene group or $-CH_2O-$.

U.S. Patent 4,461,773 issued to W. A. Gregory on July 24, 1984 discloses antibacterial agents of the formula



wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound,
$R_1$ is $R_2SO_2$,

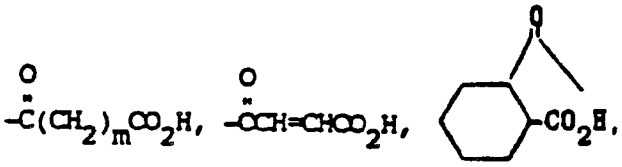
$R_3R_4NC$ , or

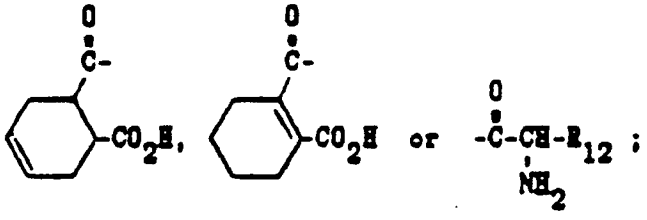


$R_2$ is $-NR_3R_4$, $-N(OR_3)R_4$, $-N_3$, $-NHNH_2$, $-NX_2$, $-NR_6X$, -NXZ, -NH  $R_7$, -NZ  $R_7$

or $-N=S(O)_nR_8R_9$;
$R_3$ and $R_4$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;
$R_5$ is $NR_3R_4$ or $OR_3$;
$R_6$ is alkyl of 1-4 carbons;
$R_7$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;
$R_8$ and $R_9$ are independently alkyl of 1-4 carbons or, taken together are $-(CH_2)_p-$;

$R_{10}$ is H, alkyl of 1-3 carbons,  ,

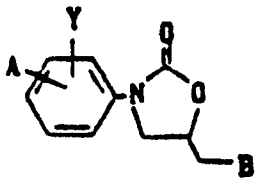




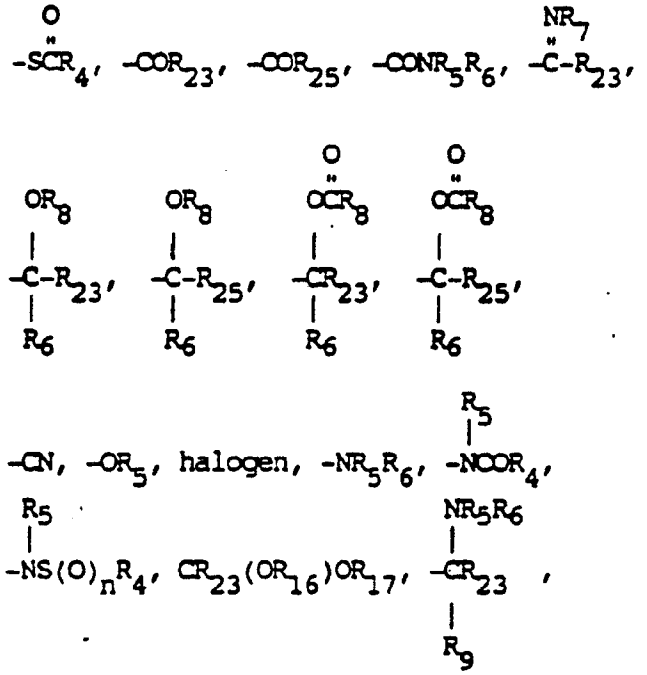
$R_{11}$ is alkyl of 1-12 carbons;
$R_{12}$ is H, alkyl of 1-5 carbons, $CH_2OH$ or $CH_2SH$;
X is Cl, Br or I;
Z is a physiologically acceptable cation;
m is 2 or 3;
n is 0 or 1; and
p is 3, 4 or 5;
and when $R_{10}$ is alkyl of 1-3 carbons, $R_1$ can also be $CH_3S(O)_q$ where q is 0, 1 or 2;
or a pharmaceutically acceptable salt thereof.

U.S. Patent 4,705,799 issued to Gregory on November 10, 1987 discloses antibacterial agents of the

formula:



wherein, for the *l*, and the mixtures of the d and *l* stereoisomers of the compound,
A is $-NO_2$, $-S(O)_nR_1$, $-S(O)_2-N=S(O)_pR_2R_3$, -SH,



alkyl of 1 to 8 carbons, optionally substituted with one or more halogen atoms, OH, =0 other than at alpha position, $S(O)_nR_{24}$, $NR_5R_6$, alkenyl of 2-5 carbons, alkynyl of 2-5 carbons or cycloalkyl of 3-8 carbons;
$R_1$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms, OH, CN, $NR_5R_6$ or $CO_2R_8$; $C_2$-$C_4$ alkenyl; $-NR_9R_{10}$;
$-N_3$;
$-NH\overset{O}{\overset{\|}{C}}R_4$; $-NZ\overset{O}{\overset{\|}{C}}R_4$; $-NX_2$; $NR_9X$ $-{}^{-}NXZ^{+}$;
$R_2$ and $R_3$ are independently $C_1$-$C_2$ alkyl or, taken together are $-(CH_2)_q-$;
$R_4$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;
$R_5$ and $R_6$ are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;
$R_7$ is $-NR_5R_6$, $-OR_5$ or
$NH\overset{O}{\overset{\|}{C}}R_5$;
$R_8$ is H or alkyl of 1-4 carbons;
$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;
$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11A}$;
$R_{11}$ and $R_{11A}$ are independently H or $C_1$-$C_4$ alkyl, or taken together, are $-(CH_2)_r-$;
X is Cl, Br or I;
Y is H, F, Cl, Br, alkyl of 1-3 carbons, or $NO_2$, or A and Y taken together can be $-O-(CH_2)_tO-$;
Z is a physiologically acceptable cation;

n is 0, 1 or 2;
p is 0 or 1;
q is 3, 4 or 5;
r is 4 or 5;
t is 1, 2 or 3;

B is $-NH_2$, $-N(R_{12})-C(=O)-R_{13}$, $-N(R_{12})-S(O)_uR_{14}$, or $N_3$;

$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;
$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH^2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-CR_{15}=O$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$; the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $C(NH_2)R_{21}R_{22}$;
$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;
$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;
$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_2$ alkyl;
$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;
u is 1 or 2;
v is 0, 1 or 2;
m is 2 or 3;
s is 2, 3, 4 or 5; and
$R_{23}$ is H, alkyl of 1-8 carbons optionally substituted with one or more halogens, or cycloalkyl of 3-8 carbons;
$R_{24}$ is alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;
$R_{25}$ is alkyl of 1-4 carbons substituted with one or more of $-S(O)_nR_{24}$, $-OR_8$, $-O-CR_8=O$, $-NR_5R_6$, or alkenyl of 2-5 carbons optionally substituted with CHO; or a pharmaceutically suitable salt thereof; provided that:

1) when A is $CH_3S-$, then B is not

$-N(CH_3)-CO_2CH_3$;

2) when A is $CH_3SO_2-$, then B is not

$-N(CH_3)-COCH_3$ or $-N(CH_3)-COCF_3$;

3) when A is $H_2NSO_2-$ and B is

$-N(R_{12})-CR_{13}=O$,

then $R_{12}$ is H;

4) when A is -CN, B is not $-N_3$;

5) when A is $(CH_3)_2CH$, B is not $NHCOCH_2Cl$;

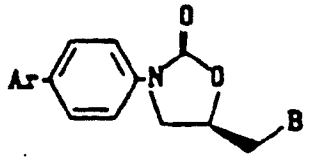
6) when A is $OR_5$, then B is not $NH_2$;

7) when A is F, then B is not $NHCO_2CH_3$.

None of the above-mentioned references suggest the novel antibacterial compounds of this invention.

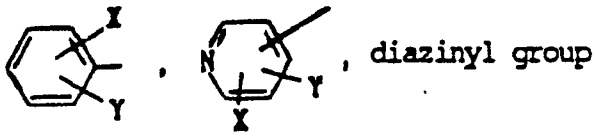
## Summary of the Invention

According to the present invention, there is provided an arylbenzene oxazolidinone of the formula:

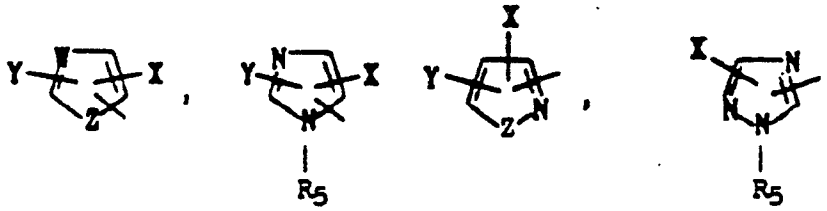


(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound
Ar is an aromatic group selected from the group consisting of



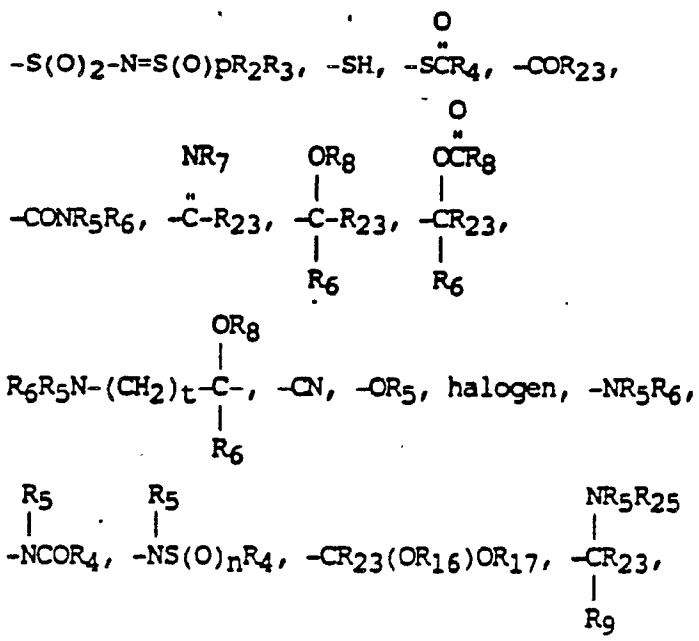

optionally substituted with X and Y, a triazinyl group optionally substituted with X and Y,



and

;

Z is O, S, or $NR_5$;
W is CH or N, or also can be S or O when Z is $NR_5$;
X independently is H, $-NO_2$, $-S(O)_nR_1$, tetrazoyl,



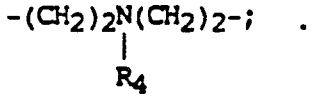
alkyl of 1 to 8 carbons optionally substituted with one or more halogen atoms, OH, =O other than at alpha position, $S(O)_nR_{24}$, or $NR_5R_6$, alkenyl of 2-5 carbons or cycloalkyl of 3-8 carbons;

$R_1$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms, OH, CN, $NR_5R_6$ or $CO_2R_8$; $C_2$-$C_4$ alkenyl; $-NR_9R_{10}$; $-N_3$;

$R_2$ and $R_3$ independently $C_1$-$C_2$ alkyl or, taken together are $-(CH_2)_q-$;

$R_4$ is alkyl of 1-4 carbons, optionally substituted with one or more halogens;

$R_5$ and $R_6$ are independently H, alkyl of 1-8 carbons, cycloalkyl of 3-8 carbons $-(CH_2)_tOR_8$, $-(CH_2)_tNR_{11}R_{11a}$, or $-O(CH_2)_tNR_{11}R_{11a}$; or taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_tCH(COR_4)-$, or



$R_7$ is $-NR_5R_6$, $-OR_5$ or



$R_8$ is H or alkyl of 1-4 carbons;

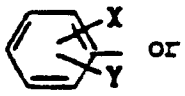
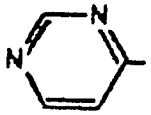
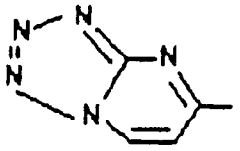
$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;

$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11A}$;

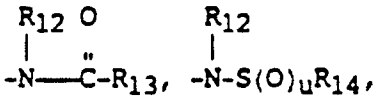
$R_{11}$ and $R_{11A}$ are independently H or $C_1$-$C_4$ alkyl, or taken together, are $-(CH_2)_r-$;

G is Cl, Br or I;

Y independently is H, F, Cl, Br, $OR_8$, alkyl of 1-3 carbons, or $NO_2$;

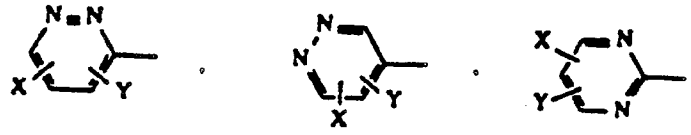
X and Y taken together (a) when Ar is  or  to form a fused six-membered carbocyclic ring, or (b) when Ar is  to form  ;

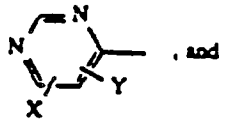
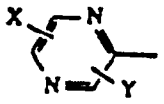
M is a physiologically acceptable cation;
n is 0, 1 or 2;
p is 0 or 1;
q is 3, 4 or 5;
r is 4 or 5;
t is 1, 2 or 3;
B is $-NH_2$,



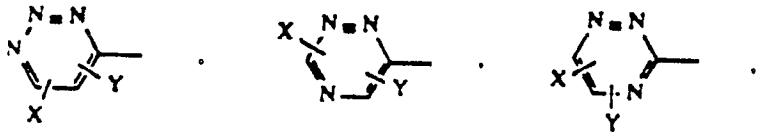
or $N_3$;
$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;
$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$; $-\overset{O}{\overset{\|}{C}}R_{15}$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$; the aminoalkyl groups derived from $\alpha$-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $-C(NH_2)R_{21}R_{22}$;
$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;
$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;
$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_2$ alkyl;
$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;
u is 1 or 2;
v is 0, 1 or 2;
m is 2 or 3;
s is 2, 3, 4 or 5;
$R_{23}$ is H, alkyl of 1-8 carbons optionally substituted with one or more halogens, cycloalkyl of 3-8 carbons, alkyl of 1-4 carbons substituted with one or more of $-S(O)_nR_{24}$, $-OR_8$, $-O\overset{O}{\overset{\|}{C}}R_8$, or $-NR_5R_6$; or alkenyl of 2-5 carbons optionally substituted with CHO or $CO_2R_8$;
$R_{24}$ is alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons; and
$R_{25}$ is $R_5$ or $NR_5R_6$;
or a pharmaceutically suitable salt thereof; provided that:
1) when B is $NH_2$, then Ar is not phenyl optionally substituted with halogen or $CF_3$.

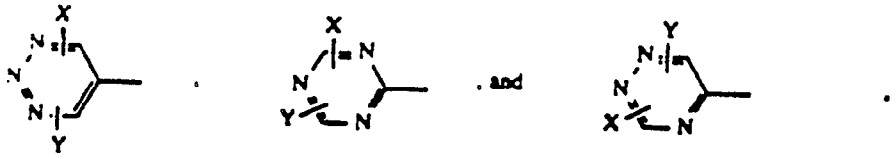
When used herein, the term "a diazinyl group optionally substituted with X and Y" means the following groups:




and


When used herein, the term "a triazinyl group optionally substituted with X and Y" means the following groups:



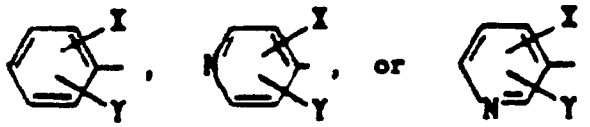


Also provided is a pharmaceutical composition consisting essentially of a suitable pharmaceutical carrier and a compound of Formula (I) and a method of using a compound of Formula (I) to treat bacterial infection in a mammal.

Further provided is a process for preparing compounds of Formula (I), such a process being described in detail hereinafter.

Preferred Embodiments

1. Preferred Ar groups are:



where X and Y are as defined.

More preferred Ar groups are those preferred Ar groups where Y is H.

Most preferred Ar groups are the preferred Ar groups where Y is H and X is H, alkyl of 1-5 carbon atoms, $-SCH_3$, $-SOCH_3$, $-SO_2CH_3$, $-\overset{\overset{O}{\|}}{C}CH_3$,

$OR_5$, $-CH_2NR_5R_6$, $R_6R_5N(CH_2)_2CH(OH)-$, or -CN.

2. A preferred B group is:

$-NH\overset{\overset{O}{\|}}{C}R_{13}$ where $R_{13}$ is H, $CH_3$, $-OR_{18}$, $CH_2Cl$, $CH_2OH$, or $CH_2OCH_3$.

Preferred B groups are

-NH $\overset{O}{\overset{\|}{C}}CH_3$, -NH $\overset{O}{\overset{\|}{C}}OCH_3$, and -NH $\overset{O}{\overset{\|}{C}}CH_2Cl$; and -NH $\overset{O}{\overset{\|}{C}}CH_3$ is specifically preferred.

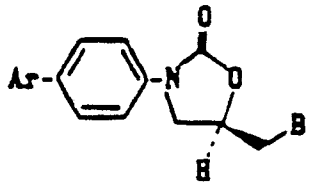
Specifically preferred compounds are:

- (ℓ)-N-[3-(4-phenylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-acetylphenyl)phenyl)-2-oxooazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-methylsulfinylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-methylsulfonylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-cyanophenyl)phenyl-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-diethylaminomethylphenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-di-n-propylaminomethylphenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-(3-N,N-dimethylamino-1-hydroxypropyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;
- (ℓ)-N-[3-(4-(4′-(1-hydroxy-3-(4-morpholinyl)-propyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-(4-(4′-pyridylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, hydrochloride;
- (ℓ)-N-[3-(4-(3′-pyridylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, hydrochloride.

## Detailed Description

The compounds of Formula (I) contain at least one chiral center, and as such exist as two individual isomers or as a mixture of both. This invention relates to the levorotatory isomer (ℓ) which for many of the compounds in this invention can be referred to as the (S) isomer, as well as mixtures containing both the (d) or (R) and (S) isomers. Additional chiral centers may be present in the groups Ar and/or B; and this invention relates to all possible stereoisomers in these groups.

For the purpose of this invention, the ℓ-isomer of compounds of Formula (I) is intended to mean compounds of the configuration depicted; when B is NHAc, and closely related groups, this isomer is described as the (S)-isomer in the Cahn-Ingold-Prelog nomenclature:

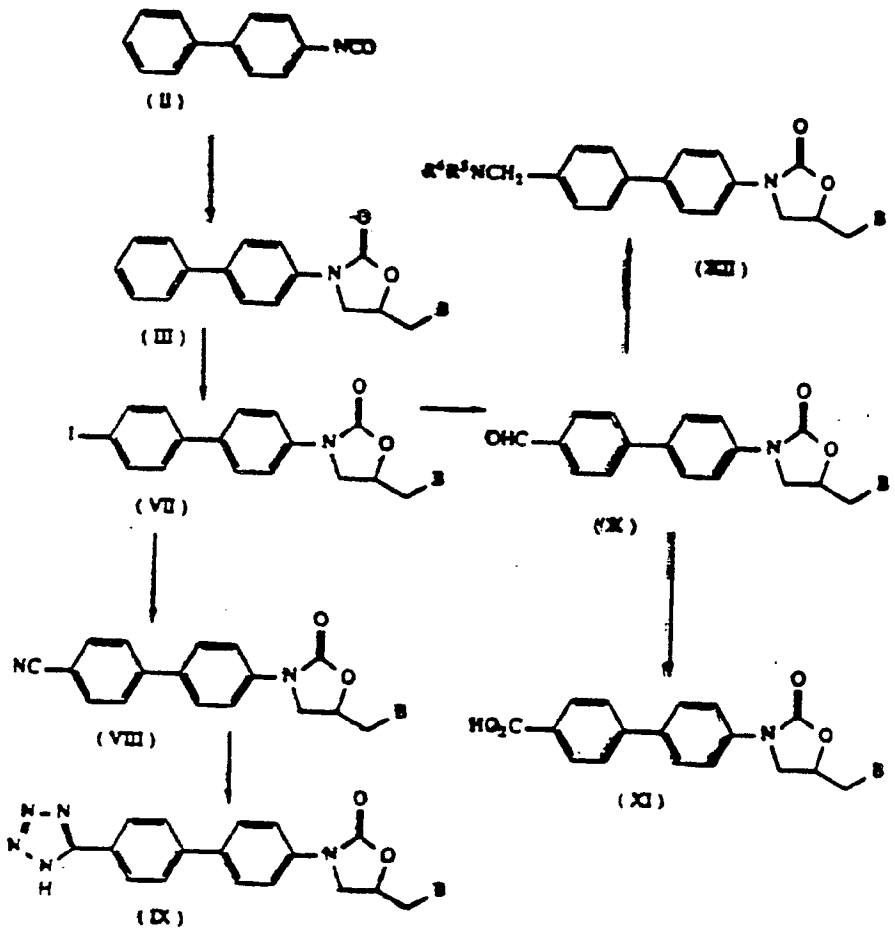



(I)

## Synthesis

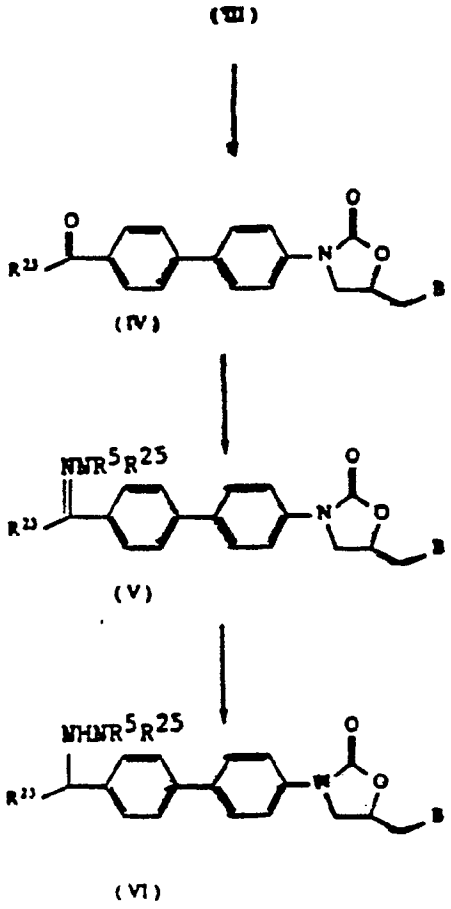
Compounds of Formula (I) can be prepared as follows:

Scheme 1



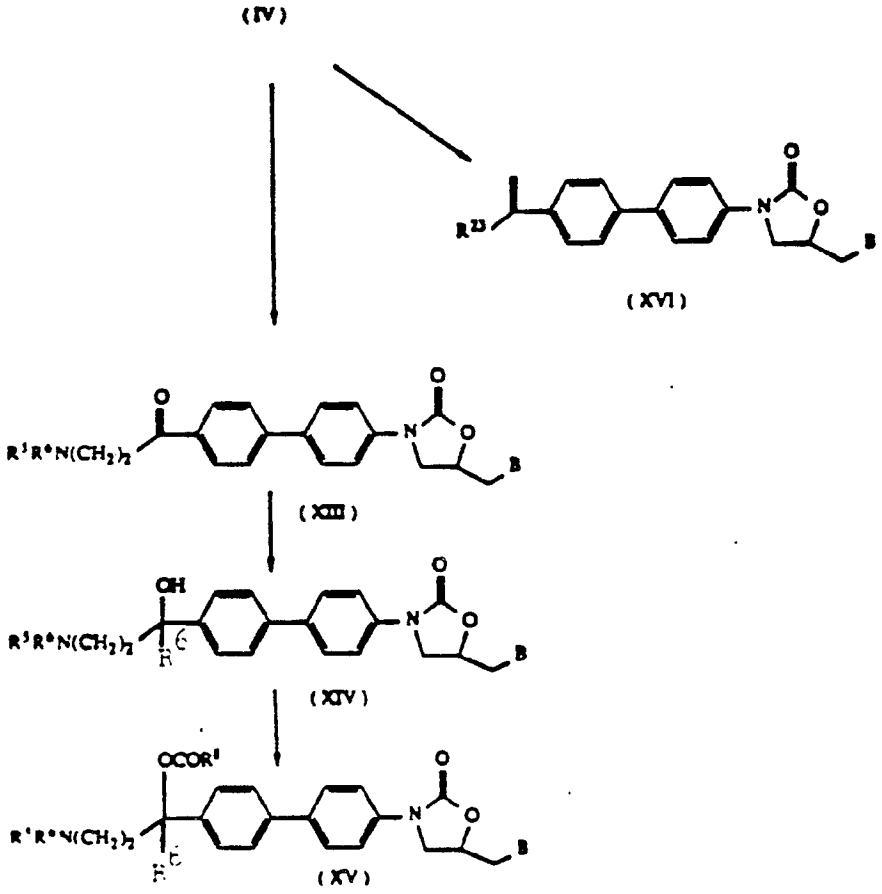
Scheme 1

(Continued)



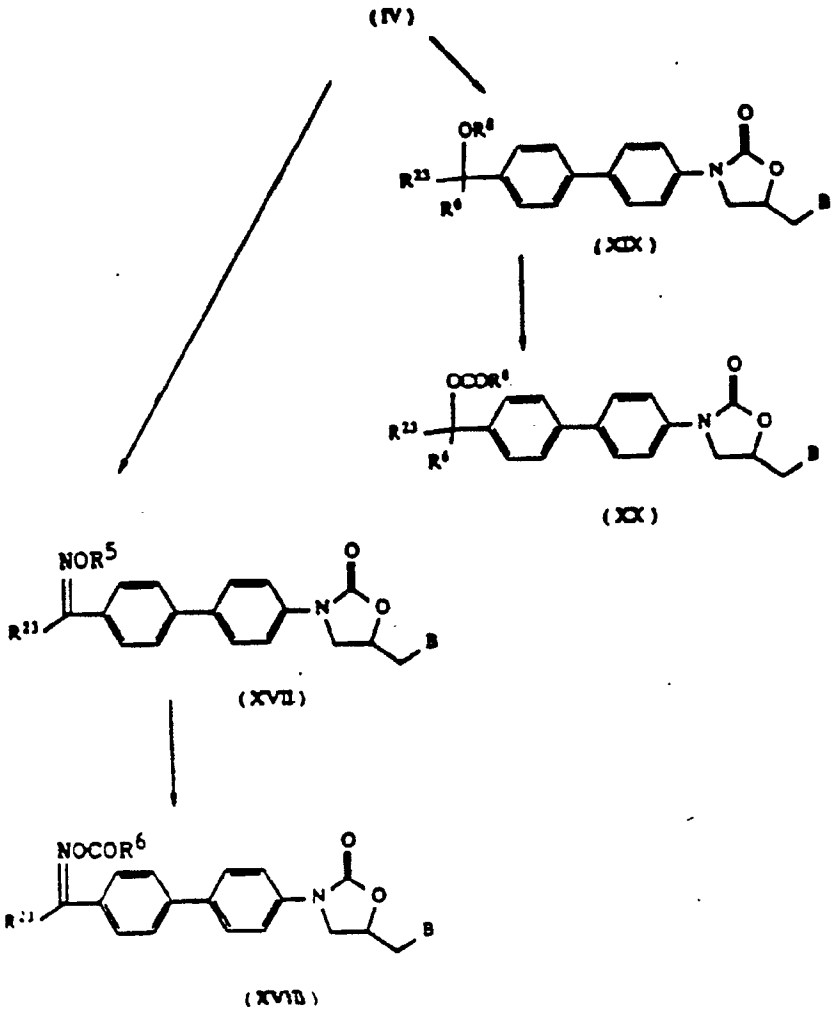
Scheme 1

(Continued)



Scheme 1

(Continued)




In Scheme 1, $R_{23}$ is H or alkyl of 1-8 carbons optionally substituted with a halogen or a terminal carboxylic acid or its salts. $R_5$, $R_6$, and B are as described previously. $R_8$ is H or alkyl of 1-4 carbons optionally substituted with a terminal carboxylic acid or its salts.

The compound (II) is converted to a compound of Formula (III) according to the process exactly paralleling that which was previously described in U.S. Patent 4,705,799. The B groups in Formula (I) can be selected from a variety of groups described and prepared according to the procedures disclosed in the above patent.

A compound of Formula (III) is acylated with acetic anhydride, propionic anhydride, chloroacetic anhydride or succinic anhydride also according to the process described in the aforesaid patent to give a compound of Formula (IV). Reaction of a compound of Formula (IV) with a substituted hydrazine in a solvent such as ethanol, methanol or THF at 20° C to under refluxing temperature of the solvent chosen gives a hydrazone of Formula (V), which can be reduced to a hydrazine derivative of Formula (VI) by reduction using a borohydride such as sodium cyanborohydride in methanol at 25° to 55° C.

A compound of Formula (III) is iodinated with iodine monochloride in an acetic acid-trifluoroacetic acid mixture at 40 to 70° C to a compound of Formula (VII), which can be converted to a cyano compound of Formula (VIII) by reaction with cuprous cyanide. The cyano group of a compound of (VIII) can be converted to a tetrazole derivative of Formula (IX) by reaction with trimethylsilyl azide in DMF at 120-145° C. An

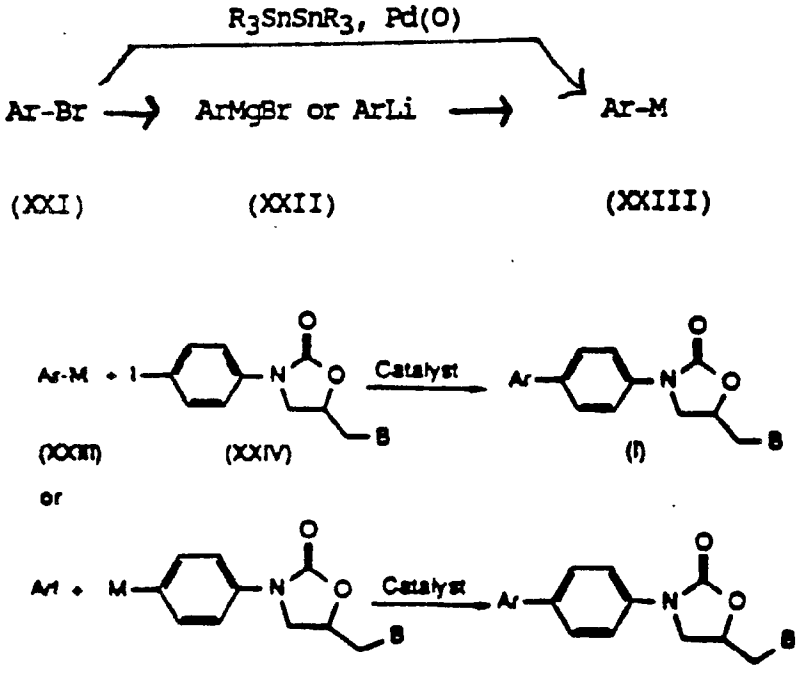
iodocompound (VII) can also be converted to an aldehyde of Formula (X) by addition of carbon monoxide in a suitable solvent such as THF, glyme and DMF or mixtures thereof at 40° to 70° C in the presence of a catalyst such as tributyltin hydride and tetrakis(triphenylphosphine)palladium(0). An aldehyde of (X) can be converted to the corresponding carboxylic acid of Formula (XI) by oxidation with variety of oxidants such as chromic acid. An aldehyde of (X) can also be reductively aminated with an alkylamine such as diethylamine, ethylmethylamine or methylpiperidine in an alcoholic solvent using a reducing agent such as sodium cyanoborohydride and zinc chloride at 0° to 35° C to give an amine of Formula (XII).

Mannich reaction of a ketone of Formula (IV) with variety of alkylamines previously described gives a Mannich base of Formula (XIII) which can be reduced to an alcohol of Formula (XIV) with a borohydride reducing agent such as sodium cyanoborohydride in methanol. An alcohol of Formula (XIV) can be converted to a half ester of a dibasic acid of Formula (XV) by treatment with a dibasic acid anhydride such as succinic or glutaric anhydrides. When the Mannich reaction is carried out with a ketone of Formula (IV), where $R_{23}$ is ethyl, with dimethylamine, an unsaturated ketone of Formula (XVI) is also obtained.

A ketone of Formula (IV), when reacted with an hydroxylamine or a carboxymethyloxyamine in ethanol in the presence of pyridine, produces the corresponding oxime of Formula (XVII). An oxime of Formula (XVII) can be converted to the oximino half ester of a dibasic carboxylic acid of Formula (XVIII) by reaction with a dibasic acid anhydride such as succinic and glutaric anhydrides.

A ketone or aldehyde of Formulae (IV) and (X) can be reduced to a corresponding alcohol of Formula (XIX) by a reducing agent such as sodium borohydride. An alcohol of Formula (XIX) can be esterified with a mono- or dibasic acid anhydride to give a corresponding ester of Formula (XX).

Scheme 2

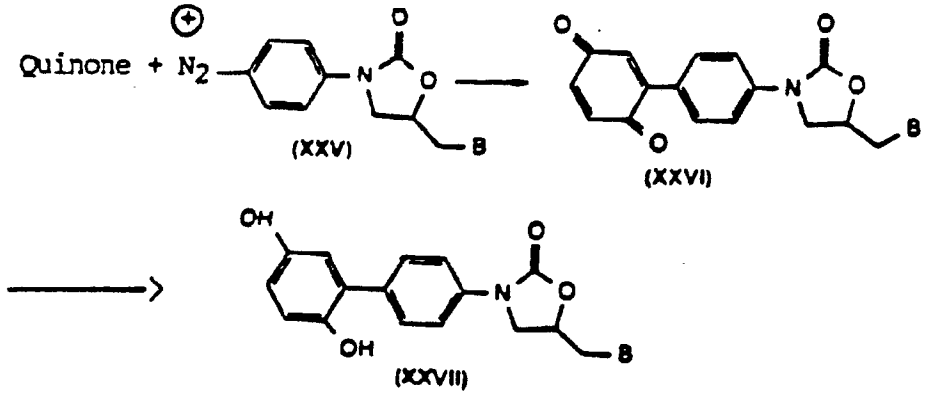



As shown in Scheme 2, Ar is as described previously provided that it contains no active hydrogen, (i.e., no NH, OH or SH), M is a zinc chloride, trialkyltin or boronic acid radical and the catalyst can be selected from one of the many palladium or nickel coordination compounds such as bis(triphenylphosphine)-palladium(II) chloride, tri(2-tolyl)phosphine and palladium(II) acetate, or bis(triphenylphosphine)nickel(II) chloride. An aromatic bromide of Formula (XXI) is converted to a corresponding Grignard reagent with magnesium or to a lithium reagent with alkyllithium by the usual procedures which are well known in the art. A reagent of Formula (XXII) is converted to an organozinc chloride compound with zinc chloride, to a trialkyltin compound with trialkyltin chloride or to a boronic acid with triisopropylborate, each followed by basic hydrolysis in a suitable solvent such as ester, THF or glyme. Alternatively, when Ar contains active hydrogens, an organotin compound of Formula (XXIII) can be prepared by a palladium catalyzed reaction with a bistrialkyltin reagent. A resulting organometallic compound of Formula (XXIII) is cross coupled with a

3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl derivative of Formula (XXIV) in a suitable solvent such as THF or DMF in the presence of a catalyst usually selected from those previously described. The cross coupling reaction works equally well when an aryliodide and a 3-(4-trialkylstannylphenyl)-2-oxooxazolidinyl derivative is reacted in the same manner. The iodo compound of Formula (XXIV) is prepared by iodinating (ℓ)-N-(3-phenyl-2-oxooxazolidin-5-ylmethyl)acetamide using iodine and silver trifluoroacetate or iodine monochloride in a solvent such as chloroform, acetonitrile, acetic acid or mixtures of solvents thereof at a temperature of 0° to 60° C, followed by normal work-up procedures.

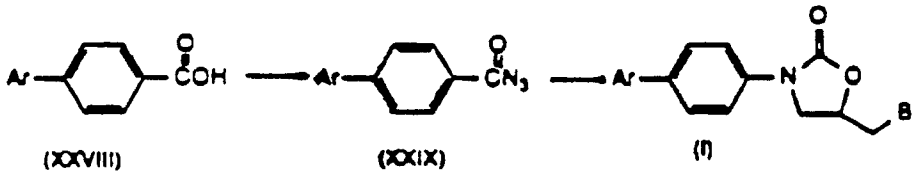
Another coupling reaction, although limited in its applicability, can be used to prepare a compound of Formula (I) where Ar is a dihydroxyphenyl as described in synthetic Scheme 3.

Scheme 3



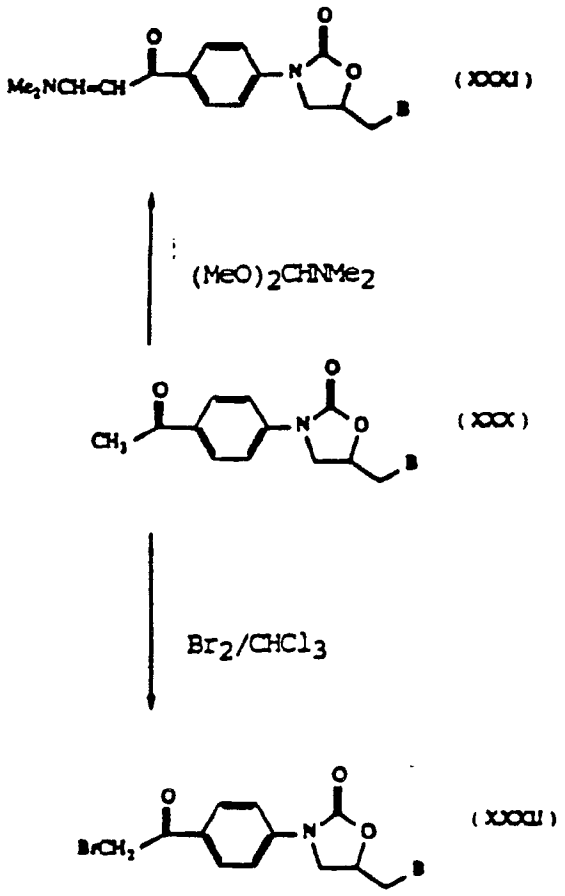

Quinone is reacted with a diazonium salt (XXV) prepared from a 3-(4-aminophenyl)-2-oxooxazolidin-5-ylmethyl derivative to give an adduct of Formula (XXVI), which can be reduced with a borohydride reducing agent such as sodium borohydride to give a dihydroxy compound of Formula (XXVII). The hydroxy groups can be converted to the corresponding ethers using conventional techniques.

Scheme 4



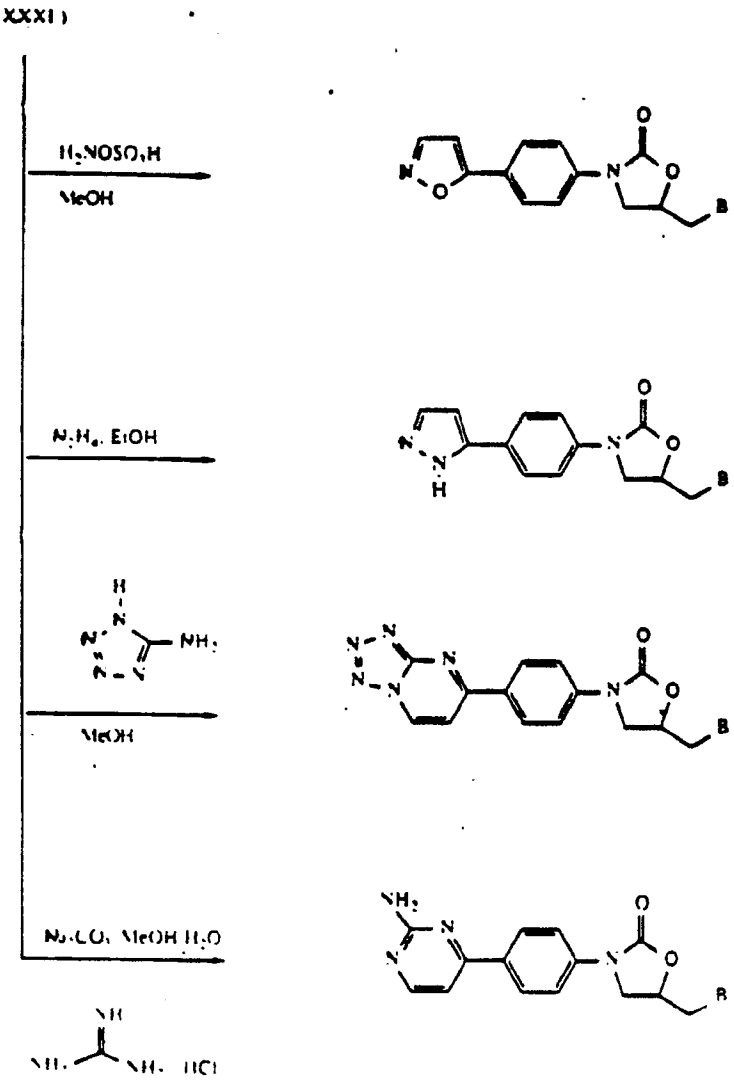

Synthetic Scheme 4 is widely applicable to prepare most of the compounds of Formula (I) provided that there are no active hydrogen atoms (i.e., no NH, OH or SH) present in Ar as described previously. Compounds containing these excluded groups can be prepared via Schemes 1, 3 or 5. A compound of Formula (XXVIII) can be prepared in variety of ways. For example, many of such compounds can be prepared by procedures described in D. J. Byron, G. W. Gray and R. C. Wilson, J. Chem. Soc. (C), 840 (1966). A compound of Formula (XXVIII) can be converted to the corresponding acid chloride followed by reaction with sodium azide according to standard organic reaction procedures to a compound of Formula (XXIX). A compound of Formula (XXIX) is then employed in place of the compound of Formula (II) in Scheme 1 to give the compound of Formula (I).

Scheme 5



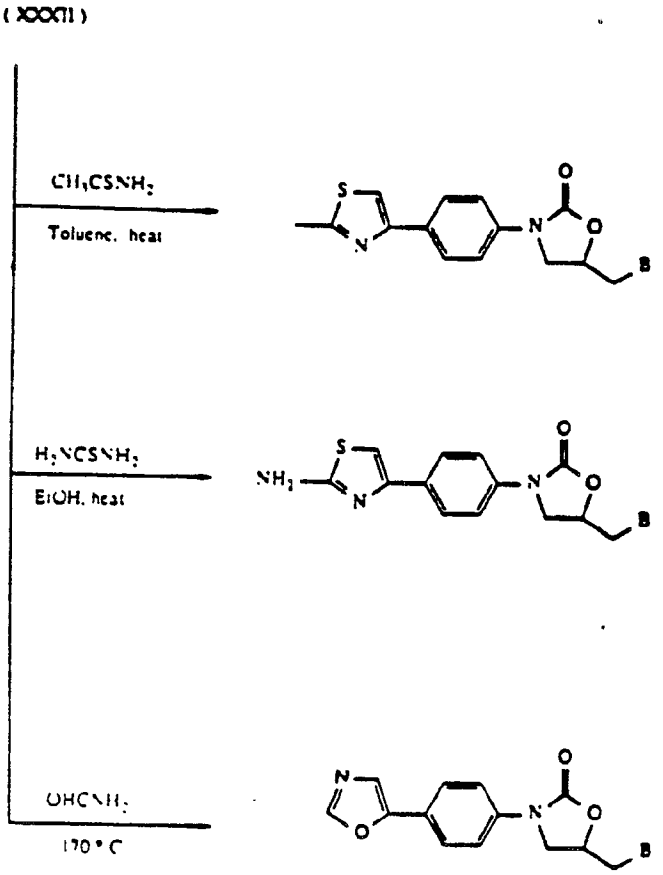
Scheme 5

(Continued)



Scheme 5

(Continued)




Compounds of Formula (I) which can be prepared according to the synthetic Scheme 5 are those with Ar groups made up of 5- and 6-membered ring heterocycles as illustrated.

A 3-(4-acetylphenyl)-2-oxooxazolidin-5-yl derivative (XXX) prepared according to U.S. Patent 4,705,799 is converted to a compound of Formula (XXXI) by reacting it with dimethoxydimethyl-formamide at 100° to 120° C. Reaction of a compound of Formula (XXXI) with a variety of amines give compounds of Formula (I) where Ar is an heteroaromatic moiety as shown.

Similarly, a bromoacetyl derivative (XXXII) where B is azide ($N_3$) obtained by bromination of a compound (XXX) can be reacted with a variety of amides to produce more compounds of Formula (I) where Ar is an heteraromatic moiety. Azides can be reduced to amines as described in U.S. 4,705,799.

Pharmaceutically suitable salts of compounds of Formula (I) can be prepared in a number of ways known in the art. When B is $NH_2$, pharmaceutically suitable salts include those resulting from treatment with mineral and organic acids such as acetic, hydrochloric, sulfuric, phosphoric, succinic, fumaric, ascorbic, and glutaric acids.

The invention can be further understood by reference to the following examples in which parts and percentages are by weight unless otherwise indicated.

Example 1

Preparation of (ℓ)-5-Azidomethyl-3-(4-phenylphenyl)-2-oxoazolidinone (I, Ar = $C_6H_5$, B = $N_3$)

Part A: Preparation of (ℓ)-5-Hydroxymethyl-3-(4-phenyl phenyl)-2-oxazolidinone (I, Ar = $C_6H_5$, B = OH)

A solution containing 10 g (51.2 mmol) of 4-phenylphenylisocyanate and 7.5 g (52.0 mmol) of (ℓ)-glycidyl butyrate in 20 mL of dry xylene was added dropwise to 160 mL of boiling dry xylene containing 0.30 g of lithium bromide and 0.75 g of tributylphosphine oxide over a period of 30 minutes. The mixture was heated under reflux for 1 hour after the addition was complete, allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was triturated with hexane and the resulting solid was dissolved in 150 mL of methanol. To this solution was added 0.7 mL of 25% sodium methoxide in methanol, stirred overnight and the white precipitate formed was collected on a filter to give 13 g (95% theory) of the desired alcohol, mp 236-240 °C, shown to be at least 99% pure by HPLC. The alcohol can be further purified by recrystallization from methanol.

Part B: Preparation of (ℓ)-5-Hydroxymethyl-3-(4-phenylphenyl)-2-oxazolidinone p-toluenesulfonate (I, Ar = $C_6H_5$, B = OTs)

To a solution of 12.94 g (48.05 mmol) of (ℓ)-5-hydroxymethyl-3-(4-phenylphenyl)-2- oxazolidinone in 100 mL of dry pyridine was added 10.6 g (15% excess) of p-toluenesulfonyl chloride at 0-5 °C, and the mixture was stirred at 10-15 °C until all of the alcohol was converted to the tosylate (Ts) as shown by HPLC analysis. The mixture was poured into 500 mL of ice water with vigorous stirring and the resulting white precipitate was collected and recrystallized from an ethanol-acetonitrile mixture to give 16.2 g of the tosylate, mp 157.5-158.5 °C.

Part C:

A mixture of 15.3 g (37.4 mmol) of (ℓ)-5-hydroxymethyl-3-(4-phenylphenyl)-2-oxazolidinone p-toluenesulfonate, 0.2 g of 18-crown-6 and 2.7 g (41.1 mmol, 10% excess) of sodium azide in 60 mL of dry dimethylformamide (DMF) was heated at 70 °C (±5°) for 5 hours and the mixture was poured into 300 mL of ice water to give a white precipitate. The precipitate was collected on a filter to give 10.4 g of the desired azide as a colorless solid, mp 163.5-164.5 °C.

## Example 2

Preparation of (ℓ)-5-Aminomethyl-3-(4-phenylphenyl)-2-oxazolidinone (I, Ar = $C_6H_5$, B = $NH_2$)

(ℓ)-5-Azidomethyl-3-(4-phenylphenyl)-2-oxazolidinone (10.4 g) suspended in 200 mL of 95% ethanol was hydrogenated in the presence of 0.7 g of platinum oxide under 40-50 psig ($2.76x10^5$-$3.45x10^5$ pascals) of hydrogen. The catalyst was removed by filtration through a celite bed, the bed was washed with tetrahydrofuran (THF) and the combined ethanol filtrate and THF washings were concentrated under reduced pressure to give 9.2 g of the desired amine as a colorless solid, mp 140-141 °C.

## Example 3

Preparation of (ℓ)-N-[3-(4-Phenylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = $C_6H_5$, B = $NHCOCH_3$)

To a solution containing 9.2 g of (ℓ)-5-aminomethyl-3-(4-phenylphenyl)-2-oxazolidinone and 8 mL of triethylamine in 200 mL of dry THF was added 3.5 mL of acetyl chloride dissolved in 10 mL of THF

dropwise at 0-10 °C. The mixture was concentrated under reduced pressure and the residue was triturated with water to give a solid which was recrystallized from ethanol to give 8.7 g of the pure amide as a colorless solid, mp 226-227 °C.

| | | | |
|---|---|---|---|
| Anal. Calcd for $C_{18}H_{18}N_2O_3$: | C, 69.66; | H, 5.85; | N, 9.03. |
| Found: | C, 69.44; | H, 5.94; | N, 9.03. |
| | 69.48 | 5.85 | 9.04. |

Example 4

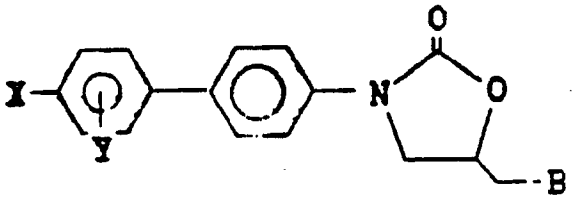
Preparation of (ℓ)-N-[3-(4-(4'-Acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = $CH_3COC_6H_4$, B = $NHCOCH_3$)

To 50 g of trifluoromethanesulfonic acid was added 7.5 mL of acetic anhydride dropwise at 0-5 °C followed by 2.5 g of (ℓ)-N-[3-(4-phenylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide. The mixture was stirred at room temperature for 3 hours and added dropwise to 500 mL of ice water with vigorous stirring. The resulting yellowish precipitate was collected and recrystallized from ethanol to give 2.6 g of the product as a faintly yellowish white solid, mp 261.5-262.5 °C.

| | | | |
|---|---|---|---|
| Anal. Calcd for $C_{20}H_{20}N_2O_4$: | C, 68.17; | H, 5.72; | N, 7.95. |
| Found: | C, 67.87; | H, 5.73; | N, 7.92. |
| | 67.93 | 5.79 | 7.84. |

By using the procedures described in Examples 1-4, the following compounds in Table I were prepared or can be prepared.

Table I



| Ex. | X | Y | B | Isomer | m.p.(°C) |
|---|---|---|---|---|---|
| 1 | H | H | $N_3$ | ℓ | 163.5-164.5 |
| 2 | H | H | $NH_2$ | ℓ | 140-141 |
| 3 | H | H | $NHCOCH_3$ | ℓ | 226-227 |
| 4 | 4'-$CH_3CO$ | H | $NHCOCH_3$ | ℓ | 261.5-262.5 |
| 5 | 4'-$CH_3CO$ | H | $NHCO_2CH_3$ | ℓ | |
| 6 | 4'-$CH_3CO$ | H | $NHSO_2CH_2Cl$ | ℓ | |
| 7 | 4'-$CH_3CH_2CO$ | H | $NHCOCH_3$ | ℓ | 253 |
| 8 | 4'-$ClCH_2CO$ | H | $NHCOCH_3$ | ℓ | 225 |
| 9 | 4'-$HO_2C(CH_2)_2CO$ | H | $NHCOCH_3$ | ℓ | 240-241 |
| 10 | 4'-$HO_2CC(CH_3)_2CH_2CO$ | H | $NHCOCH_3$ | ℓ | 222 (dec) |
| 11 | n-$C_3H_7$ | H | $-NH_2$ | ℓ | |
| 12 | n-$C_3H_7$ | H | $-NHCOCH_3$ | ℓ | |
| 13 | n-$C_5H_{11}$ | H | $-NHCOCH_3$ | ℓ | |
| 14 | $C_2H_5$ | 3'-$CH_3$ | $-N_3$ | ℓ | |
| 15 | $C_2H_5$ | 3'-$CH_3$ | $-NHCOCH_3$ | ℓ | |
| 16 | H | 3'-Cl | $-NHCOCH_3$ | ℓ | |
| 17 | Cl | 3'-$CH_3$ | $-NHCOCH_3$ | ℓ | |
| 18 | $C_2H_5$ | 3'-F | $-NHCOCH_3$ | ℓ | |
| 19 | $CH_3$ | 3'-F | $-NHCOCH_3$ | ℓ | |

Example 20

Preparation of (ℓ)-N-[3-(4-(4'-Iodophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4'-$IC_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-(3-(4-Phenylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (20 g, 0.064 mole) in a mixture of trifluoroacetic acid (170 mL) and acetic acid (570 mL) was stirred and heated at 60°C while adding dropwise a solution of iodine monochloride (139.2 g, 0.86 mole) in acetic acid (225 mL) during 6-7 hours.

The mixture was stirred at 60° C overnight, cooled to room temperature and filtered. The resulting filter cake was washed with ether (to remove excess iodine) and dried to give the desired iodo compound as a tan solid (20.8 g, 74%) which was 94% pure by HPLC. The filtrate was diluted with water and filtered to separate additional product 3.4 g. The main fraction was dissolved in dimethylformamide (200 mL) and filtered through a shallow bed of Darco® or Celite® (which one?). The filtrate was diluted with water (30 mL) and cooled to give pure product (9.1 g), mp 265-267° C.

## Example 21

Preparation of (ℓ)-N-[3-(4-(4′-Formylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$HCOC_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-[3-(4-(4′-Iodophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (4.41 g, 0.01 mole) was refluxed in dry tetrahydrofuran (500 mL) and flushed thoroughly with gaseous CO. Tetrakis(triphenyl-phosphine)palladium(O) (2.35 g, 0.002 mole) was added and the mixture stirred and heated at 50° C under slight positive pressure of CO (balloon) while adding tributyltinhydride (2.94 g, 0.01 mole) in dry toluene (50 mL) during 6 hours. Heating and stirring under gaseous CO pressure was continued overnight. The reaction mixture was cooled to room temperature, added to petroleum ether (600 mL) and filtered to separate the desired aldehyde (3.33 g, 97%). Recrystallization from acetonitrile gave pure aldehyde product as fibrous white needles, mp 210° C.

The aldehyde can be readily converted to the corresponding carboxylic acid by oxidation with chromic acid in acetic acid.

## Example 22

Preparation of (ℓ)-N-[3-(4-(4′-(1-Hydroxyiminoethyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3C(=NOH)C_6H_4$, B = $NHCOCH_3$)

A mixture of 2.8 g of (ℓ)-N-[3-(4-(4′-acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 5.6 g of hydroxylamine hydrochloride and 11.2 mL of pyridine in 560 mL of absolute ethanol was heated under reflux for 3 hours and the mixture was allowed to cool to room temperature. The solid formed was collected and washed with ethanol to give 2.58 g of the desired crude oxime, mp 268-272° C. It can be further purified by recrystallization from ethanol.

## Example 23

Preparation of Sodium Salt of Succinate Hemiester of (ℓ)-N-[3-(4-(4′-(1-Hydroxyiminoethyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3C(=NOCOCH_2CH_2CO_2Na)C_6H_4$, B = $NHCOCH_3$)

To a suspension of 1 g (2.27 mmol) of (ℓ)-N-[3-(4-(4′-(1-hydroxyiminoethyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide in 30 mL of DMF was added 135 mg (2.8 mmol) of NaH (50% dispersion in mineral oil) and the mixture was heated slowly to 40° C when it became clear momentarily, then a massive precipitate formed as it was heated to 50° C for 1 hour. The mixture was allowed to cool to 40° C, and 0.272 g (2.72 mmol) of succinic anhydride dissolved in a minimum volume of DMF was added. The thick white precipitate became opaque and easier to stir. It was heated at 50° C for 0.5 hour, cooled to room temperature, and the precipitate was filtered and washed successively with DMF, glyme and ether to give 1.05 g of the sodium salt as a colorless white solid, mp 297-300° (dec).

## Example 24

Preparation of (ℓ)-N-[3-(4-(4′-(1-Carboxymethoxyliminoethyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide (I, Ar = 4′-$CH_3C(=NOCH_2CO_2H)C_6H_4$, B = $NHCOCH_3$)

A mixture containing 1 g of (ℓ)-N-[3-(4-(4′-acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 2 g of carboxymethoxylamine hydrochloride and 4 mL of pyridine in 180 mL of absolute ethanol was heated under reflux for 3 hours. The mixture was allowed to cool and white precipitate formed was collected and washed with ethanol to give 0.8 g of the desired product, mp 232° C (dec). The sodium salt of the acid can be prepared by treating with aqueous sodium hydroxide and removing the water.

## Example 25

Preparation of (ℓ)-N-[3-(4-(4′-Acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 4-Methyl-piperazinylhydrazone (I, Ar = 4′-$CH_3C(=NN(CH_2CH_2)_2NCH_3)C_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-[3-(4-(4′-Acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (2.5 g, 0.0071 mole) and 1-amino-4-methylpiperazine (2.04 g, 0.018 mole) were heated at reflux in dry dioxane (350 mL) with borontrifluoride etherate (0.30 mL) overnight. The solvent was removed on a rotary evaporator and the product dried (80° C/0.1 mm) to give the titled hydrazine (3.19 g, 100%), mp 200° C (dec).

## Example 26

Preparation of (ℓ)-N-[3-(4-(4′-(1-(4-Methylpiperazinylamino)ether))phenyl)phenyl-2-oxooaxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3CH(NHN(CH_2CH_2)_2NCH_3)C_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-[3-(4-(4′-Acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 4-Methylpiperazinyl-hydrazone (3.57 g, 0.0079 mole) was heated in methanol (250 mL) at reflux and then cooled to room temperature. A solution of $NaBH_3CN$ (0.5 g, 0.0079 mole) and $ZnCl_2$ (0.5 g, 0.004 mole) in methanol (20 mL) was added and the mixture stirred at room temperature overnight followed by reflux for 0.5 hour. The reaction mixture was added to saturated $Na_2CO_3$ (75 mL) and water (200 mL) and extracted with $CH_2Cl_2$/MeOH (9/1, 5 x 100 mL). The extract was dried ($MgSO_4$) and the solvent removed on a rotary evaporator to give the product (2.91 g, 82%). The product was dissolved in 1 N HCl (10 mL) and water (200 mL) and filtered to separate a solid (0.24g). The clear filtrate was divided into two equal parts. One part was made basic with sodium carbonate and extracted with $CH_2Cl_2/CH_3OH$ (9/1, 3 x 100 mL), dried and the solvent removed to give pure produce (1.26 g), mp 120° C. The second portion was freeze dried to give the hydrochloride salt of the product (1.2 g), mp 168° C (dec).

## Example 27

Preparation of (ℓ)-N-[3-(4-(4′-(1-Hydroxyethyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3CH(OH)C_6H_4$, B = $NHCOCH_3$)

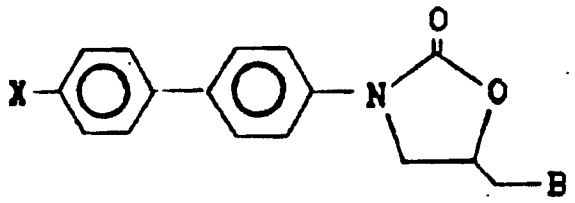
To a suspension of 0.39 g of (ℓ)-N-[3-(4-(4′-Acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide in 100 mL of 95% ethanol was added 0.2 g of $NaBH_4$. The mixture was slowly heated to its boiling point when the mixture became homogeneous. Heating was continued for 15 minutes, diluted with 100 mL of water, brought it back to boiling, allowed to cool to room temperature and stripped to dryness. The resulting

solid was triturated with water to give 0.36 g of white solid, mp 203.5-208.5 °C. It was recrystallized once from ethanol to give 0.26 g of the desired alcohol as white solid, mp 207.5-212.5 °C.

| | |
|---|---|
| Anal. Calcd for $C_{20}H_{22}N_2O_4$: | 354.1577 (M+) |
| Observed m/e by HRMS: | 354.1567. |

By using the procedures described in Examples 20-27, the following compounds in Table II were prepared or can be prepared.

Table II



| Ex. | X | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 20 | 4'-I | $NHCOCH_3$ | ℓ | 265-267 |
| 21 | 4'-HCO | $NHCOCH_3$ | ℓ | 210 |
| 22 | 4'-$CH_3C(=NOH)$ | $NHCOCH_3$ | ℓ | 268-272 |
| 23 | 4'-$CH_3C(=NOCOCH_2CH_2CO_2Na)$ | $NHCOCH_3$ | ℓ | 297-300 (dec) |
| 24 | 4'-$CH_3C(=NOCH_2CO_2H)$ | $NHCOCH_3$ | ℓ | 232 (dec) |
| 25 | 4'-$CH_3C(=NN(CH_2CH_2)_2NCH_3)$ | $NHCOCH_3$ | ℓ | 200 (dec) |
| 26 | 4'-$CH_3CH(NHN(CH_2CH_2)_2NCH_3)$ | $NHCOCH_3$ | ℓ | 168 (dec) |
| 27 | 4'-$CH_3CH(OH)$ | $NHCOCH_3$ | ℓ | 207.5-212.5 |
| 28 | 4'-$HOCH_2$ | $NHCOCH_3$ | ℓ | 235 |
| 29 | 4'-$CH_3CH(OCOCH_2CH_2CO_2H)$ | $NHCOCH_3$ | ℓ | 156 |
| 30 | 4'-$CH_3CH(OCOCH_2CH_2CO_2Na)$ | $NHCOCH_3$ | ℓ | |
| 31 | 4'-$CH(=NOH)$ | $NHCOCH_3$ | ℓ | |
| 32 | 4'-$CH(=NOCH_2CO_2H)$ | $NHCOCH_3$ | ℓ | |
| 33 | 4'-$CH(=NN(CH_2CH_2)_2NCH_3)$ | $NHCOCH_3$ | ℓ | |
| 34 | 4'-$CH_3CH_2C(=NOH)$ | $NHCOCH_3$ | ℓ | |
| 35 | 4'-$CH_3CH_2C(=NOCOCH_2CH_2CO_2H)$ | $NHCOCH_3$ | ℓ | |
| 36 | 4'-$CH_3CH_2CH(OH)$ | $NHCOCH_3$ | ℓ | |

Example 37

Preparation of (ℓ)-N-[3-(4-(4′-Cyanophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$NCC_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-[3-(4-(4′-Iodophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (20.10 g, 0.046 mole) and cuprous cyanide (16.0 g, 0.16 mole) in N-methylpyrrolidinone (270 mL) were stirred and heated at 125° C for 24 hours. The reaction mixture was cooled to room temperature, poured into ice water, and filtered to separate a brown solid. The solid was added to a column packed with silica (84 g) and eluted with $CHCl_3/CH_3OH$ (9/1, 1000 mL) and methanol (750mL). The combined eluents were evaporated to dryness on a rotary evaporator to give the product (12.6 g, 81%) which was 96% pure by HPLC. This material was recrystallized from chloroform to give the pure cyano compound, mp 208-209° C.

| | | | |
|---|---|---|---|
| Anal calcd: | C, 68.05; | H, 5.11; | N, 12.53 |
| Found: | C, 68.14; | H, 5.14; | N, 12.40 |
| | 68.05 | 5.06 | 12.49 |
| HRMS m/e calcd:335.1270, measured 335.1268 | | | |

Example 38

Preparation of (ℓ)-N-[3-(4-(4′-(5-Tetrazolyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$N_4CC_6H_4$, B = $NHCOCH_3$

(ℓ)-N-[3-(4-(4′-Cyanophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (2.68 g, 0.0080 mole) was heated in dimethylformamide (25 mL) with trimethylsilyl azide (1.89 g, 0.016 mole) at 140° C for 5.5 hours. More azide (1.8 g, 0.016 mole) was added and heating at 140° C was continued for a total of 45 hours. The reaction mixture was poured onto ice and centrifuged to separate a brown solid which was washed with water and dried (2.71 g, 90%). The product was purified by chromatography on silica and eluted with $CHCl_3/CH_3OH$ (9/1) and then with methanol. The methanol fraction proved to be the pure product, mp 244° C (dec). The sodium salt of the product can be prepared by treating with aqueous sodium hydroxide and removing the water.

Example 39

Preparation of (ℓ)-N-[3-(4-(4′-((N,N-Methylethylamino)methyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide (I, Ar = 4′-$CH_3CH_2N(CH_3)CH_2C_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-[3-(4-(4′-Formylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (1.7 g, 0.005 mole) and ethylmethylamine (1.48 g, 0.025 mol) were heated at reflux in methanol (170mL). The mixture was cooled to 25° C and a solution of sodium cyanoborohydride (0.315 g, 0.005 mole) in methanol (12.1 mL) was added and the mixture stirred at room temperature overnight. The reaction mixture was added to saturated sodium bicarbonate (25 mL) and water (100 mL) and extracted with $CH_2Cl_2$/MeOH (9/1, 3 x 100 mL). The extract was dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator to give a white solid which was triturated with ether and dried to give the product (1.65 g, 86%). The product was dissolved in 1 N HCl (10 mL) and water (150 mL) to give a clear solution. One half of this solution was made basic with sodium carbonate and extracted with $CH_2Cl_2/CH_3OH$ (9/1, 3 x 100 mL). The extract was dried ($MgSO_4$), filtered and the solvent removed to give pure amine (0.84 g), mp 162-164° C. The residual acidic solution was freeze dried to give the hydrochloride salt of the amine (0.32 g), mp 145-147° C (dec).

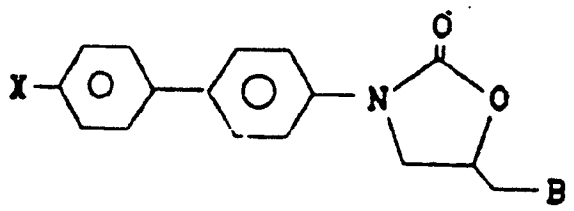
With primary amines, the reaction may stop at the imine stage when the reduction is carried out at room temperature. Refluxing the reaction mixture for 1-3 hours with a small excess of $NaBH_3CN$ or $NaBH_4$

completes the reduction.

Reductive alkylation of ketones frequently fails with $NaBH_3CN/ZnCl_2$ but the intermediate hydrazone can be prepared and reduced as described previously in Example 27.

By using the procedures described in Examples 37-39, the following compounds in Table III were prepared.

Table III



| Ex. | X | B | Isomer | m.p. (°C) |
|---|---|---|---|---|
| 37 | 4'-NC | $NHCOCH_3$ | ℓ | 208-209 |
| 38 | 4'-$N_4C$ | $NHCOCH_3$ | ℓ | 244 (dec) |
| 39 | 4'-$CH_3CH_2N(CH_3)CH_2$ | $NHCOCH_3$ | ℓ | 162-164 |
| 40 | 4'-$CH_3NHCH_2$ | $NHCOCH_3$ | ℓ | 197 (dec) |
| 41 | 4'-$(CH_3)_2NCH_2$ | $NHCOCH_3$ | ℓ | 197 |
| 42 | 4'-$CH_3CH_2NHCH_2$ | $NHCOCH_3$ | ℓ | 180 |
| 43 | 4'-$(CH_3CH_2)_2NCH_2$ | $NHCOCH_3$ | ℓ | 137 (dec) |
| 44 | 4'-$(\underline{n}\text{-}Pr)_2NCH_2$ | $NHCOCH_3$ | ℓ | 128 |
| 45 | 4'-$\underline{n}$-$C_4H_9NHCH_2$ | $NHCOCH_3$ | ℓ | 200 |
| 46 | 4'-$(\underline{n}\text{-}C_4H_9)_2NCH_2$ | $NHCOCH_3$ | ℓ | 107 |
| 47 | 4'-$(\underline{n}\text{-}C_5H_{11})_2NCH_2$ | $NHCOCH_3$ | ℓ | 142 |
| 48 | 4'-$\underline{n}$-$C_8H_{17}N{=}CH$ | $NHCOCH_3$ | ℓ | 210 |
| 49 | 4'-$\underline{n}$-$C_8H_{17}NHCH_2$ | $NHCOCH_3$ | ℓ | 209 |
| 50 | 4'-$(HOCH_2CH_2)_2NCH_2$ | $NHCOCH_3$ | ℓ | 123 |
| 51 | 4'-$CH_3N(CH_2CH_2)_2NNHCH_2$ | $NHCOCH_3$ | ℓ | 194 (dec) |
| 52 | 4'-$CH_3COCH(-NCH_2)\cdot HCl$ | $NHCOCH_3$ | ℓ | 100 |
| 53 | 4'-  | $NHCOCH_3$ | ℓ | |
| 54 | 4'-$CH_3OCH_2CH_2CH_2NHCH_2$ | $NHCOCH_3$ | ℓ | |
| 55 | 4'-$(CH_3)_2NCH_2CH_2NHCH_2$ | $NHCOCH_3$ | ℓ | |
| 56 | 4'-  | $NHCOCH_3$ | ℓ | |

## Example 57

Preparation of (ℓ)-N-[3-(4-(4′-(3-N,N-dimethylaminopropionyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide (I, Ar = 4′-$(CH_3)_2NCH_2CH_2COC_6H_4$, B = $NHCOCH_3$)

N,N,N′,N′-Tetramethyldiaminomethane (0.29 g, 0.0028 mole) was added dropwise to trifluoroacetic acid (5 mL) cooled at -10° C and stirred for 10 minutes. (ℓ)-N-[3-(4-(4′-Acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (1.0 g, 0.0028 mol) was added slowly as a solid at -10° C. The cooling bath was removed and the mixture stirred while warming slowly to room temperature. The reaction temperature was then gradually raised to 60-65° C and heated at this temperature overnight. The reaction mixture was added dropwise to saturated sodium carbonate (50 mL) cooled in an ice bath. The resulting mixture was filtered and the yellow solid washed with water and dried to give the product, 1.12 g, 97%, mp 192-194° C.

A portion of the product (0.5 g) was dissolved in 1 N HCl (10 mL) and water (50 mL), filtered and the clear yellow solution freeze dried to give hydrochloride salt of the ketoamine (0.4 g), mp 150° C gassing, 195° C (dec).

When the Mannich resection was carried out using bis-(N-methylpiperidinyl)methane and propionyl derivative (I, Ar = 4′-$CH_3CH_2COC_6H_4$-, B = $NHCOCH_3$), an elimination product (I, Ar = 4′-$CH_2 = C(CH_3)$-$COC_6H_4$-, B = $NHCOCH_3$) was also obtained (Example 63).

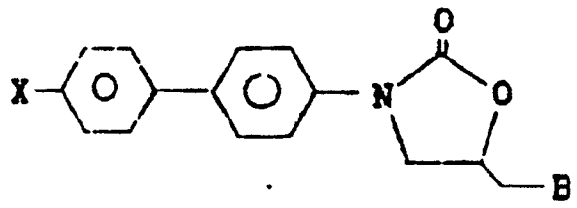
## Example 58

Preparation of (ℓ)-N-[3-(4-(4′-(3-N,N-Dimethylamino-1-hydroxypropyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$(CH_3)_2NCH_2CH(OH)C_6H_4$, B = $NHCOCH_3$)

(ℓ)-N-[3-(4-(4′-3-N,N-Dimethylaminopropionyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (3.14 g, 0.0077 mole) in acetic acid (35 mL) was stirred with $NaBH_3CN$ (1.93 g) at room temperature overnight. The solution was added dropwise to saturated sodium carbonate (400 mL) and the pH adjusted to 9-10. The mixture was extracted with $CH_2Cl_2/CH_3OH$, (9/1, 4 x 150 mL). The extract was dried and the solvent removed to give the crude reduced amine (2.74 g, 87%). The compound was chromatographed on silica gel by eluting with $CHCl_3/CH_3OH$ (9/1) to give pure amine, mp 194° C. A portion of the amine was dissolved in dilute HCl and freeze dried to give the hydrochloride salt.

By using the procedures described in Examples 57 and 58, the following compounds in Table IV were prepared or can be prepared.

Table IV



| Ex. | X | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 57 | 4'-$(CH_3)_2NCH_2CH_2CO$ | $NHCOCH_3$ | ℓ | 192-194 |
| 58 | 4'-$(CH_3)_2NCH_2CH_2CH(OH)$ | $NHCOCH_3$ | ℓ | 194 |
| 59 | 4'-$O(CH_2CH_2)_2NCH_2CH_2CH(OH)$ | $NHCOCH_3$ | ℓ | 165 |
| 60 | 4'-$CH_3N(CH_2CH_2)_2NCH_2CH_2CO$ | $NHCOCH_3$ | ℓ | 221 |
| 61 | 4'-$CH_3N(CH_2CH_2)_2NCH_2CH_2CH(OH)$ | $NHCOCH_3$ | ℓ | 151 (dec) |
| 62 | 4'-$CH_3N(CH_2CH_2)_2NCH_2CH(CH_3)CO$ | $NHCOCH_3$ | ℓ | 105 |
| 63 | 4'-$CH_2=C(CH_3)CO$ | $NHCOCH_3$ | ℓ | 216 |
| 64 | 4'-$CH_3N(CH_2CH_2)_2NCH_2CH(CH_3)CH(OH)$ | $NHCOCH_3$ | ℓ | 180 |

Example 65

Preparation of (ℓ)-N-[3-(4-(3'-Methylsulfenylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 3'-$CH_3SOC_6H_4$, B = $NHCOCH_3$)

To a mixture containing 23.4 g (0.1 mol) of (ℓ)-N-(3-phenyl-2-oxooxazolidin-5-ylmethyl)acetamide and 29 g (0.13 mol) of silver trifluoroacetate, 300 mL of acetonitrile and 200 mL of chloroform was added 27 g of iodine in one portion and allowed to stir at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a brown solid which was triturated with distilled water, filtered and washed thoroughly with distilled water. The resulting solid was recrystallized from 200 mL of acetonitrile (activated charcoal used) to give 27.5 g (77%) of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (XXIV) as a colorless crystalline solid, m.p. 194.5-195.5 °C.

A Grignard reagent was prepared from 25 g (0.123 mol) of m-bromothioanisole and 3.59 g (0.148 mol) of magnesium in 125 mL of tetrahydrofuran. This solution was added to 56.8 mL (0.246 mol) of triisopropylborate in tetrahydrofuran at -70 °C. The borate ester was hydrolyzed with 10% sodium hydroxide solution, then acidified to give the boronic acid. Recrystallization from water gave 11.0 g of the boronic acid, mp 162-163 °C.

A mixture of 2.5 g (0.015 mol) of the above boronic acid in 40 mL of DMF, 4.2 mL of triethylamine, 3.6 g of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 0.2 g of tri-2-tolylphosphine and 80 mg of palladium acetate was subjected to four "Firestone" cycles. The homogeneous solution was held at 100 °C under nitrogen for 72 hours, cooled, and filtered. The DMF was removed at 70 °C (0.5 mm Hg) and

the residue dissolved in methylene chloride and washed with 10% ammonium hydroxide solution, dried over magnesium sulfate and solvent evaporated to give 2.31 g of crude material which was chromatographed on 70 g of silica gel with an eluent of methylene chloride-acetone to give 1.24 g of material consistent with product. Recrystallization from acetonitrile gave 0.8 g of pure (ℓ)-N-[3-(4-(3′-methylthiophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

A mixture of 0.51 g (0.0014 mol) of the sulfide in 155 mL of chloroform was held at reflux to dissolve the solid, then cooled to -30° C, and a solution of 0.30 g (0.0014 mol) of 82% m-chloroperbenzoic acid in 15 mL of methylene chloride was added at -30° C, then allowed to warm to -20° C. After addition of 0.1 mL of dimethylsulfide, the mixture was warmed to 20° C and the solvent removed. The residue was dissolved in chloroform and washed with saturated sodium bicarbonate solution, dried over potassium carbonate and solvent evaporated. The residue was chromatographed on 25 g of silica gel with methylene chloride-acetone as the eluent. The product was dissolved in water, filtered (0.2 micron membrane filter) and the water removed. The residue was recrystallized from isopropanol to give 180 mg of the sulfoxide, mp 162-167° C. $^1$H-NMR ($d_6$-DMSO) δ 8.27 (m,1H), 7.93 (s,1H), 7.80 (m,3H), 7.67 (m,4H), 4.73 (m,1H), 4.20 (t,1H), 3.80 (t,1H), 3.45 (m,2H), 2.80 (s,3H), 1.83 (s,3H); IR (KBr): 3280, 1750; 1665, 1610, 1520, 1050 cm$^{-1}$.

The sulfoxide can further oxidize to sulfone by reacting with excess MCPBA in chloroform under reflux for 3 hours.

## Example 66

Preparation of (ℓ)-N-[3-(4-(4′-N,N-Dimethylaminoethyloxyphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide (I, Ar = 4′-$(CH_3)_2NCH_2CH_2OC_6H_4$, B = $NHCOCH_3$)

A freshly prepared solution of 4-benzyloxyphenyl magnesium bromide (from 21.05 g of 4-benzyloxybromobenzene and 2.2 g of magnesium metal) in tetrahydrofuran (80 mL) was added carefully to a stirred solution of freshly fused zinc chloride (17.14 g) in tetrahydrofuran maintained at 0-5° C. The resulting mixture was stirred at room temperature for 30 minutes and then treated with (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-yl]methylacetamide (14.4 g), added in one lot, followed by the addition of bis-(triphenylphosphine)nickel(II) chloride (4.0 g). The mixture was stirred at room temperature for 90 minutes and then poured into an excess of ice and 1 N HCl and the solid that separated filtered off, washed with water, boiled with tetrahydrofuran and filtered. The solid was washed with a small quantity of tetrahydrofuran followed by hexanes and air-dried to yield 9.72 g of (ℓ)-N-[3-(4-(4′-benzyloxyphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide as a colorless solid, mp 235-237° C (dec). It was pure enough to be used in the next step. An analytical sample was prepared by recrystallizing a small quantity of the product from acetic acid, mp 243-245° C (dec).

A suspension of the benzyloxy compound (6.74 g) in a solution of hydrogen bromide in acetic acid (72 mL; 30.32%) was stirred and heated under reflux for 10 to 15 minutes, cooled and filtered. The colorless solid was washed with ether and air-dried to yield (ℓ)-N-[3-(4-(4′-hydroxyphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (4.03 g), mp 280-281° C (dec).

Sodium hydride (0.5 g; 50% oil dispersion) was added in small portions to a stirred solution of the phenolic compound (3.26 g) in warm dimethylformamide (75 mL) and, after the addition was complete, the mixture was stirred at room temperature for 15 minutes and then treated with a freshly prepared solution of 2-dimethylaminoethyl chloride (from 6.0 g of the hydrochloride and aq $NaHCO_3$) in benzene (30 mL) added in one lot. The resulting mixture was stirred and heated at 90-100° C overnight and then stripped of the solvents under reduced pressure. The residue was triturated with water and filtered. The solid was dissolved in requisite volume of methylene chloride and the solution extracted twice with 1 N HCl (50 mL each time). The combined acid extracts were filtered to remove traces of undissolved material and the filtrate cooled and basified with conc. ammonium hydroxide. The mixture was extracted twice with methylene chloride and the combined methylene chloride extracts were washed with $H_2O$, dried over $MgSO_4$ and stripped of the solvent under reduced pressure to yield a solid which was recrystallized from isopropanol to furnish 1.4 g of (ℓ)-N-[3-(4-(4′-N,N-Dimethylaminoethyloxyphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide as a colorless solid, mp 202-204° C.

## Example 67

Preparation of (ℓ)-N-[3-(4-4′-Methylthiophenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3SC_6H_4$-, B = $NHCOCH_3$)

A Grignard reagent was prepared from 12.2 g (0.06 mol) of p-bromothioanisole and 1.7 g (0.07 mol) of magnesium in 70 mL of tetrahydrofuran. This solution was added to 22.7 mL of triisopropylborate in tetrahydrofuran at -70° C. The borate ester was hydrolyzed with 150 mL of 1 N sodium hydroxide solution and most of the tetrahydrofuran from the mixture was removed under reduced pressure. Acidification of the basic solution with 10% hydrochloric acid gave 9.28 g of the crude boronic acid. Recrystallization from water gave 3.8 g of pure p-methylmercaptophenyl-boronic acid as a colorless, crystalline solid, m.p. 211.5-212° C.

A mixture of 2.52 g (0.015 mol) of the above boronic acid in 40 mL of DMF, 4.2 mL of triethylamine, 3.6 g of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 0.2 g of tri-2-tolylphosphine and 80 mg of palladium acetate under nitrogen atmosphere was heated at 100° C for 72 hrs. cooled, and diluted with 40 mL of ether. The solid precipitate formed was filtered, washed successively with ether, water, sodium bicarbonate and water to give a crude product. The crude product was recrystallized once from ethanol to give 1.3 g of pure (ℓ)-N-[3-(4-(4′-methylthiophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, m.p. 244.5-246.5° C. HRMS: Calcd. 356.1195; Measured, 356.1168.

## Example 68

Preparation of (ℓ)-N-[3-(4-(4′-Methylsulfenylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3SOC_6H_4$-, B = $NHCOCH_3$)

A mixture of 0.6 g (1.68 mmol) of the sulfide of Example 67 in 250 mL of chloroform was heated to dissolve the solid, then cooled to -30° C, and 0.36 (1.68 mmol) of 82% m-chloroperbenzoic acid was added at -30° C, then allowed to slowly warm to -10° C. Trace of insoluble material was removed by filtration and the filtrate was diluted with ether to precipitate 0.59 g of the sulfoxide, m.p. 217-219° C. The product was shown to be at least 99% pure by hplc. An nmr ($CDCl_3$) showed absence of any sulfone resonance. HRMS: Calcd. 372.1144; Measured, 372.1156.

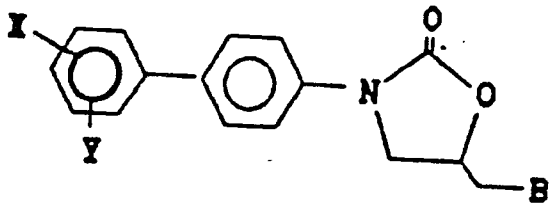
## Example 69

Preparation of (ℓ)-N-[3-(4-(4′-Methylsulfonylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4′-$CH_3SO_2C_6H_4$-, B = $NHCOCH_3$)

A mixture of 0.4 g (1.1 mmol) of the sulfide of Example 67 and 0.53 g (2.45 mmol) of 82% m-chloroperbenzoic acid in 200 mL of chloroform was heated under reflux for 2.5 h. The mixture was cooled and diluted with ether to precipitate the desired sulfone, 0.4 g, m.p. 259-260.5° C dec. The product was shown to be homogeneous by hplc. HRMS: Calcd. 338.1089; Measured, 338.1126.

By using the procedures described in Examples 65-69, the following compounds in Table V were prepared or can be prepared.

Table V



| Ex. | X | Y | B | Isomer | m.p.(°C) |
|---|---|---|---|---|---|
| 65 | 3'-$CH_3SO$ | H | $NHCOCH_3$ | ℓ | 162-167 |
| 66 | 4'-$(CH_3)_2NCH_2CH_2O$ | H | $NHCOCH_3$ | ℓ | 202-204 |
| 67 | 4'-$CH_3S$ | H | $NHCOCH_3$ | ℓ | 244.5-246.5 |
| 68 | 4'-$CH_3SO$ | H | $NHCOCH_3$ | ℓ | 217-219 |
| 69 | 4'-$CH_3SO_2$ | H | $NHCOCH_3$ | ℓ | 259-260.5 (dec) |
| 70 | 3'-$CH_3CH_2$ | H | $NHCOCH_3$ | ℓ | 121-122 |
| 71 | 2'-$CH_3$ | H | $NHCOCH_3$ | ℓ | 181-183 |
| 72 | 3'-HCO | H | $NHCOCH_3$ | ℓ | 146-147 |
| 73 | 3'-$NH_2$ | H | $NHCOCH_3$ | ℓ | 220-221 |
| 74 | 3'-$(CH_3)_2N$ | H | $NHCOCH_3$ | ℓ | 163-163.5 |
| 75 | 4'-$CH_3O$ | H | $NHCOCH_3$ | ℓ | 239-241 (dec) |
| 76 | 4'-$(CH_3)_2N(CH_2)_3O$ | H | $NHCOCH_3$ | ℓ | 191-193 |
| 77 | 4'-$C_6H_5CH_2OCOCH_2O$ | H | $NHCOCH_3$ | ℓ | 186-187 |
| 78 | 4'-$HO_2CCH_2O$ | H | $NHCOCH_3$ | ℓ | 228-230 (dec) |
| 79 | 4'-F | H | $NHCOCH_3$ | ℓ | 229-230 (dec) |
| 80 | 4'-Cl | H | $NHCOCH_3$ | ℓ | 249-250 (dec) |
| 81 | 4'-$CH_3$ | 5'-$CH_3$ | $NHCOCH_3$ | ℓ | 168-169 |
| 82 | 3'-$CH_3$ | 5'-$CH_3$ | $NHCOCH_3$ | ℓ | 106-107 |
| 83 | 4'-F | 5'-F | $NHCOCH_3$ | ℓ | 201.5-203 |
| 84 | 3'-F | 5'-F | $NHCOCH_3$ | ℓ | 204-204.5 |

Example 85

Preparation of (ℓ)-N-[3-(4-(4-Pyridyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 4'-$NC_5H_4$, B = $NHCOCH_3$

To a stirred solution of 75 g (0.386 mol) of 4-bromopyridine hydrochloride in 400 mL of ether and 200 mL of water (2 layer system) was added 40 g of sodium carbonate (0.38 mol) in several portions. The water was separated, the ether layer was washed once with brine, dried ($MgSO_4$) and most of the solvent was

removed under reduced pressure. As soon as the vacuum started to improve indicating that most of the ether was removed, 200 mL of fresh anhydrous ether was added and the solvent was again removed. This process was repeated once more to minimize any moisture present. To the residue still containing small amount of ether was added 750 mL of ether immediately. The solution was cooled to -78° C, and 185 mL (0.462 mol, 20% excess) of 2.5 N n-butyllithium (in hexane) was added at such a rate that the temperature of the reaction mixture remained below -65° C (~20 min). When the temperature returned to below -70°, 92.2 g (0.463 mol) of trimethyltin chloride dissolved in 200 mL of ether was added at below -65° C. When the addition was complete, it was stirred at -75° C for 0.5 hour, and then the cooling bath was removed to allow the temperature of the reaction to slowly rise. When the temperature of the reaction reached -20° C, 10 mL of methanol followed by 200 mL of water were added and the mixture was allowed to come to room temperature. The ether layer was washed once with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give 114 g of a light tan liquid. The pure product was isolated by distillation through a 30 cm Vigreux column, bp 40-42° C (0.1 mm), [bp 32-34° C (0.07 mm)]. n-Butyltrimethyltin, a by-product, distills at below room temperature at this pressure and separates well by distillation through the 30 cm Vigreux column.

A mixture containing 74.5 g (0.204 mol) of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide, 60 g (0.248 mol) of 4-pyridyltrimethyltin, 23 g (0.033 mol) of freshly prepared bis-(triphenylphosphine)palladium(II) chloride and 71 mL of triethylamine in 1300 mL of dry dimethyformamide (DMF) was heated at 50-60° C until all of the iodophenyloxazolidinone is used up (24-28 hours) as monitored by HPLC. The insoluble catalyst was removed by filtration through a bed of Celite® and the volatile material and all of the solvent (DMF) from the filtrate was removed under reduced pressure (<40° C). The resulting oil was taken up in 500 mL of chloroform and diluted with 1.5 L of ether to give a tan precipitate. The precipitate was filtered and dried under a stream of nitrogen, digested with 1 L of 1 N HCl, filtered to remove insoluble material and neutralized to pH of 8 using conc. ammonium hydroxide at 10-20° C. The off-white precipitate was collected on a filter, dissolved in 400 mL of hot 95% ethanol, treated with charcoal, and diluted with 700 mL of water. The solution was concentrated under reduced pressure to remove most of the ethanol to give an off-white precipitate. The precipitate was collected on a filter and washed with a small amount of ice water and dried to give 26 g (40.3% theory) of the product, mp 188-190° C. Several other runs conducted under the same conditions gave products in 40-45% yields. The material can be further purified by recrystallization from absolute ethanol, or repeated the work-up procedure to give analytically pure sample of (ℓ)-N-[3-(4-(4-pyridyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide as a colorless white solid, mp 191-192° C.

| | | | |
|---|---|---|---|
| Anal. Calcd for $C_{17}H_{17}N_3O_3$: | C, 65.58; | H, 5.50; | N, 13.50 |
| Found: | C, 65.33; | H, 5.67; | N, 13.37 |
| | 65.35 | 5.53 | 13.38 |

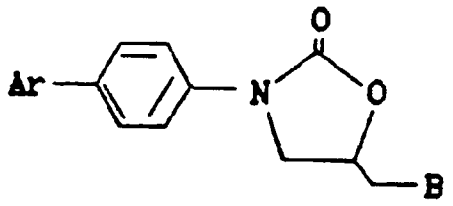
Following a procedure similar to the one described in Example 65, amine oxide derivatives of the pyridyl compounds were prepared by treating with excess MCPBA.

ℓ-N-[3-(4-Tri-n-butylstannylphenyl)-2-oxooxazolidin-5-yl-methyl]acetamide was prepared as follows.

To a mixture of 7.0 mL of hexabutylditin, 3.60 g of (ℓ)-N-[3-(4-iodophenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide and 25 mL of DMF under nitrogen, which had been subjected to several Firestone cycles to remove oxygen, was added 0.16 g of $(PhCN)_2PdCl_2$ with stirring and the mixture was stirred at 70° C overnight. The mixture was poured into 500 mL of water and extracted with ethyl acetate, which was dried ($MgSO_4$), filtered through a Celite® pad to remove both Pd and the $MgSO_4$, and evaporated in vacuo. The mixture was chromatographed on silica with chloroform to give the pure (ℓ)-N-[3-(4-tri-n-butylstannyl-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide free from tributyltin iodide by-product as a contaminant. Isolated was 3.21 g.

By using the procedures described in Example 85, the following compounds in Table VI were prepared or can be prepared.

Table VI



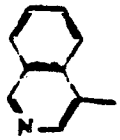
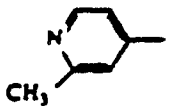
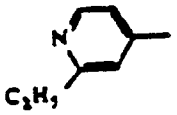
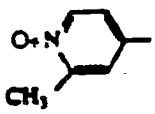
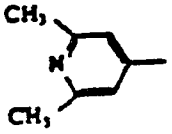
| Ex. | Ar | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 85 | 4'-$NC_5H_4$ | $NHCOCH_3$ | ℓ | 191-192 |
| 86 | 2'-$NC_5H_4$ | $NHCOCH_3$ | ℓ | 170-173 |
| 87 | 2'-$ONC_5H_4$ | $NHCOCH_3$ | ℓ | 110 (dec) |
| 88 | 3'-$NC_5H_4$ | $NHCOCH_3$ | ℓ | 183-185 |
| 89 | 3'-$ONC_5H_4$ | $NHCOCH_3$ | ℓ | 220 (dec) |
| 90 | 4'-$ONC_4H_4$ | $NHCOCH_3$ | ℓ | |
| 91 | 4'-$ClC_6H_4$ | $NHCOCH_3$ | ℓ | 249-250 |
| 92 |  | $NHCOCH_3$ | ℓ | 221-222 (dec) |
| 93 |  | $NHCOCH_3$ | ℓ | 196 (dec) |
| 94 |  | $NHCOCH_3$ | ℓ | |
| 95 |  | $NHCOCH_3$ | dℓ | |
| 96 |  | $NHCOCH_3$ | dℓ | |

Table VI
(Continued)

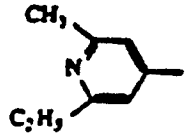
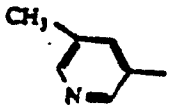
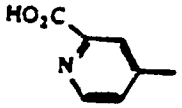
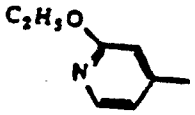
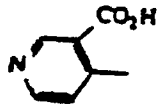
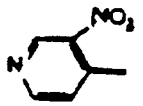
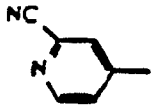
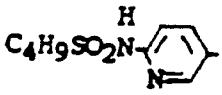
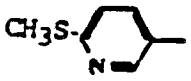
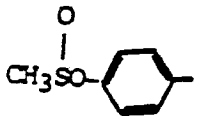
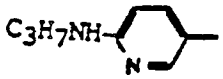
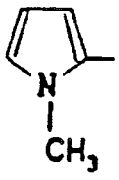
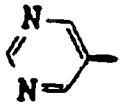
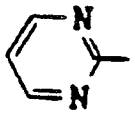
| Ex. | Ar | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 97 |  | $NHCOCH_2Cl$ | ℓ | |
| 98 |  | $NHSOCH_3$ | ℓ | |
| 99 |  | $NHCOC_3H_7$ | ℓ | |
| 100 |  | $NHSO_2C_2H_5$ | ℓ | |
| 101 |  | $NHCOCH_3$ | ℓ | |
| 102 |  | $N_3$ | ℓ | |
| 103 |  | $NH_2$ | ℓ | |
| 104 |  | $NHCOCH_3$ | ℓ | |

Table VI
(Continued)

| Ex. | Ar | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 105 |  | $NHCOCH_3$ | ℓ | |
| 106 |  | $NHCOCH_3$ | ℓ | |
| 107 |  | $NHCOCH_3$ | ℓ | |
| 108 |  | $NHCOCH_3$ | ℓ | |
| 109 |  | $NHCOCH_3$ | ℓ | |
| 110 |  | $NHCOCH_3$ | ℓ | |
| 111 |  | $NHCOCH_3$ | ℓ | |
| 112 |  | $NHCOCH_3$ | ℓ | |

## Example 113

Preparation of (ℓ)-N-[3-(4-(2′,5′-Dihydroxyphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I,Ar=2′,5′-$(HO)_2C_6H_4$, B=$NHCOCH_3$)

(ℓ)-N-[3-(4-Nitrophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide was prepared according to the procedures previously described in U.S. Patent 4,705,799. The nitro compound was reduced to the corresponding amino derivative by catalytic hydrogenation in 95% ethanol in the presence of platinum oxide under 40 psig of hydrogen pressure.

To a mixture containing 1 g (4 mmol) of (ℓ)-N-[3-(4-aminophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, 1 mL of 28% HCl and 4 g of ice was added a solution of 0.28 g of sodium nitrite in 1 mL of water dropwise at 0-5° C. After the addition was complete, the mixture was tested with starch/iodide paper to insure the reaction was complete. The mixture after being made neutral (pH 6-7) by cautious addition of sodium carbonate dropwise to a solution of 0.65 g (50% excess) of benzoquinone dissolved in a minimum amount (~15 mL) of 95% ethanol with vigorous stirring at 10-15° C. The mixture was allowed to come to room temperature, stirred for 1 hour and diluted with 200 mL of water. The desired benzoquinone attached phenyloxazolidinone was obtained as a brick colored solid, 0.95 g, mp 218-219.5° C. It was recrystallized once from acetonitrile to give 0.4 g of the pure quinone derivative as a golden orange solid, mp 235-236° C.

To the orange solid (1.6 g, 4.7 mmol) suspended in 45 mL of 95% ethanol was added 0.5 g of sodium borohydride. A slight exotherm was noted and the mixture became homogeneous in 10 minutes. Water (50 mL) was added and the mixture was warmed to 50° C. After allowing to cool, most of the ethanol was removed under reduced pressure and the resulting aqueous solution was made acidic (pH 1) with 6 M HCl to precipitate the product. The product was obtained as a light grayish purple solid, 1.03 g, mp 227-228.5° C.

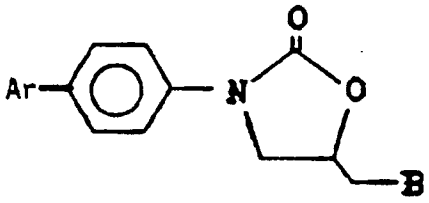
## Example 114

Preparation of (ℓ)-N-[3-(4-(4′-Ethylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar=4′-$CH_3CH_2C_6H_4$, B=$NHCOCH_3$)

To 4′-ethylbiphenylcarboxylic acid (20 mmol) dissolved in 50 mL dry DMF was added 25 mmol of triethylamine and the mixture was cooled in an ice bath, added 38.5 mmol of methyl chloroformate dropwise at 0-5° C, and the stirred at room temperature for 15 minutes. The mixture was cooled to 0° C again, and a cold solution of 38.5 mmol of sodium azide dissolved in a minimum amount of water (<8 mL) was added as rapidly as possible (in one portion if possible) at <5° C. The reaction mixture was stirred at 0° C for 1 hour and poured into 500 mL of ice-water. The resulting precipitate was filtered while still cold (<10 min), washed with cold water and dried under a stream of nitrogen to give the crude 4′-ethylbiphenylcarbonyl azide. The azide was used in place of 4′-ethylbiphenylisocyanate for the subsequent reactions according to the procedures exactly paralleling those described previously for Examples 1 through 3 to give the desired product as a colorless solid, mp 223-224° C.

By using the procedures described in Examples 113 and 114, the following compounds in Table VII were prepared or can be prepared.

Table VII



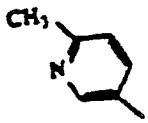
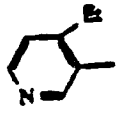
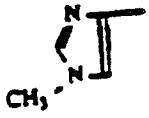
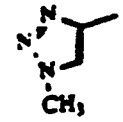
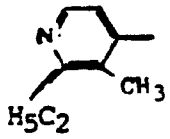
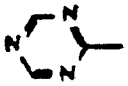
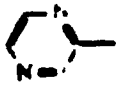
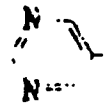
| Ex. | Ar | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 113 | 2',5'-diOHC$_6$H$_3$ | NHCOCH$_3$ | ℓ | 227-228.5 |
| 114 | 4'-C$_2$H$_5$C$_6$H$_4$ | NHCOCH$_3$ | ℓ | 223-224 |
| 115 | 4'-(CH$_3$)$_2$NC$_6$H$_4$ | NHCOCH$_3$ | dℓ | |
| 116 | 4'-(CH$_3$)$_2$N(O)C$_6$H$_4$ | NHCOCH$_3$ | dℓ | 125-127 |
| 117 | 4'-(9-fluorinon-2-yl) | NHCOCH$_3$ | ℓ | 237.5-238.5 |
| 118 | 4'-(9-fluorinol-2-yl) | NHCOCH$_3$ | ℓ | 214-221 |
| 119 | 3'-O$_2$NC$_6$H$_4$ | NHCOCH$_3$ | ℓ | 140-141 |
| 120 |  | NHCOCH$_3$ | dℓ | |
| 121 |  | NHCOCH$_3$ | dℓ | |
| 122 |  | NHCOCH$_3$ | ℓ | |

Table VII (continued)

| Ex. | Ar | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 123 |  | $NHCOCH_3$ | ℓ | |
| 124 |  | $NHCOCH_3$ | ℓ | |
| 125 |  | $NHCOCH_3$ | ℓ | |
| 126 |  | $NHCOCH_3$ | ℓ | |
| 127 |  | $NHCOCH_3$ | ℓ | |
| 128 |  | $NHCOCH_3$ | ℓ | |
| 129 |  | $NHCOCH_3$ | ℓ | 209-211 |

67

## Example 130

Preparation of (ℓ)-N-[3-(4-(5-Isoxazolyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I, Ar = 5-isoxazolyl, B = $NHCOCH_3$)

A mixture of (ℓ)-N-[3-(4-acetylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (500 mg, 1.8 mmol) in 2 mL of dimethoxyformamide was heated at 110° C overnight (16 hours). Excess dimethoxyformamide was removed in vacuo and the residue was purified by flash column chromatography to give 328 mg (55%) of (ℓ)-N-[3-(4-(3-dimethylamino-2-ethenylketo)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide as a white solid. mp 191-192° C; $^1$H-NMR ($CDCl_3$) δ: 7.95 (d,J = 7Hz,2H), 7.83 (d,J = 13Hz,1H), 7.58 (d,J = 7Hz,2H), 6.50 (m,1H), 5.75 (d,J = 13Hz,1H), 4.83 (bs,1H), 4.12 (t,1H), 3.83 (dd,1H), 3.67 (m,2H), 3.17 (bs,3H), 3.00 (bs,3H), 2.05 (s,3H); MS: m/e 331.1537 ($M^+$), calcd. for $C_{17}H_{21}N_3O_4$: 331.1530.

A solution of the above compound (325 mg, 0.98 mmol) in methanol (3 mL) was treated with hydroxylamine-O-sulfonic acid (125 mg, 1.08 mmol) at room temperature for 45 minutes. It was poured into saturated sodium bicarbonate solution. The resulting solid was collected and washed with water to give, after drying, 167 mg (57%) of the product as a white solid. mp 175-178° C (dec); $^1$H-NMR ($d_6$-DMSO) δ: 8.63 (bs,1H), 8.28 (bs,1H), 7.92 (d,J = 7Hz,2H), 7.72 (d,J = 7Hz,2H), 7.00 (bs,1H), 4.77 (bs,1H), 4.20 (t,1H), 3.82 (t,1H), 3.43 (m,2H), 1.87 (s,3H); MS: m/e 301.1081 ($M^+$), calcd. for $C_{15}H_{15}N_3O_4$: 301.1061.

## Example 131

Preparation of (ℓ)-[3-(4-(2-Methyl-4-thiazolyl)phenyl)-2-oxooxazolidin-5-ylmethyl]azide (I, Ar = 2-methyl-4-thiazolyl, B = $N_3$)

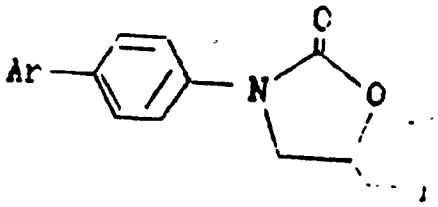
A solution of (ℓ)-5-azidomethyl-N-[3-(4-acetylphenyl-2-oxooxazolidin] (2.47 g, 9.5 mmol) in chloroform (30 mL) was treated with bromine (0.53 mL, 10.45 mmol) at room temperature for 15 minutes. The solvent was removed and the residue was taken up with 10% methanol/ methylene chloride. The resulting solid was filtered off and the solvent of the filtrate was removed to afford the crude product which was purified by flash column chromatography to yield 2.15 g (68%) of the bromoacetyl compound. $^1$H-NMR ($CDCl_3$) δ: 8.00 (d,J = 7Hz,2H), 7.67(d,J = 7Hz,2H), 4.83 (m,1H), 4.40 (s,2H), 4.15 (t,1H), 3.93 (dd,1H), 3.70 (2dd,2H).

A mixture of the above bromoacetyl compound (200 mg, 0.59 mmol) and thioacetamide (55 mg, 0.7 mmol) in toluene (3 mL) was refluxed for six hours. The solvent was removed, the residue was diluted with 10% methanol/methylene chloride, washed with saturated brine and dried ($NA_2SO_4$). The crude product was purified by flash column chromatography to give 140 mg (76%) of the title compound, $^1$H-NMR ($d_6$-acetone) δ: 8.00 (d,J = 7Hz,2H), 7.70 (d,J = 7Hz,2H), 7.67(s,1H), 5.00 (m,1H), 4.30 (t,1H), 4.00 (dd,1H), 3.83 (m,2H), 2.73 (s,3H).

The title compound was converted into its acetamide compound (I, Ar = 2-methyl-4-thiazolyl, B = $NHCOCH_3$) by the procedure described in U.S. Patent 4,705,799.

By using the procedures described in Examples 130 and 131, the following compounds in Table VIII were prepared or can be prepared.

Table VIII



| Ex. | Ar | B | Isomer | m.p.(°C) |
|---|---|---|---|---|
| 130 | 5-isoxazolyl | $NHCOCH_3$ | ℓ | 175-178 |
| 131 | 2-methyl-4-thiazolyl | $N_3$ | ℓ | NMR |
| 132 | 2-methyl-4-thiazolyl | $NHCOCH_3$ | ℓ | 179-180 |
| 133 | 1H-pyrazol | $NHCOCH_3$ | ℓ | 235-236 (dec) |
| 134 | 2-amino-4-thiazolyl | $NHCOCH_3$ | ℓ | 171-174 (dec) |
| 135 | 2-amino-4-pyrimidinyl | $NHCOCH_3$ | ℓ | 258 (dec) |
| 136 | 5-oxazolyl | $NHCOCH_3$ | ℓ | 200 (dec) |

Dosage Forms

The antibacterial agents of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration with standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and the effect desired. Usually, a daily dosage of active ingredient can be about 5 to 20 milligrams per kilogram of body weight. Ordinarily, when the more potent compounds of this invention are used, 5 to 15, and preferably 5 to 7.5 milligrams per kilogram per day, given in divided doses 2 to 4 times a day or in sustained release form, is effective to obtain desired results. These drugs may also be administered parenterally.

Projected therapeutic levels in humans should be attained by the oral administration of 5-20 mg/kg of body weight given in divided doses two to four times daily. The dosages may be increased in severe or life-threatening infections.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 600 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelation capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, manitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and, if necessary, buffer substances. Antiooxidants such as sodium bisulfate, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

## Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 75 milligrams of powdered active ingredient, 150 milligrams of lactose, 24 milligrams of talc, and 6 milligrams of magnesium stearate.

## Soft Gelatin Capsules

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 75 milligrams of the active ingredient. The capsules are washed and dried.

## Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 75 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 250 milligrams for microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

## Injectables

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

## Suspensions

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 75 milligrams of finely-divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

Utility

Test results indicate that the compounds of this invention are biologically active against gram positive bacteria including multiple antibiotic resistant strains of staphylococci and streptococci. These compounds are potentially useful for the treatment of both human and animal bacterial infections including diseases of the respiratory, gastrointestinal, genito-urinary systems; blood; interstitial fluids; and soft tissues.

As shown in Table IX, compounds of Formula (I) exert an in vitro antibacterial effect. A standard microdilution method (National Committee for Clinical Standards. Tentative standard M7-T. Standard methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, PA, 1982) with Mueller-Hinton broth is used to determine the 24-hour minimal inhibitory concentrations (MIC's) for test strains of Staphylococcus aureus and Escherichia coli.

The in vivo potency of these compounds is exemplified by the data summarized in Table X. Determinations of in vivo efficacy are performed by inoculating mice intraperitoneally with cultures of the infecting organism diluted to produce 100% mortality in control animals within twenty-four hours. The culture of S. aureus used to infect the animals was diluted to the required bacterial density using 5% aqueous hog gastric mucin. The compounds are dissolved or suspended in 0.25% aqueous Methocel® (Methocel®: Hydroxypropyl Methylcullulose, E15 Premium, Dow Chemical Company) for oral administration or sterile distilled water containing 5% dimethylsulfoxide (Fisher Scientific Company, Fairlawn, NJ) for subcutaneous administration. The mice are dosed at one hour and at four hours post-infection. Mortality is recorded daily until test determination seven days post infection. The number of survivors in each treatment group on the seventh day after infection is used in the calculation of the $ED_{50}$, the dose of compound that protects 50% of the mice (Litchfield, J. T. and Wildoxon. A simulated method for evaluating dose-effect experiments. J. Pharmacol Exp. Ther., 98:99-113, 1949).

Table IX

In Vitro Broth Microdilution
Minimal Inhibitory Concentrations (MIC's)

| Example No. | Minimum Inhibitory Concentration (μg/mL) | |
|---|---|---|
| | Staphylococcus aureus | Escherichia coli |
| 3 | 0.5 | >128 |
| 4 | 0.5 | >128 |
| 7 | 2 | >128 |
| 8 | <0.13 | >128 |
| 9 | <0.13 | >128 |
| 10 | 0.5 | >128 |
| 20 | 8 | >128 |
| 21 | <0.13 | >128 |
| 22 | 0.25 | >128 |
| 23 | 1 | >128 |
| 24 | 8 | >128 |
| 25 | 2 | >128 |
| 26 | 1 | >128 |
| 27 | 0.5 | >128 |
| 28 | <0.13 | >128 |
| 29 | 4 | >128 |
| 30 | 4 | >128 |
| 37 | 0.25 | >128 |
| 38 | 64 | >128 |
| 43 | 4 | >128 |
| 44 | 4 | >128 |
| 45 | 0.5 | >128 |
| 46 | 4 | >128 |
| 47 | 0.5 | >128 |

Table IX
(Continued)

| Example No. | Minimum Inhibitory Concentration (μg/mL) | |
|---|---|---|
| | Staphylococcus aureus | Escherichia coli |
| 48 | <0.13 | >128 |
| 49 | 1 | >128 |
| 50 | 0.5 | >128 |
| 57 | 1 | >128 |
| 58 | 1 | >128 |
| 59 | 2 | >128 |
| 60 | 1 | >128 |
| 61 | 2 | >128 |
| 62 | 2 | >128 |
| 63 | 0.25 | >128 |
| 64 | 4 | >128 |
| 65 | 2 | >128 |
| 66 | 0.5 | >128 |
| 67 | 0.25 | >128 |
| 68 | 0.25 | >128 |
| 69 | 0.25 | >128 |
| 70 | 2 | >128 |
| 71 | 2 | >128 |
| 73 | 0.5 | >128 |
| 74 | 8 | >128 |
| 75 | <0.13 | >128 |
| 85 | <0.13 | >128 |
| 86 | 2 | >128 |
| 87 | 32 | >128 |
| 88 | <0.13 | >128 |
| 89 | 2 | >128 |
| 92 | 2 | >128 |
| 113 | 16 | >128 |

Table IX
(Continued)

| Example No. | Minimum Inhibitory Concentration (μg/mL) | |
|---|---|---|
| | Staphylococcus aureus | Escherichia coli |
| 114 | 0.5 | >128 |
| 115 | 16 | >128 |
| 116 | 16 | >128 |
| 117 | 4 | >128 |
| 118 | 4 | >128 |
| 119 | <0.13 | >128 |
| 130 | 1 | >128 |
| 132 | 4 | >128 |
| 133 | 4 | >128 |
| 134 | 8 | >128 |
| 135 | 4 | >128 |
| 136 | 1 | >128 |

Table X

In Vivo Activity of Compounds Against Staphylococcus Aureus in an Acute Lethal Mouse Model

| Example No. | $ED_{50}$ (mg/kg) | |
|---|---|---|
| | Oral Administration | Subcutaneous Administration |
| 3 | 2.9 | 2 |
| 4 | 22 | 39.7 |
| 7 | NT | >90 |
| 8 | >90 | >90 |
| 9 | >90 | 16.8 |
| 10 | NT | NT |
| 20 | >90 | >90 |
| 21 | 44.7 | >90 |
| 22 | >90 | >90 |
| 23 | 17.3 | 24.3 |
| 24 | >90 | >90 |
| 25 | 13.9 | 5.8 |
| 26 | NT | NT |
| 27 | 6.6 | 7.6 |
| 28 | 52.6 | 30 |
| 29 | 16.1 | 9.8 |
| 30 | 16.1 | 9.8 |
| 37 | <1.2 | 0.6 |
| 38 | NT | >90 |
| 43 | 6.4 | 3.7 |
| 44 | 8.6 | 3.7 |
| 45 | NT | 13.9 |
| 46 | NT | 30 |
| 47 | NT | NT |
| 48 | NT | NT |

Table X
(Continued)

| Example No. | $ED_{50}$ (mg/kg) | |
|---|---|---|
| | Oral Administration | Subcutaneous Administration |
| 49 | 65.2 | >90 |
| 50 | NT | 6.5 |
| 57 | 18 | 10 |
| 58 | 13.8 | 2 |
| 59 | 7 | 2.7 |
| 60 | 30 | 5.5 |
| 61 | 47.4 | 2.7 |
| 62 | 51.9 | 10 |
| 63 | >90 | >90 |
| 64 | 50 | 11 |
| 65 | NT | 4.3 |
| 66 | NT | NT |
| 67 | 4.5 | 30 |
| 68 | 2.2 | 0.7 |
| 69 | 4 | 1.2 |
| 70 | 17 | 10 |
| 71 | 51.9 | >90 |
| 73 | 11.8 | 5 |
| 74 | NT | 17.1 |
| 75 | NT | NT |
| 85 | 1.3 | 0.5 |
| 86 | NT | 15.5 |
| 87 | 16.1 | 9.8 |
| 88 | 1.6 | 0.5 |
| 89 | 2 | <3.3 |
| 92 | NT | NT |
| 113 | >90 | 68.3 |

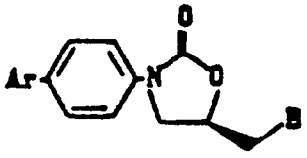
Table X
(Continued)

| Example No. | $ED_{50}$ (mg/kg) | |
|---|---|---|
| | Oral Administration | Subcutaneous Administration |
| 114 | 8.1 | >100 |
| 115 | NT | NT |
| 116 | NT | 6.4 |
| 117 | NT | NT |
| 118 | NT | NT |
| 119 | 6.2 | 5 |
| 130 | 6 | 6 |
| 132 | NT | 17 |
| 133 | 22 | 22 |
| 134 | 56.5 | 47 |
| 135 | 68 | NT |
| 136 | 14.8 | 51.9 |

NT = Not Tested

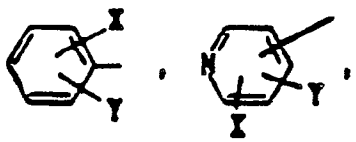
## Claims

1. An aryl benzene oxazolidinone of the formula

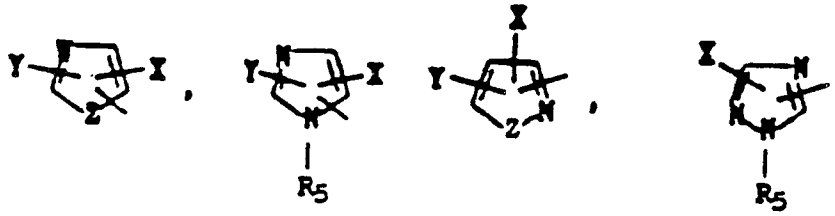



(I)

wherein, for the ℓ, and mixtures of the d and ℓ stereoisomers of the compound Ar is an aromatic group selected from the group consisting of

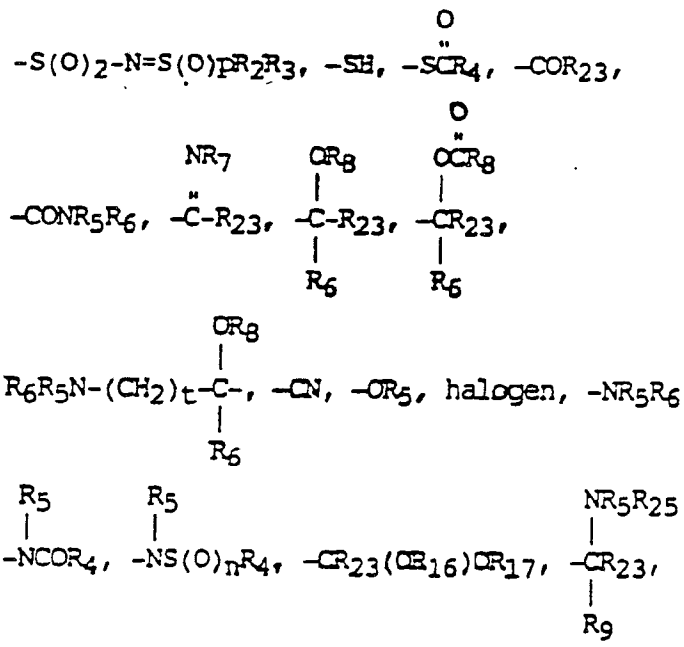


a diazinyl group optionally substituted with X and Y, a triazinyl group optionally substituted with X and Y,

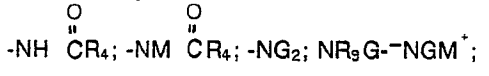


and  ;

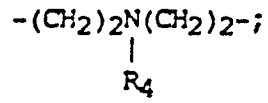
Z is O, S, or $NR_5$;
W is CH or N, or also can be S or O when Z is $NR_5$;
X independently is H, $-NO_2$, $-S(O)_nR_1$, tetrazoyl,



alkyl of 1 to 8 carbons optionally substituted with one or more halogen atoms, OH, =O other than at alpha position, $S(O)_nR_{24}$, or $NR_5R_6$, alkenyl of 2-5 carbons or cycloalkyl of 3-8 carbons;
$R_1$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms, OH, CN, $NR_5R_6$ or $CO_2R_8$;
$C_2$-$C_4$ alkenyl; $-NR_9R_{10}$; $-N_3$;

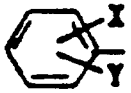
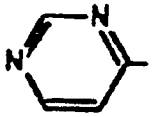
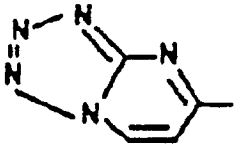


$R_2$ and $R_3$ are independently $C_1$-$C_2$ alkyl or, taken together are $-(CH_2)_q-$;
$R_4$ is alkyl or 1-4 carbons, optionally substituted with one or more halogens;
$R_5$ and $R_6$ are independently H, alkyl of 1-8 carbons, cycloalkyl of 3-8 carbons $-(CH_2)_tOR_8$, $-(CH_2)_tNR_{11}R_{11a}$, or $-O(CH_2)_tNR_{11}R_{11a}$; or taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_tCH(COR_4)-$, or

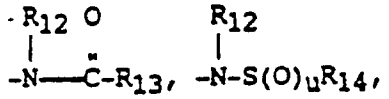


$R_7$ is $-NR_5R_6$, $-OR_5$ or

$R_8$ is H or alkyl of 1-4 carbons;
$R_9$ is H, $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl;
$R_{10}$ is H, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, $-OR_8$ or $-NR_{11}R_{11A}$;
$R_{11}$ and $R_{11A}$ are independently H or $C_1$-$C_4$ alkyl, or taken together, are $-(CH_2)_r-$;
G is Cl, Br or I;
Y independently is H, F, Cl, Br, $OR_8$, alkyl of 1-3 carbons, or $NO_2$;

X and Y taken together (a) when Ar is  or  to form a fused six-membered carbocyclic ring, or (b) when Ar is  to form  ;

M is a physiologically acceptable cation;
n is 0, 1 or 2
p is 0 or 1;
q is 3, 4 or 5;
r is 4 or 5;
t is 1, 2 or 3; B is $-NH_2$,



or $N_3$;
$R_{12}$ is H, $C_1$-$C_{10}$ alkyl or $C_3$-$C_8$ cycloalkyl;
$R_{13}$ is H; $C_1$-$C_4$ alkyl optionally substituted with one or more halogen atoms; $C_2$-$C_4$ alkenyl; $C_3$-$C_4$ cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$; $-CH_2S(O)_vR_{14}$;
$-\overset{O}{\overset{\|}{C}}R_{15}$; $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$;
the aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or $-C(NH_2)R_{21}R_{22}$;
$R_{14}$ is $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{15}$ is H or $C_1$-$C_4$ alkyl, optionally substituted with one or more halogen atoms;
$R_{16}$ and $R_{17}$ are independently $C_1$-$C_4$ alkyl or, taken together, are $-(CH_2)_m-$;

$R_{18}$ is $C_1$-$C_4$ alkyl or $C_7$-$C_{11}$ aralkyl;
$R_{19}$ and $R_{20}$ are independently H or $C_1$-$C_2$ alkyl;
$R_{21}$ and $R_{22}$ are independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;
u is 1 or 2;
v is 0, 1 or 2;
m is 2 or 3;
s is 2, 3, 4 or 5;
$R_{23}$ is H, alkyl of 1-8 carbons optionally substituted with one or more halogens, cycloalkyl of 3-8 carbons, alkyl of 1-4 carbons substituted with one or more of $-S(O)_nR_{24}$, $-OR_8$, $-O\overset{O}{\overset{\|}{C}}R_8$, or $-NR_5R_6$; or alkenyl of 2-5 carbons optionally substituted with CHO or $CO_2R_8$;
$R_{24}$ is alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons; and
$R_{25}$ is $R_6$ or $NR_5R_6$;
or a pharmaceutically suitable salt thereof; provided that:
1) when B is $NH_2$, then Ar is not phenyl optionally substituted with halogen or $CF_3$.

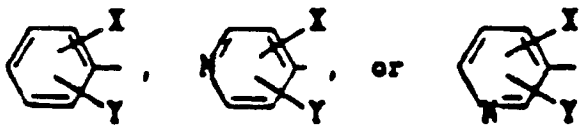
2. An oxazolidinone of claim 1 wherein B is is

$NH\ \overset{O}{\overset{\|}{C}}R_{13}$ where $R_{13}$ IS H, $CH_3$, $-OR_{18}$, $CH_2Cl$, $CH_2OH$, or $CH_2OCH_3$.

3. An oxazolidinone of Claim 2 wherein B is

$-NH\ \overset{O}{\overset{\|}{C}}CH_3$.

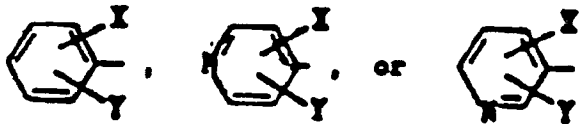
4. An oxazolidinone of Claim 1 wherein Ar is



5. An oxazolidinone of Claim 4 wherein Y is H.

6. An oxazolidinone of Claim 5 wherein X is H, alkyl of 1-5 carbon atoms, $-S(O)_nCH_3$ where n is 0, 1 or 2, $-\overset{O}{\overset{\|}{C}}CH_3$, $-OR_5$, $-CH_2NR_5R_6$, $R_6R_5N(CH_2)_2$ CH(OH)-, or -CN.

7. An oxazolidinone of Claim 3 wherein Ar is



8. An oxazolidinone of Claim 7 wherein Y is H.

9. An oxazolidinone of Claim 8 wherein X is H, alkyl of 1-5 carbon atoms, $-S(O)_nCH_3$ where n is 0, 1 or 2, $-\overset{O}{\overset{\|}{C}}CH_3$, $-OR_5$, $-CH_2NR_5R_6$, $R_6R_5N(CH_2)_2$ CH(OH)-, or -CN.

10. An oxazolidinone of Claim 7 selected from (j)-N-[3-(4-phenylphenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide ,
(j)-N-[3-(4-(4′-acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-methylsulfinylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-methylsulfonylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-cyanophenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-diethylaminomethylphenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-di-n-propylaminomethylphenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-(3-N,N-dimethylamino-1-hydroxypropyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-(1-hydroxy-3-(4-morpholinyl)propyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide,
(j)-N-[3-(4-(4′-pyridylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, hydrochloride, and
(j)-N-[3-(4-(3′-pyridylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, hydrochloride.

11. A pharmaceutical composition consisting essentially of a suitable pharmaceutical carrier and an effective amount of a compound of anyone of claims 1 to 10.

12. Use of a compound selected from the group consisting of:

(a) (ℓ)-N-[3-(4-phenylphenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

(b) (ℓ)-N-[3-(4-(4′-acetylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

(c) (ℓ)-N-[3-(4-(4′-methylsulfinylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

(d) (ℓ)-N-[3-(4-(4′-methylsulfonylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

(e) (ℓ)-N-[3-(4-(4′-cyanophenyl)phenyl-2-oxooxazolidin-5-ylmethyl]acetamide.

(f) (ℓ)-N-[3-(4-(4′-diethylaminomethylphenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

(g) (ℓ)-N-[3-(4-(4′-di-n-propylaminomethylphenyl)-phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide.

(h) (ℓ)-N-[3-(4-(4′-(3-N,N-dimethylamino-1-hydroxypropyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide.

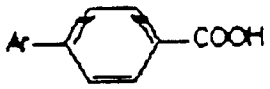
(i) (ℓ)-N-[3-(4-(4′-(1-hydroxy-3-(4-morpholinyl)-propyl)phenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide.

(j) (ℓ)-N-[3-(4-(4′-pyridylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, hydrochloride.

(k) (ℓ)-N-[3-(4-(3′-pyridylphenyl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide, hydrochloride, for preparing an antibacterial medicament.

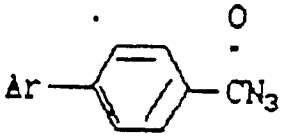
13. A process for preparing a compound of Claim 1 which comprises:

(1) reacting a carboxylic acid of the formula



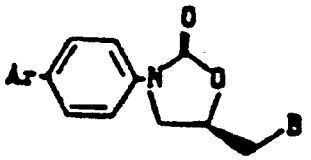

(XXVII)

where Ar is defined in Claim 1 with methyl chloroformate followed by sodium azide to prepare an acylazide of the formula




(XXIX);

(2) reacting a compound of formula (XXIX) with glycidyl azide to prepare an oxazolidinone of the formula




(I)

where B is $N_3$, and optionally

(3) reacting a compound of formula (I) from step (2) with hydrogen to prepare the corresponding compound where B is $NH_2$; and optionally

(4) reacting a compound as prepared in step (3) with acetyl chloride to prepare a corresponding compound where B is NH $\overset{\overset{O}{\|}}{C}CH_3$

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 352 781**
**A3**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **89113837.2**

(22) Date of filing: **27.07.89**

(51) Int. Cl.5: **C07D 263/20, C07D 413/10, A61K 31/42, C07D 413/14, C07D 417/10**

(30) Priority: **29.07.88 US 225809**

(43) Date of publication of application:
**31.01.90 Bulletin 90/05**

(84) Designated Contracting States:
**AT BE CH DE ES FR GB GR IT LI LU NL SE**

(88) Date of deferred publication of the search report:
**11.07.90 Bulletin 90/28**

(71) Applicant: **E.I. DU PONT DE NEMOURS AND COMPANY**
**1007 Market Street**
**Wilmington Delaware 19898(US)**

(72) Inventor: **Carlson, Randall Kent**
**121 Scarborough Drive, Apt. 10**
**Wilmington Delaware 19804(US)**
Inventor: **Gregory, Walter Adelman**
**104 Rockingham Drive**
**Wilmington Delaware 19803(US)**
Inventor: **Park, Chung-ho**
**5 Woodley Circle**
**Wilmington Delaware 19803(US)**

(74) Representative: **von Kreisler, Alek,**
**Dipl.-Chem. et al**
**Patentanwälte Von Kreisler-Selting-Werner**
**Deichmannhaus am Hauptbahnhof**
**D-5000 Köln 1(DE)**

(54) **Aminomethyloxooxazolidinyl arylbenzene derivatives useful as antibacterial agents.**

(57) Novel aminomethyloxooxazolidinyl arylbenzene derivatives, wherein the aryl includes the phenyl, substituted phenyl, pyridyl, and substituted pyridyl groups, such as (ℓ)-N-{3-[4-(4′-pyridyl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide, possess useful antibacterial activity.

EP 0 352 781 A3

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 89 11 3837

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| D,X | FR-A-2 500 450 (DELALANDE S.A.)<br>* Claims 1-3,6-7 * | 1,4-6, 10-12 | C 07 D 263/20<br>C 07 D 413/10<br>A 61 K 31/42<br>C 07 D 413/14<br>C 07 D 417/10 |
| A | EP-A-0 184 170 (E.I. DU PONT DE NEMOURS)<br>* Claims * | 1-13 | |
| D,A | EP-A-0 127 902 (E.I. DU PONT DE NEMOURS)<br>* Claims * | 1-13 | |
| P,X | EP-A-0 312 000 (E.I. DU PONT DE NEMOURS)<br>* Claims * | 1-13 | |
| P,X | EP-A-0 316 594 (E.I. DU PONT DE NEMOURS)<br>* Claims * | 1-13 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 263/00
C 07 D 413/00
C 07 D 417/00

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 25-04-1990 | HENRY J.C. |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

**(51) International Patent Classification 5 :**
**C07D 263/20, 413/10, 417/10**
**A61K 31/42, 31/44, 31/47**
**A61K 31/425**

**A1**

**(11) International Publication Number:** **WO 93/09103**

**(43) International Publication Date:** 13 May 1993 (13.05.93)

**(21) International Application Number:** PCT/US92/08267

**(22) International Filing Date:** 5 October 1992 (05.10.92)

**(30) Priority data:**

| | | |
|---|---|---|
| 07/786,107 | 1 November 1991 (01.11.91) | US |
| 07/831,213 | 7 February 1992 (07.02.92) | US |

**(60) Parent Applications or Grants**
(63) Related by Continuation

| | |
|---|---|
| US | 07/786,107 (CIP) |
| Filed on | 1 November 1991 (01.11.91) |
| US | 07/831,213 (CIP) |
| Filed on | 7 February 1992 (07.02.92) |

**(71) Applicant** *(for all designated States except US):* THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

**(72) Inventors; and**
**(75) Inventors/Applicants** *(for US only) :* BARBACHYN, Michael, Robert [US/US]; 1216 Miles Avenue, Kalamazoo, MI 49001 (US). BRICKNER, Steven, Joseph [US/US]; 1304 Dogwood Drive, Portage, MI 49002 (US).

**(74) Agent:** STEELE, Gregory, W.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

**(81) Designated States:** AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

**Published**
*With international search report.*

**(54) Title:** SUBSTITUTED ARYL- AND HETEROARYLPHENYLOXAZOLIDINONES USEFUL AS ANTIBACTERIAL AGENTS

**(57) Abstract**

The present invention discloses novel substituted aryl- and heteroarylphenyloxazolidinones which are useful as antibacterial agents. More specifically, the substituted aryl- and heteroarylphenyloxazolidinones of the invention are characterized by oxazolidinones having an aryl or heteroaryl group at the *p*-position of the 3-phenyl ring and additional substitutions at the *m*-position(s) of the 3-phenyl ring. A compound representative of this new class of oxazolidinones is (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | |
|---|---|
| **AT** | Austria |
| **AU** | Australia |
| **BB** | Barbados |
| **BE** | Belgium |
| **BF** | Burkina Faso |
| **BG** | Bulgaria |
| **BJ** | Benin |
| **BR** | Brazil |
| **CA** | Canada |
| **CF** | Central African Republic |
| **CG** | Congo |
| **CH** | Switzerland |
| **CI** | Côte d'Ivoire |
| **CM** | Cameroon |
| **CS** | Czechoslovakia |
| **CZ** | Czech Republic |
| **DE** | Germany |
| **DK** | Denmark |
| **ES** | Spain |
| **FI** | Finland |
| **FR** | France |
| **GA** | Gabon |
| **GB** | United Kingdom |
| **GN** | Guinea |
| **GR** | Greece |
| **HU** | Hungary |
| **IE** | Ireland |
| **IT** | Italy |
| **JP** | Japan |
| **KP** | Democratic People's Republic of Korea |
| **KR** | Republic of Korea |
| **KZ** | Kazakhstan |
| **LI** | Liechtenstein |
| **LK** | Sri Lanka |
| **LU** | Luxembourg |
| **MC** | Monaco |
| **MG** | Madagascar |
| **ML** | Mali |
| **MN** | Mongolia |
| **MR** | Mauritania |
| **MW** | Malawi |
| **NL** | Netherlands |
| **NO** | Norway |
| **NZ** | New Zealand |
| **PL** | Poland |
| **PT** | Portugal |
| **RO** | Romania |
| **RU** | Russian Federation |
| **SD** | Sudan |
| **SE** | Sweden |
| **SK** | Slovak Republic |
| **SN** | Senegal |
| **SU** | Soviet Union |
| **TD** | Chad |
| **TG** | Togo |
| **UA** | Ukraine |
| **US** | United States of America |
| **VN** | Viet Nam |

# SUBSTITUTED ARYL- AND HETEROARYLPHENYLOXAZOLIDINONES USEFUL AS ANTIBACTERIAL AGENTS

## Field of the Invention

The present invention relates to novel substituted aryl- and heteroarylphenyloxazolidinones which are useful as anti-bacterial agents.

## Background of the Invention

The oxazolidinones are a class of orally-active, synthetic antibacterial agents and there are numerous references in the art disclosing a variety of oxazolidinone derivatives. For example, there are a number of references to 3-phenyl-2-oxazolidinone compounds having one or two substitutions on the phenyl ring. References disclosing a single substitution to the phenyl ring include U.S. Patent 4,948,801; 4,461,773; 4,340,606; 4,476,136; 4,250,318; 4,128,654, and Re 29,607. Additional references to 3-[(monosubstituted)phenyl]-2-oxazolidinones can be found in EP Publication 0 312 000, Gregory, et al., J. Med. Chem. 32:1673 (1989), Gregory, et al., J. Med. Chem. 33:2569 (1990), and Wang, et al., Tetrahedron 45:1323 (1989). Compounds of this type also include the antibacterial DuP721.

3-[(di- or fused-ring substituted)phenyl]-2-oxazolidinones are reported in U.S. Patents 4,977,173, 4,921,869, and 4,801,600; EP Publications 0 316 594, 0 184 170, and 0 127 902; and PCT Applications PCT/US89/03548 and PCT/US90/06220.

We have discovered 3-[(di- and tri-substituted)phenyl]-2-oxazolidinones which are effective as antibacterial agents. The compounds of the invention are characterized by oxazolidinones having an aryl or heteroaryl group at the *p*-position of the 3-phenyl ring and additional substitution(s) at the *m*-position of the phenyl ring with radicals having an electron-withdrawing effect. These compounds are surprisingly effective as antibacterial agents, since early work by Gregory, et al, J. Med. Chem. 33:2569 (1990), suggests compounds having such radicals in the *p*-position of the phenyl ring are less effective antibacterial agents.

Synthesis of 3-phenyl-2-oxazolidinones and derivatives thereof are well known in the art. However, due to the nature of the radicals, the substituted phenyls of the invention are difficult to synthesize. Thus, we also disclose a process by which the compounds of the invention may be synthesized.

## Information Disclosure

The following references disclose 3-phenyl-2-oxazolidinones having a single substitution on the phenyl ring:

U.S. Patent 4,948,801 discloses 3-[(aryl and heteroaryl)phenyl]-2-oxazolidinones having antibacterial activity.

U.S. Patent 4,476,136 discloses 3-[(*p*-arylalkyl, arylalkenyl, and arylacetylenic substituted)phenyl]-5-(aminomethyl)-2-oxazolidinones which have antibacterial activity.

U.S. Patent 4,461,773 discloses substituted 3-phenyl-5-(hydroxymethyl)-2-

oxazolidinones which have antibacterial activity.

U.S. Patent 4,340,606 discloses substituted 3-[(p-alkylsulfonyl)phenyl]-5-(hydroxymethyl)- or (acyloxymethyl)-2-oxazolidinones having antibacterial activity in mammals.

U.S. Patent 4,250,318 discloses substituted 3-phenyl-5-(hydroxymethyl)-2-oxazolidinones having antidepressive utility.

U.S. Patent 4,128,654 discloses substituted 3-phenyl-5-(halomethyl)-2-oxazolidinones which are useful in controlling fungal and bacterial diseases of plants.

U.S. Reissue Patent 29,607 discloses substituted 3 phenyl-5-(hydroxymethyl)-2-oxazolidinones having antidepressive, tranquilizing and sedative utility.

Belgian Patent 892,270 discloses the 3-[(arylalkyl, arylalkenyl or arylacetylenic substituted)phenyl]-5-(aminomethyl)-2-oxazolidinones corresponding to U.S. Patent 4,476,136 listed above.

European Patent Publication 0 352 781 discloses aryl and heteroaryl substituted 3-phenyl-2- oxazolidinones corresponding to U.S. Patent 4,948,801 listed above.

European Patent Publication 0 312 000, as reported in Chemical Abstracts 89-116142/16, discloses phenylmethyl and pyridinylmethyl substituted 3-phenyl-2-oxazolidinones.

W. A. Gregory, et al., J. Med. Chem. 33:2569 (1990) and J. Med. Chem. 32:1673 (1989); C. J. Wang, et al., Tetrahedron 45:1323 (1989); and A. M. Slee, et al. Antimicrobial Agents and Chemotherapy 1791 (1987) are additional recent references disclosing 3-[(*p*-substituted) phenyl]-2-oxazolidinones.

The above references do not disclose the 3-[(di- or tri-substituted)phenyl]-2-oxazolidinones of the present invention.

The following references disclose 3-[(di-substituted)phenyl]- or 3-[(fused-ring substituted)phenyl]-2-oxazolidinones:

U.S. Patent 4,977,173 discloses 3-phenyl-2-oxazolidinones having a lactam at the *p*-position and fluorine at the *m*-position of the phenyl ring (Formula XIII). However, the 3-[(di- or tri-substituted)phenyl]-2-oxazolidinones of the present invention have an aromatic ring at the *p*-position.

U.S. Patents 4,921,869 and 4,801,600 disclose 6'-indolinyl- or alkanoneoxazolidinones (where the indolinyl nitrogen is meta to the oxazolidinone nitrogen).

U.S. Patent 4,705,799 discloses substituted aminomethyloxooxazolidinyl benzene derivatives including sulfides, sulfoxides, sulfones and sulfonamides which possess antibacterial activity. However, compounds of the present invention have an aryl or heteroaryl at the *p*-position of the phenyl ring.

European Patent Publication 0 316 594 discloses substituted 3-(styryl)-2-oxazolidinones corresponding to U.S. Patent 4,977,173 listed above.

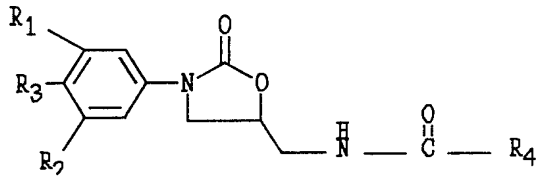
European Patent Publications 0 184 170 and 0 127 902 correspond to U.S. Patent 4,705,799, discussed above.

PCT/US89/03548 and PCT/US90/06220 disclose 3-[(fused-ring substituted)phenyl]-2-oxazolidinones which are useful as antibacterial agents.

The above references do not disclose the 3-[(di- or tri-substituted)phenyl]-2-oxazolidinones of the present invention.

## SUMMARY OF THE INVENTION

Disclosed are substituted aryl- and heteroaryl-phenyl oxazolidinones of Formula (XII)



(XII)

where

(I) $R_1$ and $R_2$ are the same or different and are selected from the group consisting of

(a) -H,

(b) -F,

(c) -Cl,

(d) $-CF_3$, and

(e) $-OCH_3$, provided that only one of $R_1$ or $R_2$ may be hydrogen;

(II) $R_3$ is selected from the group consisting of

(a) phenyl,

(b) pyridyl,

(c) pyrazinyl, (d) pyridazinyl, (e) pyrimidinyl,

(f) 1,2,3-, (g) 1,2,4-, (h) 1,2,5-triazinyl,

(i) quinolinyl, (j) isoquinolinyl,

(k) quinoxalinyl, (l) quinazolinyl, (m) phthalazinyl, (n) cinnolinyl,

(o) naphthyridinyl,

(p) indolyl having nitrogen optionally substituted with $R_{5-1}$ where $R_{5-1}$ is

-H,

$C_1$-$C_4$ alkyl optionally substituted with one or more halogens,

$C_3$-$C_6$ cycloalkyl, or

$-C(O)R_{5-2}$ where $R_{5-2}$ is

-H,

$C_1$-$C_4$ alkyl optionally substituted with one or more halogens, or

phenyl optionally substituted with one or more halogens,

(q) pyrrolopyridinyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above, (r) furanopyridinyl, (s) thienopyridinyl,

(t) benzothiazolyl, (u) benzoxazolyl,

(v) imidazolyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

(w) pyrazolyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

(x) thiazolyl, (y) isothiazolyl,

(z) oxazolyl, (aa) isoxazolyl,

(bb) pyrroyl having nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

(cc) furanyl, (dd) thiophenyl,

wherein substitutents (a)-(dd) are optionally substituted with X and Y,

(ee) 1,2,3-, (ff) 1,2,4-triazolyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

wherein substituents (ee) and (ff) are optionally substituted with X;

(III) each occurrence of Y is independently selected from

(a) -H,

(b) -Fl, (c) -Cl, (d) -Br, (e) -I,

(f) $-R_{3-1}$, (g) $-OR_{3-1}$, where $R_{3-1}$ is H or $C_1$-$C_4$ alkyl, or

(h) $-NO_2$;

(IV) each occurrence of X is independently selected from

(a) -H,

(b) $C_1$-$C_8$ alkyl optionally substituted with

one or more halogens,

-OH,

=O other than at alpha position,

$-S(O)_nR_{3-2}$ where $R_{3-2}$ is $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl, or

$-NR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are the same or different and are -H, $C_1$-$C_8$ alkyl, $C_3$-$C_8$ cycloalkyl, $-(CH_2)_tCHOR_{3-5}$, $-(CH_2)_tNR_{3-6}R_{3-7}$, or taken together are $-(CH_2)O(CH_2)-$,

$-(CH_2)_tCH(CO)R_{3-8}$, or $-(CH_2)N(R_{3-8})(CH_2)_2-$ where

$R_{3-5}$ is -H or $C_1$-$C_4$ alkyl, or

$R_{3-6}$ and $R_{3-7}$ are the same or different and are -H, $C_1$-$C_4$ alkyl or taken together are $-(CH_2)_r-$,

(c) $C_2$-$C_5$ alkenyl,

(d) $C_3$-$C_8$ cycloalkyl,

(e) -$OR_{3-3}$ where $R_{3-3}$ is as defined above,

(f) -CN,

(g) -S-$(O)_n$-$R_{3-8}$ where $R_{3-8}$ is

$C_1$-$C_4$ alkyl optionally substituted with

one or more halogens,

-OH,

-CN,

-$NR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above, or

-$CO_2R_{3-5}$ where $R_{3-5}$ is as defined above,

$C_2$-$C_4$ alkenyl,

-$NR_{3-9}R_{3-10}$ where $R_{3-9}$ is -H, $C_1$-$C_4$ alkyl, or $C_3$-$C_8$ cycloalkyl and $R_{3-10}$ is -H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, -$OR_{3-5}$, or -$NR_{3-6}R_{3-7}$ where $R_{3-5}$, $R_{3-6}$, and $R_{3-7}$ are as defined above,

-$N_3$,

-NHC(O)$R_{3-11}$ where $R_{3-11}$ is $C_1$-$C_4$ alkyl optionally substituted with one or more halogens,

(h) -$S(O)_2$-N=$S(O)_p$$R_{3-14}R_{3-15}$ where $R_{3-14}$ and $R_{3-15}$ are the same or different and are $C_1$-$C_2$ alkyl, or taken together are -$(CH_2)_q$-,

(i) -S-C(O)-$R_{3-11}$ where $R_{3-11}$ is as defined above,

(j) tetrazoly,

(k) -$NR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

(l) -$N(R_{3-3})COR_{3-11}$ where $R_{3-3}$ and $R_{3-11}$ are as defined above,

(m) -$N(R_{3-3})S(O)_nR_{3-11}$ where $R_{3-3}$ and $R_{3-11}$ are as defined above,

(n) -$CONR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

(o) -$C(O)R_{3-16}$ where $R_{3-16}$ is

-H,

$C_1$-$C_8$ alkyl optionally substituted with one or more halogens,

$C_1$-$C_4$ alkyl optionally substituted with

-$OR_{3-5}$,

-$OC(O)R_{3-5}$,

-$NR_{3-3}R_{3-4}$,

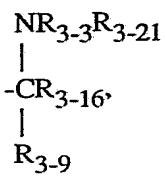
-$S(O)_nR_{3-17}$,

$C_3$-$C_8$ cycloalkyl, or

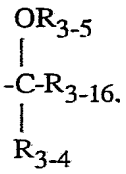
$C_2$-$C_5$ alkenyl optionally substituted with -CHO or -$CO_2R_{3-5}$, where $R_{3-3}$, $R_{3-4}$, and $R_{3-5}$ are as defined above and $R_{3-17}$ is $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl,

(p) $-C(=NR_{3-18})R_{3-16}$ where $R_{3-16}$ is as defined above and $R_{3-18}$ is $-NR_{3-3}R_{3-4}$, $-OR_{3-3}$, or $-NHC(O)R_{3-3}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

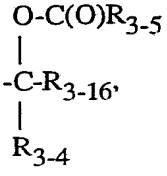
(q) $-CR_{3-16}(OR_{3-19})OR_{3-20}$ where $R_{3-16}$ is as defined above and $R_{3-19}$ and $R_{3-20}$ are the same or different and are $C_1$-$C_4$ alkyl, or taken together are $-(CH_2)_m-$,



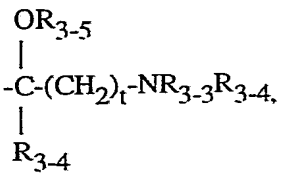
(r)



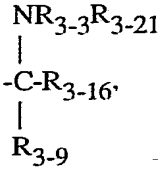
(s)



(t)



(u)



(v)

where $R_{3-3}$, $R_{3-4}$, $R_{3-5}$, $R_{3-9}$, and $R_{3-16}$ are as defined above and $R_{3-21}$ is $R_{3-4}$ or $-NR_{3-4}R_{3-5}$ where $R_{3-4}$ and $R_{3-5}$ are as defined above;

m is 2 or 3;

n is 0, 1, or 2;

p is 0 or 1;

q is 3, 4, or 5;

t is 1, 2, or 3;

(V) $R_4$ is selected from the group consisting of

(a) -H,

(b) $C_1$-$C_{12}$ alkyl optionally substituted with 1-3 Cl,

(c) $C_3$-$C_{12}$ cycloalkyl,

(d) $C_5$-$C_{12}$ alkenyl containing one double bond,

(e) phenyl optionally substituted with 1-3 -OH, $-OCH_3$, $-OC_2H_5$, $-NO_2$, -F, -Cl, -Br, -COOH and $-SO_3H$, $-N(R_{4-1})(R_{4-2})$ where $R_{4-1}$ and $R_{4-2}$ are the same or different and are -H and $C_1$-$C_5$ alkyl,

(f) furanyl,

(g) tetrahydrofuranyl,

(h) 2-thiophene,

(i) pyrrolidinyl,

(j) pyridinyl,

(k) -O-$R_{4-3}$ where $R_{4-3}$ is $C_1$-$C_4$ alkyl,

(l) -$NH_2$,

(m) -$NHR_{4-4}$ where $R_{4-4}$ is $C_1$-$C_3$ alkyl or -$\phi$,

(n) -$NR_{4-4}R_{4-5}$ where $R_{4-4}$ is as defined above and $R_{4-5}$ is $C_1$-$C_3$ alkyl, or taken together with the attached nitrogen atom to form a saturated mono-nitrogen $C_5$-$C_7$ heterocyclic ring including -O- (morpholine),

(o) -$CH_2$-OH,

(p) -$CH_2$-$OR_{4-6}$ where $R_{4-6}$ is $C_1$-$C_4$ alkyl or -CO-$R_{4-7}$ where $R_{4-7}$ is $C_1$-$C_4$ alkyl or -$\phi$;

and pharmaceutically acceptable salts thereof.

More particularly, the invention discloses compounds of formula (XII) where $R_3$ is a pyridyl or phenyl ring which are optionally substituted with -H, $C_1$-$C_4$ alkyl, or -$NR_{3-3}R_{3-4}$.

Most particularly, disclosed are the compounds (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone and (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone.

Another aspect of the invention discloses a process for making a compound of formula (XII) comprising:

(a) converting a substituted aniline to a stabase derivative,

(b) treating the stabase derivative to form an aryl- or heteroaryl-substituted aniline, and

(c) converting the aryl- or heteroaryl-substituted aniline to a aryl- or heteroaryl-substituted phenyloxazolidinone.

More particularly, this aspect of the invention discloses a process for making a compound of formula (XII) wherein step (b) comprises treatment of the stabase derivative with an appropriate alkyl- or aryllithium to form a lithiated derivative, transmetallation with an appropriate electrophilic metal species, addition of an appropriate aryl- or heteroaryl halide or sulfonate precursor in the presence of an appropriate metal catalyst to form a protected aryl- or heteroarylaniline, and removal of the stabase protecting group with aqueous mineral acid.

Most particularly, this aspect of the invention discloses a process for making a compound of formula (XII) wherein step (b) is carried out in a one-pot reaction sequence involving deprotonation of the stabase derivative with *n*-butyllithium in tetrahydrofuran to form a lithiated derivative, transmetallation with zinc chloride, addition of an aryl- or heteroaryl-bromide, iodide, triflate, or fluorosulfonate in the presence of tetrakis(triphenylphosphine)-palladium catalyst to form a protected aryl- or heteroaryl- aniline, and deprotection with aqueous hydrochloric acid.

Still another aspect of the invention discloses a process for making an oxazolidinone iodide comprising reacting a carbobenzyloxy allyl compound in the presence of an excess of pyridine and iodine, said excess being of equal amounts in the range of 2-20 molar equivalents.

More particularly, this aspect of the invention discloses a process for making an oxazolidinone iodide comprising reacting a carbobenzyloxy allyl compound in the presence of an excess of pyridine and iodine, wherein said excess is in the range of 5-15 molar equivalents.

Most particularly, this aspect of the invention discloses a process for making an oxazolidinone iodide comprising reacting a carbobenzyloxy allyl compound in the presence of an excess of pyridine and iodine, wherein said excess is in the range of 8-10 molar equivalents.

## DETAILED DESCRIPTION OF THE INVENTION

It is preferred that $R_1$ or $R_2$ are -F or $-CF_3$; it is most preferred that $R_1$ or $R_2$ are -F.

It is preferred that $R_3$ is phenyl or pyridyl; it is most preferred that $R_3$ is 3-pyridyl or 4-pyridyl.

It is preferred that X is -H, $C_1$-$C_4$ alkyl, or $-NR_{3\text{-}3}R_{3\text{-}4}$; it is most preferred that X is -H.

It is preferred that Y is -H or $C_1$-$C_4$ alkyl; it is most preferred that Y is -H.

It is preferred that $R_4$ is an acyl group optionally substituted with $C_1$-$C_5$ alkyl optionally substituted with 1-3 halogens, $C_3$-$C_5$ cycloalkyl, $-NR_{3\text{-}3}R_{3\text{-}4}$, and $-OR_{3\text{-}3}$; it is most preferred that $R_4$ is $-CH_3$.

It is preferred that $R_5$ is $C_1$-$C_4$ alkyl.

The structures of the aryl and heteroaryl groups which comprise $R_3$ (I-XII) are shown in CHART C. Structures (o) (naphthyridinyl), (q) (pyrrolopyridinyl), (r) (furanopyridinyl), and (s) (thienopyridinyl) show the nitrogen-containing heteroaryl abbreviated as Z, where Z is an unsaturated 4-atom linker having one nitrogen and three carbons. In this way, each of the four possible positions for the heteroaryl nitrogen are encompassed by structures (o), (q), (r), and (s).

The aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the present invention are useful as antibacterial agents in treating infections in mammals caused by gram-positive and anaerobic infections. It is preferred to treat humans and warm-blooded mammals such as cattle, horses, sheep, hogs, dogs, cats, etc., with the aryl- and heteroaryl-substituted phenyl oxazolidinones (XII) of the present invention.

The aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the present invention are also useful in treating patients infected with one or more *Mycobacterium spp.* Of particular interest, the aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the invention are useful in treating patients infected with *M. tuberculosis* and *M. avium.*

The aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the invention can be administered in a manner and in dosage forms similar to those of the known phenyloxazoli-

dinones described above. For example, administration can be either parenteral (IV, IM, SQ) or oral. The daily dose is about 3 to about 30 mg/kg. This dose can preferably be given in divided doses and administered 2-4 times daily. The preferred route of administration as well as the particular dosage form for either the parenteral or oral route depends on the particular facts of the situation including the nature of the infection and condition of the patient. The usual pharmaceutical dosage forms appropriate for parenteral (solution, suspension in oil) and oral (tablet, capsule, syrup, suspension, etc) administration are known to those skilled in the art and there is nothing unusual about using those dosage forms with the aryl- and heteroaryl-substituted phenyloxazolidinones (XII). The exact dosage of the aryl- and heteroaryl-substituted phenyloxazolidinones (XII) to be administered, the frequency of administration, route of administration, and the dosage form will vary depending on a number of factors known to those skilled in the art including the age, weight, sex, general physical condition of the patient, the nature of the infection (particular microorganism involved, its virulence, the extent of the infection) other medical problems of the patient, etc., as is well known to the physician treating infectious diseases.

The aryl- and heteroaryl-substituted phenyloxazolidinones (XII) can be used either alone or in conjunction with other antibacterial agents as is known to those skilled in the art. Further, the aryl- and heteroaryl-substituted phenyloxazolidinones (XII) can be used in conjunction with non-antibacterial agents as is known to those skilled in the art.

Suitable pharmaceutical salts include the acid addition salts when a basic group is present, such as occurs with the preferred pyridyl group. The acid addition salts including those made from mineral acids, e.g., hydrochloric, hydrobromic, sulfuric, phosphoric, etc., organic sulfonic acids, e.g., methanesulfonic, organic carboxylic acids, e.g., amino, and carbohydrate acids, e.g., gluconic, galacturonic, etc. It is also appreciated by those skilled in the art that the appropriate N-oxides of $R_3$ heteroaryls and tertiary amino substituted aryls are included within the scope of the aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the invention.

The pharmaceutically active aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of this invention are prepared as described briefly here and in more detail in the examples which follow. CHART A describes the synthesis of the aryl- and heteroaryl-substituted aniline (VI) compounds.

These aniline compounds (VI) are then subsequently reacted following procedures known, or readily acquired by one skilled in the art. These subsequent procedures parallel those described in U.S. Patents 4,705,799, PCT/US90/06220, PCT/US89/03548, and W. A. Gregory, et al., J. Med. Chem., 32:1673 (1989), all of which are incorporated herein by reference. The Cardillo-Ohno reaction is discussed in Tetrahedron 43:2505 (1979) and Tetrahedron Lett. 28:3123 (1987), both of which are also incorporated herein by reference.

CHART A demonstrates a method of preparation of the aryl- and heteroaryl-substituted anilines of the invention. The starting point is a mono- or disubstituted aniline (I). These materials are readily available from a number of commercial vendors; one such vendor is Aldrich Chemical Co., Milwaukee, WI. Alternatively, the anilines (I) are known in the chemical literature and may be readily prepared by one skilled in the art. The substituted aniline (I) is treated with n-butyllithium and 1,2-bis(chlorodimethylsilyl)ethane to form the stabase (SB) derivative (II). The SB derivative (II) is converted, in a one-pot reaction sequence, to the crude aryl- and heteroaryl-substituted aniline (VI). This sequence involves slow addition of n-butyllithium to (II), resulting in the aryllithium (III). The aryllithium (III) is transmetallated with anhydrous zinc chloride in tetrahydrofuran (THF) to give an organo zinc derivative (IV). Alternatively, the transmetallation can be carried out with trimethylborate to give the corresponding boric acid, or with tributyltin chloride to give the corresponding stannane. These species react in a manner analogous to that of the organozinc derivative (IV). Addition of the appropriate aryl or heteroaryl iodide, bromide, trifluoromethane sulfonate (triflate), or fluorosulfonate and palladium catalyst, preferably, tetrakis(triphenylphosphine)palladium, followed by warming to reflux temperature gives the coupled product (V). The reaction is quenched with aqueous mineral acid, preferably hydrochloric, to give the aryl- or heteroaryl-substituted aniline (VI). The product (VI) may then be further purified following chromatographic techniques well known in the art. Alternatively, the chromatographic purification may be delayed until after the carbobenzoxy group is appended.

The remaining synthetic steps which lead to the aryl- and heteroaryl-substituted phenyl oxazolidinone (XII) of the invention are outlined in CHART B and closely parallel the procedure found in that discussed in U.S. Patent 4,705,799, PCT/US90/06220, PCT/US89/03548, and W. A. Gregory, et al., J. Med. Chem., 32:1673 (1989). Briefly, the aniline (VI) is converted to the carbobenzoxy derivative (VII) in the presence of base and THF. Alkylation of (VII) with allyl halide, preferably bromide, gives the allylated product (VIII). This intermediate (VIII) is subjected to a modified Cardillo-Ohno iodocyclocarbamation reaction wherein an excess of pyridine in combination with the iodine, is added to facilitate formation of the oxazolidinone iodide (IX). The iodocyclocarbamation reaction as disclosed by Cardillo-Ohno requires 2-3 equivalents of iodine ($I_2$), whereas when synthesizing the compounds of the invention an amount of pyridine and iodine is added which is in the range of 2-20 molar equivalents of each compound. Preferably, 5-15 equivalents should be employed, most preferred is 8-10 equivalents. In addition, we have found that this process has utility in reactions where benzyl iodide is formed and the product so formed competes in the reaction for the substrate and/or product to form unwanted benzylated products. This process, then, is useful to improve yields because it is believed that the excess pyridine traps the benzyliodide to inhibit this

competitive reaction. In the synthesis of the compounds of the invention an excessive of pyridine is necessary; when pyridine is omitted from the reaction mixture essentially none of the compounds of the invention are recovered.

After the formation of the iodide (IX) purification may be accomplished following chromatography procedures known in the art. However, this is not necessary as the iodide (IX) may be directly converted to the corresponding azide (X) by treatment with sodium azide in the presence of DMF. Reduction of (X) in the presence of hydrogen, methanol or ethyl acetate, and palladium catalyst affords the amine (XI). Acetylation of the amine (XI) provides the aryl-and heteroaryl-substituted phenyloxazolidinones (XII) of the invention.

The aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the invention contain at least one chiral center. It is apparent to one skilled in the art that when one chiral center is present, the compound can exist as one of two possible optical isomers [(R) and (S) enantiomers] or a racemic mixture of both. Both individual (R) and (S) enantiomers, as well as mixtures thereof, are within the scope of aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the invention. In the event a second chiral center is present in the aryl- and heteroaryl-substituted phenyloxazolidinones (XII) of the invention, the resultant diastereomers, in racemic and enantiomerically enriched forms, are also within the scope of the compounds (XII) of the invention.

The enantiomer which is pharmacologically active is the enantiomer with the "S" configuration. The racemic mixture is useful in the same way and for the same purpose as the pure S-enantiomer; the difference is that twice as much racemic material must be used to produce the same effect as the pure S-enantiomer. If desired, the mixture of enantiomers is resolved by means known to those skilled in the art. It is preferable to resolve the racemic mixture at the stage of the amino compounds (XI) using methods known to those skilled in the art, see for example, Optical Resolution Procedures for Chemical Compounds, Vol 1,: Amines and Related Compounds, Paul Newman, Optical Resolution Information Center, Manhattan College, Riverdale, NY, 10471, 1978. For example, treatment of the d,l-amino mixture (XI) with an optically active acid such as (+)-tartaric acid or alternatively with (-)-tartaric acid, would yield a mixture of diastereomeric salts, which can be separated most conveniently by fractional crystallization to give a salt containing only one enantiomer of the racemic mixture. Other suitable optically active acids include, (-) dibenzoyltartaric acid, (+)-camphoric acid, (+)- and (-)-malic acid and (+)-camphor-10-sulfonic acid. By reacting the diastereomeric salt with a base one obtains the enantiomer as the free amino compound (XI). These optically pure compounds are then used in the same way as the racemic mixture.

Charts D and E depict alternative and preferred routes to enantiomerically enriched substituted aryl- and heteroarylphenyloxazolidinones of formula XII which are the subject of this

invention. It will be apparent to those skilled in the art that these are merely representative examples, and that slight modifications of the provided synthetic protocols will allow for the preparation of further enantiomerically enriched examples of the oxazolidinones of the invention.

The reaction of an isocyanate with racemic and enantiomerically enriched glycidol derivatives to give oxazolidinones is a known and facile process. (See e.g., J. E. Herweh, W. J. Kauffman, Tetrahedron Letter., 809 (1971); W. A. Gregory, et al., J. Med. Chem., 32:1673 (1989); W. A. Gregory, et al., J. Med. Chem. 33:2569 (1990); C. H. Park, et al., J. Med. Chem., 35:1156 (1992); W. A. Gregory, U.S. Patent 4,705,799 (1987)). As shown in Chart D, an isocyanate of structure (1) can be reacted with commercially available (R)-glycidyl butyrate (see, e.g., W. E. Ladner, G. M. Whitesides; J. Am. Chem. Soc., 106:7250 (1984), available from Aldrich Chemical Company, Inc.) in the presence of catalytic lithium bromide and tributyl-phosphine oxide and in a suitable solvent such as xylene and at a suitable temperature (e.g. reflux) to provide the oxazolidinone intermediate (2). The butyryl group is then removed by reaction with an alkoxide, preferably sodium methoxide in methanol, to furnish the key hydroxymethyloxazolidinone intermediate (3). The most preferred route to the alcohol (3) involves the deprotonation of an appropriate CBz-protected aniline of structure (4), readily prepared by standard Schotten-Baumann conditions or other variations known to one skilled in the art, with a suitable base such as *n*-butyllithium in a suitable solvent such as tetrahydrofuran and at a suitable temperature such as -78° to -60°C. Addition of the (*R*)-glycidyl butyrate, followed by warming to ambient temperature, then directly affords the hydroxymethyloxazolidinone (3), identical in all respects with material prepared via the isocyanate sequence. Compound (3) is then converted to the corresponding methanesulfonate (mesylate) or *p*-toluenesulfonate (tosylate) derivative (5) or the like, by the action of methanesulfonyl chloride/pyridine or methanesulfonyl chloride/triethylamine/dichloromethane or *p*-toluenesulfonyl chloride/pyridine. The resultant sulfonate is then reacted with an azide source, for example sodium or potassium azide, in a dipolar aprotic solvent such as *N,N*-dimethylformamide (DMF) or 1-methyl-2-pyrrolidinone optionally in the presence of a catalyst such as 18-crown-6 at a temperature of 50° to 90°C to afford the azide (6). The azide (6) is then reduced by hydrogenation with palladium on carbon or a platinum-based catalyst in an appropriate solvent such as ethyl acetate or methanol (or combina-tions thereof) to give the aminomethyloxazolidinone (7). Alternatively, the azide may be reduced by treatment with a trivalent phosphorus compound such as triphenylphosphine in the presence of water and in a suitable solvent such as tetrahydrofuran (THF). Compound (7) is then acylated by reactions known to those skilled in the art to give the intermediates of structure (8). Compound (8) is then iodinated with iodine monochloride in acetic acid or acetic acid/trifluoroacetic acid (see, e.g., W. A. Gregory, U.S. Patent 4,705,799 (1987)) at a temperature from 0° to 70°C or with iodine and silver trifluoro-

acetate (see e.g., W. A. Gregory, *et al.*, J. Med. Chem. 33:2569 (1990); and C. H. Park, et al., J. Med. Chem., 35:1156 (1992)) to furnish the enantiomerically enriched substituted iodophenyl-oxazolidinone intermediate (9). Alternatively, (8) can be brominated with *N*-bromosuccinimide to give the corresponding bromophenyloxazolidinone of structure 9.

Further elaboration of the intermediates of formula (9) to make the enantiomerically enriched substituted aryl- and heteroarylphenyloxazolidinones of formula XII which are the subject of this invention is outlined in Chart E. Compound (9) is reacted with the desired aryl- or heteroaryl-substituted metal of formula $R^3M$ (M = trialkyltin, boronic acid or ester, or halozinc) in the presence of a suitable palladium catalyst such as tetrakis(triphenylphosphine)-palladium or bis(triphenylphosphine)palladium chloride in a suitable solvent such as DMF or 1,4-dioxane at a suitable temperature (typically 70°-100°C) to afford the coupled aryl- or heteroarylphenyloxa-zolidinone products of structure XII. Alternatively, the iodo- or bromophenyloxazolidinone of formula (9) is converted to the corresponding trimethyltin derivative (11) by treating it with hexa-methylditin in the presence of a suitable palladium catalyst such as tetrakis(triphenylphosphine)-palladium or bis(triphenylphosphine)palladium chloride in a suitable solvent such as DMF or 1,4-dioxane at a suitable temperature (typically 70° to 100°C). Intermediate (11) is then treated with the desired aryl or heteroaryl halide of formula $R^3X$ (X = Br or I) in the presence of a suitable palladium catalyst such as tetrakis-(triphenylphosphine)palladium or bis(triphenyl-phosphine)palladium chloride in a suitable solvent such as DMF or 1,4-dioxane at a suitable temperature (typically 70°-100°C) to afford the enantiomerically enriched aryl- or heteroaryl-phenyloxazolidinone products of structure XII which are the subject of this invention. This latter route (proceeding through 11) is exemplified in the supplemental experimental section by a racemic Example 55.

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

Conventions

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "$Z_1$" or "$R_i$" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group $Z_1$ would represent a bivalent variable if attached to the formula $CH_3$-C(=$Z_1$)H. Groups $R_i$ and $R_j$ would represent monoval-ent variable substituents if attached to the formula $CH_3$-$CH_2$-C($R_i$)($R_j$)$H_2$. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed

in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both $R_i$ and $R_j$ are bonded to the preceding carbon atom.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus, $CH_3$-O-$CH_2$-CH($R_i$)-$CH_3$ represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., $CH_2$=C($R_i$)-O-$CH_3$, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH($R_i$)-$CH_2$-$CH_3$. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by $N^*$=C($CH_3$)-CH=CCl-CH=$C^*$H with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by -$N^*$-$(CH_2)_2$-N($C_2H_5$)-$CH_2$-$C^*H_2$-.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C($X_1$)($X_2$)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent ($X_1$) which is "below" another substituent ($X_2$) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" ($X_2$) the other ($X_1$) is identified as being in the beta (ß) configuration and is indicated by an unbroken line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable $R_i$ attached to a carbon atom as -C(=$R_i$)- might be bivalent and be defined as oxo or keto (thus forming a carbonyl group (-CO-)) or as two separately attached monovalent variable substituents α-$R_{i-j}$ and ß-$R_{i-k}$. When a bivalent variable, $R_i$, is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form "α-$R_{i-j}$:ß-$R_{i-k}$" or some variant

thereof. In such a case both $\alpha$-$R_{i-j}$ and ß-$R_{i-k}$ are attached to the carbon atom to give -C($\alpha$-$R_{i-j}$)(ß-$R_{i-k}$)-. For example, when the bivalent variable $R_6$, -C(=$R_6$)- is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are $\alpha$-$R_{6-1}$:ß-$R_{6-2}$, .... $\alpha$-$R_{6-9}$:ß-$R_{6-10}$, etc, giving -C($\alpha$-$R_{6-1}$)(ß-$R_{6-2}$)-, .... -C($\alpha$-$R_{6-9}$)(ß-$R_{6-10}$)-, etc. Likewise, for the bivalent variable $R_{11}$, -C(=$R_{11}$)-, two monovalent variable substituents are $\alpha$-$R_{11-1}$:ß-$R_{11-2}$. For a ring substituent for which separate $\alpha$ and ß orientations do not exist (e.g. due to the presence of a carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the $\alpha$ and ß designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula -$C_1$($R_i$)H-$C_2$($R_j$)H- ($C_1$ and $C_2$ define arbitrarily a first and second carbon atom, respectively) $R_i$ and $R_j$ may be defined to be taken together to form (1) a second bond between $C_1$ and $C_2$ or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When $R_i$ and $R_j$ are taken together to form a more complex entity, such as the group -X-Y-, then the orientation of the entity is such that $C_1$ in the above formula is bonded to X and $C_2$ is bonded to Y. Thus, by convention the designation "... $R_i$ and $R_j$ are taken together to form -$CH_2$-$CH_2$-O-CO- ..." means a lactone in which the carbonyl is bonded to $C_2$. However, when designated "... $R_j$ and $R_i$ are taken together to form -CO-O-$CH_2$-$CH_2$-the convention means a lactone in which the carbonyl is bonded to $C_1$.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "$C_1$-$C_4$", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "$C_1$-$C_4$ alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus $C_2$-$C_4$ alkoxycarbonyl describes a group $CH_3$-($CH_2$)$_n$-0-CO- where n is zero, one or two. By the second method, the carbon atom content of only each portion of the definition is indicated separately by enclosing the "$C_i$-$C_j$" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention ($C_1$-$C_3$)alkoxycarbonyl has the same meaning as $C_2$-$C_4$ alkoxycarbonyl because the "$C_1$-$C_3$" refers only to the carbon atom content of the alkoxy group. Similarly while both $C_2$-$C_6$ alkoxyalkyl and ($C_1$-$C_3$)alkoxy($C_1$-$C_3$)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion

alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

Definitions

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

Brine refers to an aqueous saturated sodium chloride solution.

DMF refers to N,N-dimethylformamide.

THF refers to tetrahydrofuran.

CBZ refers to carbobenzyloxy.

n-BuLi refers to n-butyl lithium

SG refers to silica gel.

IR refers to infrared spectroscopy.

$^1$H-NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm ($\delta$) downfield from tetramethylsilane.

$\phi$ refers to phenyl ($C_6H_5$).

MS refers to mass spectrometry expressed as m/e or mass/charge unit.

$[M + H]^+$ refers to the positive ion of a parent plus a hydrogen atom.

EI refers to electron impact.

CI refers to chemical ionization.

FAB refers to fast atom bombardment.

Ether refers to diethyl ether.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

Examples Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Preparation 1 N,N-[1,2-Bis(dimethylsilyl)ethane]-3,5-difluoroaniline

A flame dried, 500 mL, 3-necked, round-bottomed flask is fitted with a Claisen tube, mechanical stirrer and a low-temperature thermometer. The flask is loaded with 8.64 g (66.9 mmol) of the starting difluoroaniline. The Claisen tube is fitted with a gas inlet adapter and a rubber septa. The starting material is placed under an atmosphere of nitrogen and 135 mL of anhydrous THF is added. The resulting solution is cooled in a dry ice-isopropanol bath and stirred mechanically. To the cold reaction solution is slowly added 88 mL (141 mmol, 2.1 eq) of n-BuLi (1.6M in hexanes). The reaction temperature is maintained between -70 and -40°C during the addition. After an additional 20 min, 14.4 g (66.9 mmol, 1eq) of 1,2-bis(chloro-dimethylsilyl)ethane in 135 mL of anhydrous THF is slowly added. The homogenous solution is allowed to stir for an additional 45 min and then warmed to room temperature. The reaction is carefully quenched with 200 mL of water and extracted with diethyl ether (4x200 mL). The combined organics are washed with brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to a tan, waxy solid (19.6 g). The crude material is purified by sublimation (5 torr, 40°C). 11.8 g (65%) of the title compound is recovered as a white solid (MP: 71-72°C).

Anal. Calc'd for $C_{12}H_{19}F_2NSi_2$: C, 53.10; H, 7.05; N, 5.15

Found: C, 52.04; H, 7.33; N, 4.99

FTIR(neat): $cm^{-1}$ 2958, 2928, 1626, 1581, 1476, 1453, 1345, 1248, 995.

MS(EI): m/z(rel. int.) 271[$M^+$](28), 256(100), 228(11), 73(10).

$^1$H-NMR($CDCl_3$): δ 6.36(dd, 2H, $J_{HF}$=8.1 Hz, $J_{HH}$=2.1 Hz), 6.29(dd, 1H, $J_{HF}$=9.0 Hz, $J_{HH}$=2.1 Hz), 0.85(s, 4H), 0.25(s, 12H).

Preparation 2 4-(3-Pyridyl)-3,5-difluoroaniline

A flame dried, 3-necked, round-bottomed flask is loaded with 1.82 g (6.72 mmol) of the protected aniline (Preparation 1) and fitted with a rubber septa, low-temperature thermometer and a gas inlet adapter. The starting material is placed under an atmosphere of nitrogen and 27 mL of anhydrous THF is added. The resulting solution is cooled to -70°C. To the cold solution is added 5.03 mL (8.06 mmol, 1.2 eq) of n-BuLi (1.6M in hexanes) *via* a syringe pump (0.12 mL/min). After the addition is complete, the yellow reaction solution is allowed to stir for an additional 20 min and then 8.06 mL (8.06 mmol, 1.2 eq) of zinc chloride (1.0 M in THF) is added. The reaction is warmed to -40 °C for 15 min. To the yellow solution is added 773 mg (0.672 mmol, 0.10 eq) of $Pd(PPh_3)_4$ in 50 mL of THF followed by 647 µL (6.72 mmol, 1.0 eq) of 3-bromopyridine. The cooling bath is removed and the reaction is warmed to room temperature. The thermometer is replaced with a condenser and the septa with a glass stopper. The reaction is heated to reflux temperature for 16 h. After this time, the reaction is quenched with 100 mL of 10% HCl(aq). The resulting suspension is vigorously stirred for 0.5 h and then washed with diethyl ether (3x50 mL). The recovered aqueous layer is adjusted to pH 14 with 50% sodium hydroxide (aq) and then extracted with (4x50 mL). The combined organics are

washed with brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to yellow solid (935 mg). This crude material is purified by silica gel chromatography (200 g of SG, eluted with 1 L x 5% $CH_3CN/CHCl_3$, 1 L x 10% $CH_3CN/CHCl_3$, 1 L x 15% $CH_3CN/CHCl_3$). 625 mg (43%) of the title compound is recovered as a white solid (MP: 141-142°C).

Anal. Calc'd for $C_{11}H_8F_2N_2$: C, 64.08; H, 3.91; N, 13.59

Found: C, 63.92; H, 3.74; N, 13.24

FTIR(mull): $cm^{-1}$ 3141, 1634, 1460, 1164, 1012, 708.

MS(EI): m/z(rel. int.) 206[$M^+$](100), 205(7), 179(5), 158(4), 89(4).

$^1$H-NMR($CDCl_3$): δ 8.67(s, 1H), 8.55(dd, 1H, J=4.9, 1.7 Hz), 7.75(dm, 1H, J=8.1 Hz), 7.35(ddd, 1H, 7.8, 4.9, 0.8 Hz), 6.31(ddd, 2H, $J_{HF}$=9.8, 1.5 Hz, $J_{HH}$=3.7 Hz), 4.01(s(b), 2H).

Preparation 3 N-Carbobenzyloxy-4-(3-pyridyl)-3,5-difluoroaniline

In 60 mL of dry THF is combined 625 mg (3.03 mmol) of the starting amine (Preparation 2) and 382 mg (4.55 mmol, 1.5 eq) of sodium bicarbonate. The resulting mixture is placed under an atmosphere of nitrogen and 394 µL (4.55 mmol, 1.5 eq) of benzylchloroformate is added. The reaction is allowed to stir at room temperature for 16 h. After this time, the reaction is added to 150 mL of methylene chloride and washed with saturated sodium bicarbonate then brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to a white solid (1.09 g). The material is puried by silica gel chromatography (200 g of SG, eluted with 1 L x 3% $CH_3CH/CHCl_3$, 2 L x 5% $CH_3CN/CHCl_3$) 990 mg (96%) of the title compound is recovered as a white solid (MP 188-190°C).

FTIR (neat): $cm^{-1}$ 3030, 1737, 1642, 1478, 1408, 1231, 1029, 723.

Anal. calc'd for $C_{19}H_{14}F_2N_2O_2$: C, 67.06; H, 4.15; N, 8.23

Found: C, 66.18; H, 4.22; N, 7.34

MS (EI): m/z (rel. int.): 340 [$M^+$] (21), 296 (5), 232 (4), 205 (2), 91 (100), 79 (3).

$^1$H NMR ($CD_3OD$): δ 8.59 (s(b), 1H), 8.53-8.51 (m, 1H), 7.95-7.92 (m, 1H), 7.56-7.51 (m, 1H), 7.44-7.31 (m, 5H), 7.28 (d, 2H, $J_{HF}$=10.4 Hz), 5.21 (s, 2H).

Preparation 4 N-Allyl-N-carbobenzyloxy-4-(3-pyridyl)-3,5-difluoroaniline

A solution of 543 mg (1.60 mmol) of the starting carbamate (Preparation 3) in 40 mL of anhydrous THF is treated with 128 mg (3.19 mmol, 2 eq) of sodium hydride (60% dispersion in mineral oil). The reaction is kept under an atmosphere of nitrogen at room temperature for 0.5 h. After this time, 691 µL (7.99 mmol, 5 eq) of allyl bromide is added. Stirring is continued at room temperature for 16 h. After this time, the reaction is carefully quenched with 20 mL of water. The layers are separated and the aqueous layer is extracted with ethyl acetate (3 x 25 mL). The combined organics are washed with brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to a dark amber oil. This material is purified by silica gel chromatography (125 g of SG, eluted with 1 L x 3% $CH_3CN/CHCl_3$) 497 mg (82%) of the title

compound is recovered as a yellow solid. An analytical sample is prepared by preparative TLC (SG, 6% $CH_3CN/CHCl_3$). The analytical sample is recovered as a white solid (MP 92-93°C).

FTIR (mull): $cm^{-1}$ 3068, 3061, 1710, 1705, 1643, 1635, 1412, 1263, 1024, 733.

Anal. calc'd for: $C_{22}H_{18}F_2N_2O_2$: C, 69.47; H, 4.77; N, 7.36

Found: C, 68.38; H, 4.83; N, 7.19

MS (EI): m/z (rel. int.) 380 [$M^+$] (15), 336 (4), 309 (3), 245 (4), 91 (100), 65 (6).

$^1H$ NMR ($CDCl_3$): δ 8.72 (s, 1H), 8.62 (s (b), 1H), 7.99 (d, 1H, J=7.8 Hz), 7.42-7.36 (m, 6H), 7.03 (d, 2H, $J_{HF}$=9.2 Hz), 5.94 (ddt, 1H, J=11.7, 10.4, 5.2 Hz), 5.23-5.18 (m, 4H), 4.34 (d, 2H, J=5.4 Hz).

Preparation 5 (±)-5-(Iodomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone

In 25 mL of chloroform is combined 496 mg (1.31 mmol) of Preparation 4, 1.58 mL (19.6 mmol, 15 eq) of pyridine and 4.97 g (19.6 mmol, 15 eq) of $I_2$. The resulting mixture is placed under an atmosphere of nitrogen and heated to 50°C with stirring. After 1.5 h, the reaction is decanted into 70 mL of chloroform. The remaining sludge is rinsed with chloroform (3x15 mL). The combined organics are washed with 20% sodium thiosulfate then brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to a yellow, solid foam (491 mg). This material is purified by silica gel chromatography (100 g of SG, eluted with 1L x 0.5% $MeOH/CHCl_3$, 1 L x 1% $MeOH/CHCl_3$). 269 mg (49%) of the title compound is recovered as a yellow solid (MP 133-134°C).

FTIR (mull): $cm^{-1}$ 3130, 1758, 1650, 1414, 1241, 1017, 846.

Anal. calc'd for $C_{15}H_{11}F_2IN_2O_4$: C, 43.29; H, 2.66; N, 6.73

Found: C, 43.19; H, 2.56; N, 6.59

$^1H$ NMR ($CDCl_3$): δ 8.72 (s, 1H), 8.62 (s(b), 1H), 7.79 (d, 1H, J=10.7 Hz), 7.43-7.38 (m, 1H), 7.32 (d, 2H, $J_{HF}$=9.9 Hz), 4.84-4.72 (m, 1H), 4.19 (dd, 1H, J=8.9, 8.9 Hz), 3.80 (dd, 1H, J=6.0, 9.2 Hz), 3.51 (dd, 1H, J=3.8, 10.5 Hz), 3.39 (dd, 1H, J=8.2, 10.5 Hz).

Preparation 6 (±)-5-(Azidomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone

In 15 mL of DMF (dried over 4A sieves) is combined 577 mg (1.31 mmol) of the starting iodide (Preparation 5) and 681 mg (10.5 mmol, 8 eq) of sodium azide. The reaction is placed under an atmosphere of nitrogen and heated to 55°C. After 2 h, the reaction is added to 100 mL of water and then extracted with ethyl acetate (4x25 mL). The combined organics are washed with water then brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to an amber oil (354 mg, 82% crude yield). The crude azide is suitable for reduction without further purification. An analytical sample is prepared by prepatative TLC (SG, 10% $CH_3CN/CHCl_3$). 22 mg of the title compound is recovered as an off white solid (MP 97-98°C).

FTIR (mull): $cm^{-1}$ 3483, 2110, 1746, 1640, 1417, 1237, 1064, 716.

Anal. calc'd for $C_{15}H_{11}F_2N_5O_2$: C, 54.38; H, 3.35; N, 21.14

Found: C, 54.33; H, 3.38; N, 19.39

MS (EI): m/z (rel. int.): 331 [$M^+$] (100), 274 (14), 258 (23), 232 (15), 217 (22), 190 (22), 43 (14).

$^1$H NMR ($CDCl_3$): δ 8.72 (s(b), 1H), 8.63 (s(b), 1H), 7.79 (d, 1H, J=7.9 Hz), 7.42-7.38 (m, 1H), 7.34 (d, 2H, $J_{HF}$=9.9 Hz), 4.90-4.82 (m, 1H), 4.11 (dd, 1H, J=8.9, 8.9 Hz), 3.88 (dd, 1H, J=6.2, 8.9 Hz), 3.77 (dd, 1H, J=4.4, 13.4 Hz), 3.63 (dd, 1H, J=4.1, 13.3 Hz).

Preparation 7 (±)-5-(Aminomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone

In 40 mL of methanol is combined 354 mg (~1.07 mmol) of the crude azide (Preparation 6) and 50 mg of 10% pd-C. The mixture is purged with nitrogen and then placed under an atmosphere of hydrogen (1 atm). The reaction is allowed to stir at room temperature for 16 h. After this time, the reaction is filtered and concentrated under reduced pressure to an amber solid foam (291 mg, ~89% crude). The crude amine is suitable for acetylation without further purification. An analytical sample is prepared by preparative TLC (SG, 10% MeOH/$CHCl_3$). The title compound is recovered as a white solid (MP 143-145°C).

FTIR (neat) $cm^{-1}$ 3368 (b), 1757, 1646, 1412, 1244, 1025, 714.

Anal. calc'd for $C_{15}H_{13}F_2N_3O_2$: C, 59.02; H, 4.29; N, 13.76

Found: C, 57.94; H, 4.21; N, 13.13

MS(EI): m/z (rel. int.) 305 [$M^+$] (67), 276 (15), 233 (66), 219 (12), 44 (13), 29 (100).

$^1$H NMR ($CDCl_3$): δ 8.71 (s, 1H), 8.62 (dd, 1H, J=1.6, 4.9 Hz), 7.79 (d, 1H, J=8.1 Hz), 7.39 (dd, 1H, J=4.9, 8.0 Hz), 7.33 (d, 2H, $J_{HF}$=10.0 Hz), 4.79-4.70 (m, 1H), 4.06 (dd, 1H, J=8.7, 8.7 Hz), 3.92 (dd, 1H, J=6.7, 8.6 Hz), 3.18 (dd, 1H, J=3.9, 14 Hz), 2.98 (dd, 1H J=5.3, 14 Hz), 1.52 (s (b), 2H).

Preparation 8 4-(4-pyridyl)-3,5-difluoroaniline

In a manner similar to that described previously for Preparation 2, 2.00 g (7.38 mmol) of Preparation 1 is transmetallated and combined with $Pd(PPh_3)_4$ (0.1 eq) and 4-bromopyridine (1 eq). The 4-bromopyridine is freshly prepared from the HCl salt as described below. The salt is neutralized in excess saturated sodium bicarbonate. The free base is then extracted with diethyl ether. The combined organics are dried over magnesium sulfate for 15 min, filtered, then concentrated under reduced pressure to a yellow oil. The free base is stored in a stoppered flask, under nitrogen and frozen in dry ice prior to use. The free base quickly decomposes at room temperature. The reaction is worked up as previously described. 889 mg of the crude product is isolated. $^1$H NMR showed this material to be a mixture of desired product and its zinc chloride complex (~1:1). An analytical sample is prepared by preparative TLC (SG, 10% $CH_3CN/CHCl_3$).

$^1$H NMR ($CDCl_3$): δ 8.63 (dd, 2H, J=1.6, 4.6 Hz), 7.38 (dd, 2H, 1.7, 4.7 Hz), 6.30 (ddd, 2H, $J_{HF}$=6.6, 10.3 Hz, $J_{HH}$=8.7 Hz), 4.06 (s(b), 2H).

Preparation 9 N-Carbobenzyloxy-4-(4-pyridyl)-3,5-difluoroaniline

In a manner to that previously described for Preparation 3, 236 mg (1.15 mmol) of the starting amine (Preparation 8) is converted to the carbamate derivative. The crude product is purified by silica gel chromatography (100 g of SG, eluted with a 3-5% $CH_3CN/CHCl_3$ gradient). 171 mg (44%) of the title compound is recovered as a white solid.

MP: 185-186°C.

FTIR (neat): $cm^{-1}$ 1743, 1642, 1605, 1254, 1072.

HRMS: calc'd for $C_{19}H_{14}F_2N_2O_2$: 340.1023. Found: 340.1029.

MS (EI): m/z (rel. int.): 340 [$M^+$] (12), 232 (16), 108 (7), 91 (100), 79 (9), 43 (28).

$^1H$ NMR ($CDCl_3$): δ 8.67 (s(b), 2H), 7.43-7.38 (m, 7H), 7.15 (d, 2H, $J_{HF}$=9.9 Hz), 5.23 (s, 2H).

Preparation 10 N-Allyl-N-carbobenzyloxy-4-(4-pyridyl)-3,5-difluoroaniline

In a manner similar to that previously described for Preparation 4, 468 mg (1.38 mmol) of the starting carbamate (Preparation 9) is allylated. The crude product is purified by silica gel chromatography (125 g of SG, eluted with 2 L x 3% $CH_3CN/CHCl_3$). 216 mg (41%) of the title compound is recovered as yellow solid.

MP: 82-83°C.

FTIR (neat): $cm^{-1}$ 1713, 1635, 1598, 1396, 1312, 1235, 1028.

Anal. calc'd for $C_{22}H_{18}F_2N_2O_2$: C, 69.47; H, 4.77; N, 7.36. Found: C, 69.06; H, 4.80; N, 7.31.

MS (EI): m/z (rel. int.) 380 [$M^+$] (16), 330 (6), 246 (26), 219 (13), 91 (100), 40 (16).

$^1H$ NMR ($CDCl_3$): δ 8.69 (d, 2H, J=5.3 Hz), 7.41-7.33 (m, 7H), 7.03 (d, 2H, $J_{HF}$=9.6 Hz), 5.92 (ddt, 1H, J=11.8, 10.4, 5.3 Hz), 5.25-5.17 (m, 4H), 4.34 (d, 2H, J=5.4 Hz).

Preparation 11 (±)-5-Iodomethyl-3-[4-(4-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone

In a manner to that previously described, 241 mg (0.634 mmol) of the cyclization precursor (Preparation 10) is converted to the oxazolidinone iodide. The crude product is not purified further.

$^1H$ NMR ($CDCl_3$): δ 8.70 (s(b), 2H), 7.44 (d, 2H, J=5.5 Hz), 7.32 (d, 2H, $J_{HF}$=10.2 Hz), 4.85-4.73 (m, 1H), 4.19 (dd, 1H, J=9.0, 9.0 Hz), 3.80 (dd, 1H, J=6.1, 9.2 Hz), 3.50 (dd, 1H, J=6.1, 10.5 Hz), 3.40 (dd, 1H, J=8.0, 10.5 Hz).

EXAMPLE 1 (±)-5-(Acetamidomethyl)3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone

In 10 mL of anhydrous methylene chloride is combined 135 mg (0.433 mmol) of the starting amine (Preparation 7), 143 µL (1.77 mmol, 4 eq.) of pyridine and 167 µL (1.77 mmol, 4 eq.) of acetic anhydride. The reaction is allowed to stir at room temperature under nitrogen. After 2.5 h the reaction is added to 30 mL of methylene chloride and washed with saturated sodium bicarbonate then brine, dried (sodium sulfate), filtered and concentrated under reduced

pressure to a yellow solid (138 mg). This material is purified by silica gel chromatography (70 g of SG, eluted with 1-4% MeOH/$CHCl_3$ gradient), 109 mg (71%) of the title compound is recovered as a white solid (MP 218-219°C).

FTIR (mull): $cm^{-1}$ 3347, 1742, 1679, 1648, 1563, 1409, 1247, 1022, 755.

Anal. calc'd for $C_{17}H_{15}F_2N_3O_3$: C, 58.79; H, 4.35; N, 12.10

Found: C, 57.29; H, 4.35; N, 11.73

MS (EI): m/z (rel. int.) 347 [$M^+$] (100), 303 (47), 275 (42), 244 (37), 219 (61), 73 (36), 56 (52).

$^1H$ NMR ($CDCl_3$): δ 8.68 (s(b), 1H), 8.59 (s(b), 1H), 7.85 (d, 1H, J=7.9 Hz), 7.48-7.41 (m, 2H), 7.31 (ddd, 2H, $J_{HF}$=3 Hz, 13.2 Hz, $J_{HH}$=7.7 Hz), 4.87-4.79 (m, 1H), 4.10 (dd, 1H, J=9.1, 9.1 Hz), 3.82 (dd, 1H, J=6.7, 9.2 Hz), 3.72-3.57 (m, 2H), 2.03 (s, 3H).

EXAMPLE 1a (±)-5-(Acetamidomethy)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone, methanesulfonic acid salt

In 4 mL of methanol is combined 74 mg (0.21 mmol) of (±)-5-(acetamidomethyl)3-[4-(3-pyridyl)]-3,5-difluorophenyl-2-oxazolidinone (EXAMPLE 1) and 14 µL (0.21 mmol) of $CH_3SO_3H$. The mixture is warmed to reflux temperature for 3 min and the reaction becomes homogeneous. The reaction is cooled to room temperature and concentrated under reduced pressure then *in vacuo* to an amber, gummy solid. The recovered solid is triturated with and the recovered yellow solid (80 mg) is dissolved in 8 mL of water, filtered and lyophilized. 55 mg (58%) of the title compound is recovered as a yellow, hygroscopic solid (MP 203-205°C).

EXAMPLE 2 (±)-5-(acetamidomethyl)3-[4-(4-pyridyl)]-3,5-difluorophenyl-2-oxazolidinone

In 10 mL of DMF (dried over 4A sieves) is combined 213 mg of Preparation 11 and 166 mg (2.56 mmol, ~5 eq) of sodium azide. The reaction is placed under an atmosphere of nitrogen and heated to 55°C. After 2 h, the reaction is complete by TLC (6% $CH_3CN/CHCL_3$). The reaction is added to 50 mL of water and extracted with ethyl acetate (5 x 25 mL). The combined organics are washed with water, then brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to an amber oil (CAUTION: Azides are known to decompose explosively). The crude material is combined with 20 mL of methanol and 30 mg of 10% Pd-C. The reaction is purged with nitrogen then placed under an atmosphere of hydrogen. After 16 h, the reaction is filtered and concentrated under reduced pressure to a white solid. This material is combined with 64 µL of acetic anhydride and 55 µL of pyridine in 11 mL of methylene chloride. The reaction is allowed to stir at room temperature under nitrogen for 12 h. After this time, the reaction is added to 50 mL of methylene chloride and washed with saturated sodium bicarbonate then brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to an amber oil. The final product is purified by silica gel chromatography (100 g of SG, eluted with a 1-4% MeOH/$CHCl_3$ gradient). 103 mg of the title

compound is recovered as a yellow solid (47% over 4 steps) (MP 147-149°C.).

FTIR (neat): $cm^{-1}$ 1741, 1651, 1646, 1412, 1246, 1027, 745.

Anal. calc'd for $C_{17}H_{15}F_2N_3O_3$: C, 58.79; H, 4.35; N, 12.10

Found: C, 57.53; H, 4.48; N, 11.65

MS (EI): m/z (rel. int.) 347 [$M^+$] (28), 303 (37), 243 (46), 219 (44), 206 (57), 58 (71), 29 (100).

$^1H$ NMR ($CDCl_3$): δ 8.70 (d, 2H, J=5.6 Hz), 7.42 (d, 2H, J=6.1 Hz), 7.29 (d, 2H, $J_{HF}$=10.3 Hz), 6.10 (s(b), 1H), 4.90-4.78 (m, 1H), 4.08 (dd, 1H, J=9.1, 9.1 Hz), 3.82 (dd, 1H, J=6.7, 9.2 Hz), 3.73-3.67 (m, 2H), 2.05 (s, 3H).

EXAMPLES 3-54

Following the general procedure of Preparations 1-11 and the above EXAMPLES, and (i) starting with the aniline REAGENT (I) listed below for each example, and (ii) using the appropriate aryl or heteroaryl iodide, bromide, triflate or fluorosulfonate for the palladium-mediated coupling reaction (IV → V), the TITLE COMPOUND for the respective EXAMPLE is obtained.

| EXAMPLE | REAGENT | TITLE COMPOUND |
|---|---|---|
| 3 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2,6-dimethylpyridin-4-yl)-3,5-difluorophenyl]-2-oxazolidinone |
| 4 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-methylpyridin-4-yl)-3,5-difluorophenyl]-2-oxazolidinone |
| 5 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-ethylpyridin-4-yl)-3,5-difluorophenyl]-2-oxazolidinone |
| 6 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-(4-phenyl-3,5-difluorophenyl)-2-oxazolidinone |
| 7 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-(dimethylamino)phenyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 8 | 3,5-dichloroaniline | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-dichlorophenyl]-2-oxazolidinone |
| 9 | 3,5-dichloroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3,5-dichlorophenyl]-2-oxazolidinone |
| 10 | 3,5-dichloroaniline | (±)-5-(acetamidomethyl)-3-(4-phenyl-3,5-dichlorophenyl)-2-oxazolidinone |
| 11 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-fluorophenyl]-2-oxazolidinone |
| 12 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-fluorophenyl]-2-oxazolidinone |

| | | |
|---|---|---|
| 13 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2,6-dimethylpyridin-4-yl)-3-fluorophenyl]-2-oxazolidinone |
| 14 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-methylpyridin-4-yl)-3-fluorophenyl]-2-oxazolidinone |
| 15 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-ethylpyridin-4-yl)-3-fluorophenyl]-2-oxazolidinone |
| 16 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-(4-phenyl-3-fluorophenyl)-2-oxazolidinone |
| 17 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-(dimethylamino)phenyl)-3-fluorophenyl]-2-oxazolidinone |
| 18 | 3-chloroaniline | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-chlorophenyl]-2-oxazolidinone |
| 19 | 3-chloroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-chlorophenyl]-2-oxazolidinone |
| 20 | 3-chloroaniline | (±)-5-(acetamidomethyl)-3-(4-phenyl-3-chlorophenyl)-2-oxazolidinone |
| 21 | 3,5-bis(trifluoromethyl)aniline | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-bis(trifluoromethyl)phenyl]-2-oxazolidinone |
| 22 | 3,5-bis(trifluoromethyl)aniline | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3,5-bis(trifluoromethyl)phenyl]-2-oxazolidinone |
| 23 | 3,5-bis(trifluoromethyl)aniline | (±)-5-(acetamidomethyl)-3-[4-phenyl-3,5-bis(trifluoromethyl)phenyl]-2-oxazolidinone |
| 24 | 3-(trifluoromethyl)-aniline | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-(trifluoromethyl)phenyl]-2-oxazolidinone |
| 25 | 3-(trifluoromethyl)-aniline | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-(trifluoromethyl)phenyl]-2-oxazolidinone |
| 26 | 3-(trifluoromethyl)-aniline | (±)-5-(acetamidomethyl)-3-[4-phenyl-3-(trifluoromethyl)phenyl]-2-oxazolidinone |
| 27 | 3,5-dimethoxyaniline | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-dimethoxyphenyl]-2-oxazolidinone |

| | | |
|---|---|---|
| 28 | 3,5-dimethoxyaniline | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3,5-dimethoxyphenyl]-2-oxazolidinone |
| 29 | 3,5-dimethoxyaniline | (±)-5-(acetamidomethyl)-3-(4-phenyl-3,5-dimethoxyphenyl)-2-oxazolidinone |
| 30 | *m*-anisidine | (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-methoxyphenyl]-2-oxazolidinone |
| 31 | *m*-anisidine | (±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-methoxyphenyl]-2-oxazolidinone |
| 32 | *m*-anisidine | (±)-5-(acetamidomethyl)-3-(4-phenyl-3-methoxyphenyl)-2-oxazolidinone |
| 33 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(5-indolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 34 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(3-quinolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 35 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-quinolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 36 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(6-quinolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 37 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-isoquinolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 38 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(1-methyl-5-indolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 39 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(6-benzothiazolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 40 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(6-benzoxazolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 41 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-dimethylamino)-4-thiazolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 42 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-amino-4-thiazolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 43 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-(dimethylamino)-4-oxazolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 44 | 3,5-difluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-amino-4-oxazolyl)-3,5-difluorophenyl]-2-oxazolidinone |
| 45 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(3-quinolyl)-3-fluorophenyl]-2-oxazolidinone |

| | | |
|---|---|---|
| 46 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-quinolyl)-3-fluorophenyl]-2-oxazolidinone |
| 47 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(6-quinolyl)-3-fluorophenyl]-2-oxazolidinone |
| 48 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(4-isoquinolyl)-3-fluorophenyl]-2-oxazolidinone |
| 49 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(5-indolyl)-3-fluorophenyl]-2-oxazolidinone |
| 50 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(1-methyl-5-indolyl)-3-fluorophenyl]-2-oxazolidinone |
| 51 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(6-benzothiazolyl)-3-fluorophenyl]-2-oxazolidinone |
| 52 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(6-benzoxazolyl)-3-fluorophenyl]-2-oxazolidinone |
| 53 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-amino-4-thiazolyl)-3-fluorophenyl]-2-oxazolidinone |
| 54 | 3-fluoroaniline | (±)-5-(acetamidomethyl)-3-[4-(2-amino-4-oxazolyl)-3-fluorophenyl]-2-oxazolidinone |

Preparation 12 (R)-[3-(3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl butyrate

A mixture of lithium bromide (0.181 g, 2.08 mmol), tri-*n*-butylphosphine oxide (0.454 g, 2.08 mmol), and dry *o*-xylene (10 mL) is azeotropically dried for 1 h. After cooling below the reflux point, a solution of (*R*)-glycidyl butyrate (5.000 g, 34.68 mmol) and 3-fluorophenyl isocyanate (4.755 g or 3.96 mL, 34.68 mmol) in dry *o*-xylene (10 mL) is added over 10 min to the hot solution (some refluxing observed during the addition). When the addition is complete, the solution is heated to reflux for 2 h and then allowed to cool to room temperature. The solvent is removed in vacuo and the residue chromatographed over silica gel, eluting with hexane/ethyl acetate (6:1, 4:1, and then 2:1), to afford 8.758 g (90%) of the title compound as a colorless syrup with the following characteristics:

$[\alpha]^{25}_{D}$ -46.7° (*c* 1.0, $CHCl_3$).

IR (mineral oil mull): 1758, 1615, 1591, 1498, 1229, 1197, 1169 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.44 ("dt", J = 11.2, 2.3 Hz, 1H), 7.34 ("dt", J = 8.3, 6.5 Hz, 1H), 7.23 (ddd, J = 8.3, 2.1, 0.9 Hz, 1H), 6.86 (dddd, J = 8.2, 8.2, 2.5, 0.9 Hz, 1H), 4.88 (m, 1H), 4.39 (dd, J = 12.3, 3.8 Hz, 1H), 4.32 (dd, J = 12.3, 4.7 Hz, 1H), 4.13 ("t", J = 9.0 Hz, 1H), 3.82 (dd, J = 9.0, 6.1 Hz, 1H), 2.33 (t, J = 7.3 Hz, 2H), 1.63 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H).

MS *m/z* (relative intensity): 281 (33.1, $M^+$), 193 (9.9), 180 (3.3), 150 (28.7), 148 (68.6),

137 (59.3), 123 (41.7), 95 (38.3), 43 (100).

HRMS *m/z*: 281.1068 (calc'd for $C_{14}H_{16}FNO_4$: 281.1063).

Anal. calc'd for $C_{14}H_{16}FNO_4$: C, 59.78; H, 5.73; N, 4.98.

Found: C, 59.98; H, 5.72; N, 4.88.

Preparation 13 (R)-3-(3-fluorophenyl)-5-(hydroxymethyl)-2-oxooxazolidine

A solution of Preparation 12 (2.789 g, 9.91 mmol) in methanol (10 mL) is treated with a 25 wt. % solution of sodium methoxide in methanol (57 µL, 0.99 mmol) at ambient temperature. After 45 min TLC (5% methanol/chloroform) reveales the starting material is consumed. The reaction mixture is carefully quenched by the addition of 1 N HCl (0.99 mL, 0.99 mmol) and then concentrated in vacuo. Chromatography of the crude product over silica gel, eluting first with 1:1 hexane/ ethyl acetate and then ethyl acetate, affords 1.903 g (91%) of the title compound as a white solid with the following characteristics:

MP: 106.5-107.5°C.

$[\alpha]^{25}_D$ -66.8° (*c* 1.1, $CH_3CN$).

IR (mineral oil mull): 3520, 1724, 1612, 1590, 1496, 1428, 1420, 1232, 1199 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.44 ("dt", J = 11.3, 2.3 Hz, 1H), 7.32 ("dt", J = 8.3, 6.5 Hz, 1H), 7.23 (ddd, J = 8.3, 2.1, 1.0 Hz, 1H), 6.84 (dddd, J = 8.2, 8.2, 2.5, 1.0 Hz, 1H), 4.77 (m, 1H), 4.07-3.96 (m, 3H), 3.76 (dd, J = 12.7, 3.9 Hz, 1H), 2.44 (br s, 1H).

MS *m/z* (relative intensity): 211 (100, $M^+$), 180 (6.8), 136 (34.3), 124 (84.7), 95 (71.6).

HRMS *m/z* 211.0641 (calc'd for $C_{10}H_{10}FNO_3$: 211.0645).

Anal. calc'd for $C_{10}H_{10}FNO_3$: C, 56.87; H, 4.77; N, 6.63.

Found: C, 56.85; H, 4.94; N, 6.56.

The enantiomeric excess of the oxazolidinone alcohol is determined by reacting it with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (DCC, DMAP, $CH_2Cl_2$, rt), and examining the $^1$H-NMR spectrum of the resultant Mosher ester. The %ee is estimated to be ≥ 95%.

Preparation 14 (R)-3-(3-fluorophenyl)-5-(hydroxymethyl)-2-oxooxazolidine

A solution of N-(carbobenzyloxy)-3-fluoroaniline (1.000 g, 4.08 mmol) in dry tetrahydrofuran (10 mL) is cooled with a dry ice/acetone bath to ca. -78°C and then *n*-butyllithium (1.87 mL of a 1.6 M solution in hexanes, 2.91 mmol) is added. (*R*)-glycidyl butyrate (0.420 g or 0.413 mL, 2.91 mmol) is then added via syringe and the cooling bath allowed to dissipate overnight, with the reaction mixture reaching ambient temperature. The reaction mixture is quenched by the careful addition of saturated aqueous ammonium chloride, the entire mixture transferred to a separatory funnel with dichloromethane washings, and the mixture extracted with dichloromethane. The combined organic extracts are dried over sodium sulfate, filtered and concentrated in vacuo to give an oil which is purified by chromatography

over silica gel, eluting with 10% acetonitrile/chloroform containing 1% methanol, to afford 0.555 g (90% based on glycidyl butyrate; 64% based on CBz derivative of the aniline) of the title compound as a white solid identical in all respects to an authentic sample obtained as described in the previous experimental procedure.

Preparation 15 (R)-[3-(3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl 4-methylbenzenesulfonate

A solution of Preparation 14 (1.800 g, 8.52 mmol) in dry pyridine (10 mL) is cooled to ca. 5°C and then treated with *p*-toluenesulfonyl chloride (1.706 g, 8.95 mmol). The solution is left at this temperature overnight. TLC (5% methanol/chloroform or 1:1 hexane/ethyl acetate) indicates the starting material is consumed. The reaction mixture is dumped into ice water (30 mL) and the resultant precipitate collected by vacuum filtration through a medium-porosity sintered glass funnel. The collected solids are thoroughly washed with cold water, dried in vacuo, and recrystallized from ethyl acetate/hexane to give 2.743 g (88%) of the title compound as a white solid with the following characteristics:

MP: 114-115°C.

$[\alpha]^{25}_{D}$ -62.6° (*c* 1.0, $CH_3CN$).

IR (mineral oil mull): 1751, 1617, 1591, 1499, 1415, 1362, 1227, 1202, 1191, 1172, 1093, 967 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.78 ("d", J = 8.4 Hz, 2H), 7.38 ("dt", J = 11.2, 2.3 Hz, 1H), 7.36 ("d", J = 7.8 Hz, 2H), 7.33 ("dt", J = 8.3, 6.6 Hz, 1H), 7.16 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H), 6.86 (dddd, J = 8.2, 8.2, 2.5, 1.0 Hz, 1H), 4.84 (m, 1H), 4.29 (dd, J = 11.1, 4.1 Hz, 1H), 4.24 (dd, J = 11.1, 4.6 Hz, 1H), 4.10 ("t", J = 9.1 Hz, 1H), 3.88 (dd, J = 9.2, 6.0 Hz, 1H), 2.46 (s, 3H).

MS *m/z* (relative intensity): 365 (70.6, $M^+$), 149 (100), 122 (32.8), 91 (52.8).

HRMS *m/z* 365.0738 (calc'd for $C_{17}H_{16}FNO_5S$: 365.0733).

Anal. calc'd for $C_{17}H_{16}FNO_5S$: C, 55.88; H, 4.41; N, 3.83.

Found: C, 55.96; H, 4.38; N, 3.80.

Preparation 16 (R)-[3-(3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl azide

A solution of the tosylate (Preparation 15; 2.340 g, 6.40 mmol) in dry DMF (60 mL) is treated with solid sodium azide (3.331 g, 51.23 mmmol) at ambient temperature. The resultant slurry is warmed to 65°C for 4.5 h and then cooled to ambient temperature and left overnight. The reaction mixture is then diluted with ethyl acetate and water, transferred to a separatory funnel, and extracted with ethyl acetate. The combined ethyl acetate extracts are washed thoroughly with water, and then dried (sodium sulfate), filtered, and concentrated in vacuo to give 1.492 g (99%) of the "crude" azide as a white solid which is essentially pure. The following characteristics are noted:

MP: 81-82°C.

$[\alpha]^{25}_D$ -136.5° (*c* 0.9, $CHCl_3$).

IR (mineral oil mull): 2115, 1736, 1614, 1591, 1586, 1497, 1422, 1233, 1199, 1081, 1049 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.45 ("dt", J = 11.2, 2.3 Hz, 1H), 7.34 ("dt", J = 8.3, 6.4 Hz, 1H), 7.23 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 6.86 (dddd, J = 8.2, 8.2, 2.5, 1.0 Hz, 1H), 4.81 (m, 1H), 4.09 ("t", J = 8.9 Hz, 1H), 3.86 (dd, J = 9.0, 6.2 Hz, 1H), 3.72 (dd, J = 13.2, 4.5 Hz, 1H), 3.60 (dd, J = 13.2, 4.4 Hz, 1H).

MS *m/z* (relative intensity): 236 (59.0, $M^+$), 179 (94.9), 136 (59.5), 122 (62.4), 109 (71.8), 95 (100), 75 (40.7).

HRMS *m/z* 236.0708 (calc'd for $C_{10}H_9FN_4O_2$: 236.0709).

Anal. calc'd for $C_{10}H_9FN_4O_2$: C, 50.85; H, 3.84; N, 23.72.

Found: C, 50.74; H, 3.76; N, 23.71.

Preparation 17 (S)-N-[[3-(3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of the azide (Preparation 16; 8.200 g, 34.71 mmol) in ethyl acetate (100 mL) is treated with 10% palladium on carbon (0.820 g) under nitrogen. The atmosphere is then replaced with hydrogen (balloon) via repeated evacuation and filling. After stirring under hydrogen for 17 h, TLC (5% methanol/chloroform) reveales the azide is consumed. The atmosphere is replaced with nitrogen and then pyridine (6 mL) and acetic anhydride (4.1 mL, 43.40 mmol) are added to the reaction mixture. The reaction mixture is stirred for 1 h at ambient temperature and then filtered through Celite, washing the pad with ethyl acetate. The filtrate is concentrated in vacuo and the residue taken-up in dichloromethane. The addition of diethyl ether affordes a precipitate. After standing in the refrigerator overnight the solids are collected by vacuum filtration, washed with cold hexane, and dried in vacuo to furnish 4.270 g of the title compound as a white solid. Another 3.700 g is obtained from the mother liquors for an overall yield of 91%. In another run, the crude product is purified by chromatography over silica gel, eluting with 5% methanol/chloroform. The following characteristics are noted:

MP: 140.0-140.5°C.

$[\alpha]^{25}_D$ -6.6° (*c* 1.0, $CHCl_3$).

Preparation 18 (S)-N-[[3-(3-fluoro-4-iodophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide

The oxazolidinone intermediate described in Preparation 17 (0.280 g, 1.11 mmol) is dissolved in a mixture of acetic acid (20 mL) and trifluoroacetic acid (5 mL) and then treated with iodine monochloride (2.343 g, 14.43 mmol) at ambient temperature. The dark red-brown mixture is stirred at room temperature under nitrogen. An orange precipitate gradually forms. After ca. 24 h the reaction mixture is diluted with diethyl ether and the solids collected by vacuum filtration through a medium-porosity sintered glass filter, washing with $Et_2O$. The

crude solids are dissolved in hot chloroform (a little methanol is added to aid dissolution), transferred to a separatory funnel, and washed with saturated aqueous sodium bicarbonate, 20% aqueous sodium thiosulfate and brine. The organic phase is dried over sodium sulfate, filtered and concentrated in vacuo to afford 0.295 g (70%) of the title compound as a white solid. The following characteristics are noted:

MP: 185.5-186.5°C.

$[\alpha]^{25}_{D}$ -37.6° (*c* 1.0, DMF).

Preparation 19 (±)-N-[[3-[3-fluoro-4-(trimethylstannyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide

In 1,4-dioxane (10 mL) is combined (±)-N-[[3-(3-fluoro-4-iodophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (Preparation 18; 0.091 g, 0.24 mmol), bis(triphenylphosphine)-palladium(II) chloride (0.017 g, 0.024 mmol) and hexamethylditin (0.105 g, 0.321 mmol). The reaction mixture is thoroughly purged with nitrogen and heated to reflux temperature for 1.5 h. After this time, the reaction is concentrated under reduced pressure and then purified by silica gel chromatography (10 g of silica gel; eluted with 100 mL each of 0.5, 1, and finally 1.5% methanol/chloroform). After concentration of appropriate fractions, 0.100 g (100%) of the racemic title compound is obtained as a yellow solid with the following characteristics:

MP: 127-130°C.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 7.38-7.33 (m, 2H), 7.19 (dd, J = 8.0, 2.1 Hz, 1H), 6.04 (bs, 1H), 4.83-4.72 (m, 1H), 4.05 (dd, J = 9.1, 9.1 Hz, 1H), 3.76 (dd, J = 9.2, 6.7 Hz, 1H), 3.71-3.59 (m, 2H), 2.02 (s, 3H), 0.34 (d, J = 28.6 Hz, 9H).

MS *m/z* (relative intensity): 415 (3, $M^+$), 401 (100), 165 (10), 139 (15), 56 (24), 43 (41).

EXAMPLE 55 (±)-N-[[3-[3-fluoro-4-(6-quinolyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide.

(±)-N-[[3-[3-fluoro-4-(trimethylstannyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Preparation 19; 0.367 g, 0.88 mmol), 6-bromoquinoline (0.239 g, 1.15 mmol) and bis(triphenyl-phosphine)palladium(II) chloride (0.062 g, 0.088 mmol) are combined with DMF (10 mL). The reaction mixture is thoroughly purged with nitrogen and then heated to 80°C under nitrogen. After 2 h, little progress is noted by TLC and so the reaction mixture is heated to 95°C for a further 2 h. At this point, TLC revealed the reaction is complete. The mixture is cooled to ambient temperature and concentrated under reduced pressure to give a crude material which is purified by chromatography over silica gel (10 g of silica gel; eluted with methanol/chloroform, 1→4%) to afford 0.136 g (51%) of the racemic title compound as an off-white solid with the following characteristics:

MP: 216-219°C (dec).

IR (internal reflectance): 3411, 3281, 1743, 1657, 1630, 1566, 1521, 1499, 1416, 1226, 1194 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$, 300 MHz): δ 8.95 (dd, J = 4.2, 1.5 Hz, 1H), 8.26-8.20 (m, 2H), 8.00 (br s, 1H), 7.92 (d br t, J = 8.8, 2.0 Hz, 1H), 7.61 (dd, J = 12.9, 2.1 Hz, 1H), 7.57 ("t", J = 8.6 Hz, 1H), 7.47 (dd, J = 8.2, 4.3 Hz, 1H), 7.35 (dd, J = 8.5, 2.1 Hz, 1H), 6.08 (b t, J = 6.0 Hz, 1H), 4.84 (m, 1H), 4.13 ("t", J = 9.0 Hz, 1H), 3.86 (dd J = 9.1, 6.8 Hz, 1H), 3.80-3.62 (m, 2H), 2.05 (s, 3H).

MS *m/z* (relative intensity): 379 (100.0, $M^+$), 335 (24.4), 307 (17.0), 276 (42.6), 264 (29.2), 251 (93.8).

EXAMPLE 56 (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide

A slurry of the oxazolidinone iodide described in Preparation 18 (0.063 g, 0.165 mmol) and trimethyl(4-pyridyl)tin (0.060 g, 0.248 mmol) in 1,4-dioxane (5 mL) is degassed by repeated evacuation and filling with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (0.012 g, 0.0165 mmol) is added, the reaction again degassed, and then the mixture is brought to reflux under nitrogen. After 4 h TLC (silica gel, 10% methanol/chloroform) reveales some of the iodide still remaines. The mixture is refluxed a further 20 h, cooled to ambient temperature, and concentrated under reduced pressure. The residue is chromatographed over silica gel, eluting with a little chloroform and then methanol/chloroform (1%, 2%, and then 5%), to afford 0.046 g (84%) of the title compound as a white solid which is identical by $^1$H-NMR and chromatographic behavior to a fully characterized racemic sample. The following characteristics are noted for the enantiomerically enriched material:

MP: 190.5-191.0°C.

$[\alpha]^{25}_D$ -16.4° (*c* 0.5, $CHCl_3$).

The following characteristics are noted for a racemic sample:

MP: 179-180°C.

IR (internal reflectance): 3279, 3063, 1756, 1752, 1657, 1626, 1600, 1542, 1522, 1485, 1412, 1407, 1377, 1222, 1198 $cm^{-1}$.

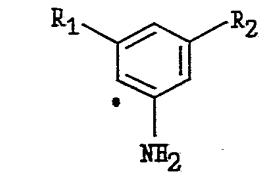
$^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.67 (dd, J = 6.1, 1.5 Hz, 2H), 7.59 (dd, J = 13.1, 2.2 Hz, 1H), 7.50 ("t", J = 8.5 Hz, 1H), 7.47 (dd, J = 6.1, 1.4 Hz, 2H), 7.33 (dd, J = 8.7, 2.2 Hz, 1H), 6.15 (bt, J = 6.0 Hz, 1H), 4.84 (m, 1H), 4.11 ("t", J = 9.1 Hz, 1H), 3.85 (dd, J = 9.2, 6.7 Hz, 1H), 3.78-3.62 (m, 2H), 2.04 (s, 3H).

MS *m/z* (relative intensity): 329 (39.8, $M^+$), 285 (29.3), 257 (14.5), 201 (52.4), 172 (27.1), 73 (27.1), 42 (100.0).

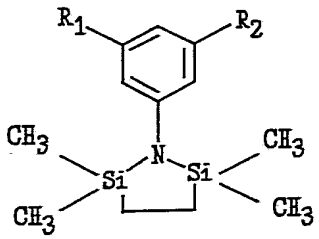
Anal. calc'd for $C_{17}H_{16}FN_3O_3$: C, 62.00; H, 4.90; N, 12.76.

Found: C, 62.01; H, 4.84; N, 12.82.

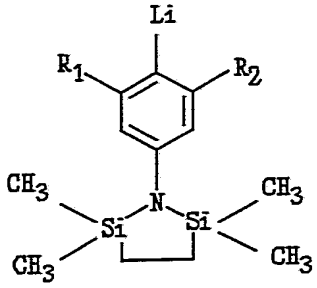
CHART A



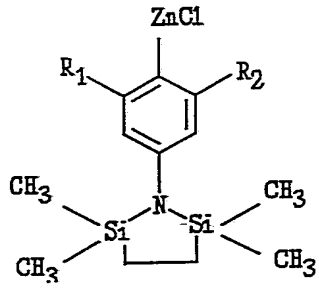

(I)




(II)

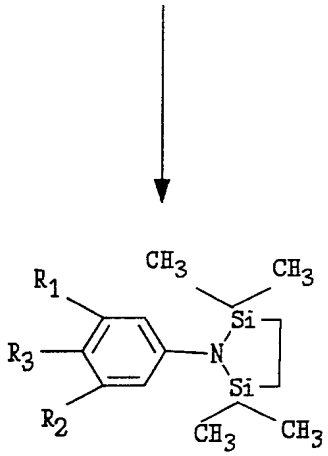



(III)

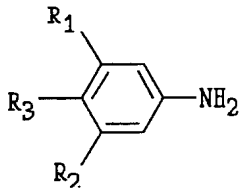



(IV)

CHART A (continued)

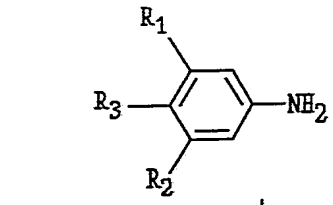


(V)

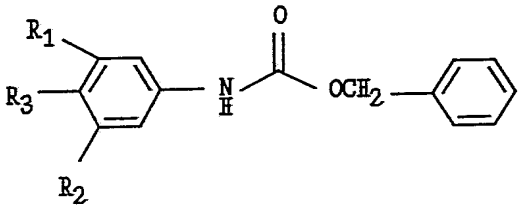


(VI)

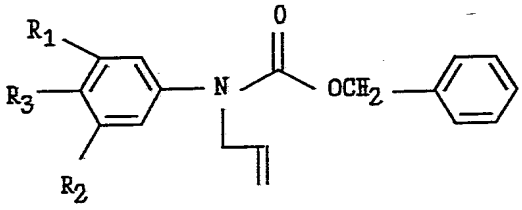
CHART B



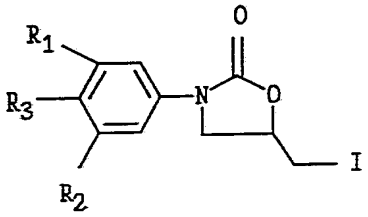

(VI)




(VII)

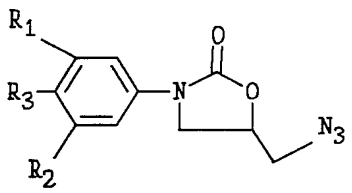



(VIII)

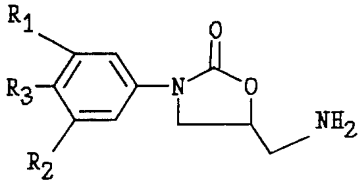



(IX)

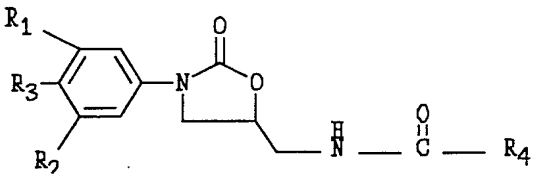
CHART B (continued)



(X)



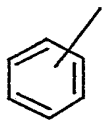
(XI)



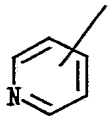
(XII)

CHART C

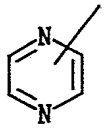
5



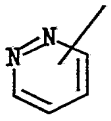
(a) phenyl



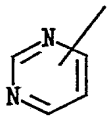
(b) pyridyl



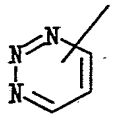
(c) pyrazinyl



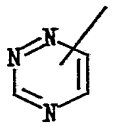
(d) pyridazinyl



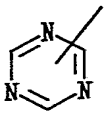
(e) pyrimidinyl



(f) 1,2,3-triazinyl

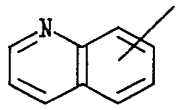


(g) 1,2,4-triazinyl

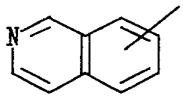


(h) 1,2,5-triazinyl

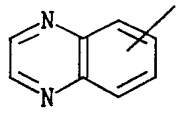
CHART C (continued)



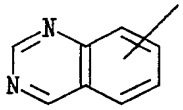
(i) quinolinyl



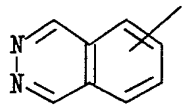
(j) isoquinolinyl



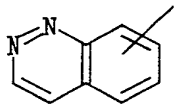
(k) quinoxalinyl



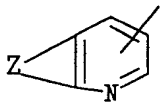
(l) quinazolinyl



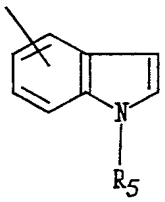
(m) phthalazinyl



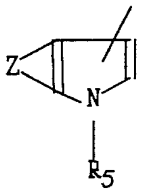
(n) cinnolinyl



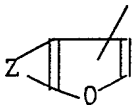
(o) napthyridinyl



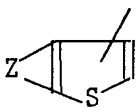
(p) indolyl



(q) pyrrolopyridinyl

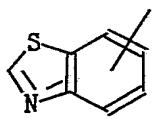


(r) furanopyridinyl

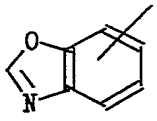


(s) thienopyridinyl

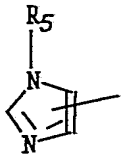
CHART C (continued)



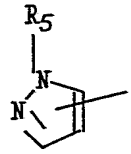
(t) benzothiazolyl



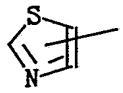
(v) benzoxazolyl



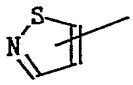
(v) imidazolyl



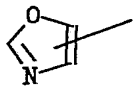
(w) pyrazolyl



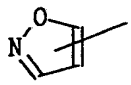
(x) thiazolyl



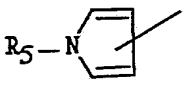
(y) isothiazolyl



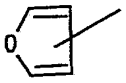
(z) oxazolyl



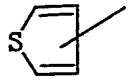
(aa) isoxazolyl



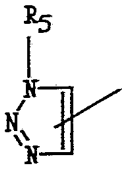
(bb) pyrrolyl



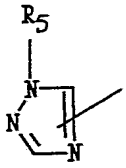
(cc) furanyl



(dd) thiophenyl

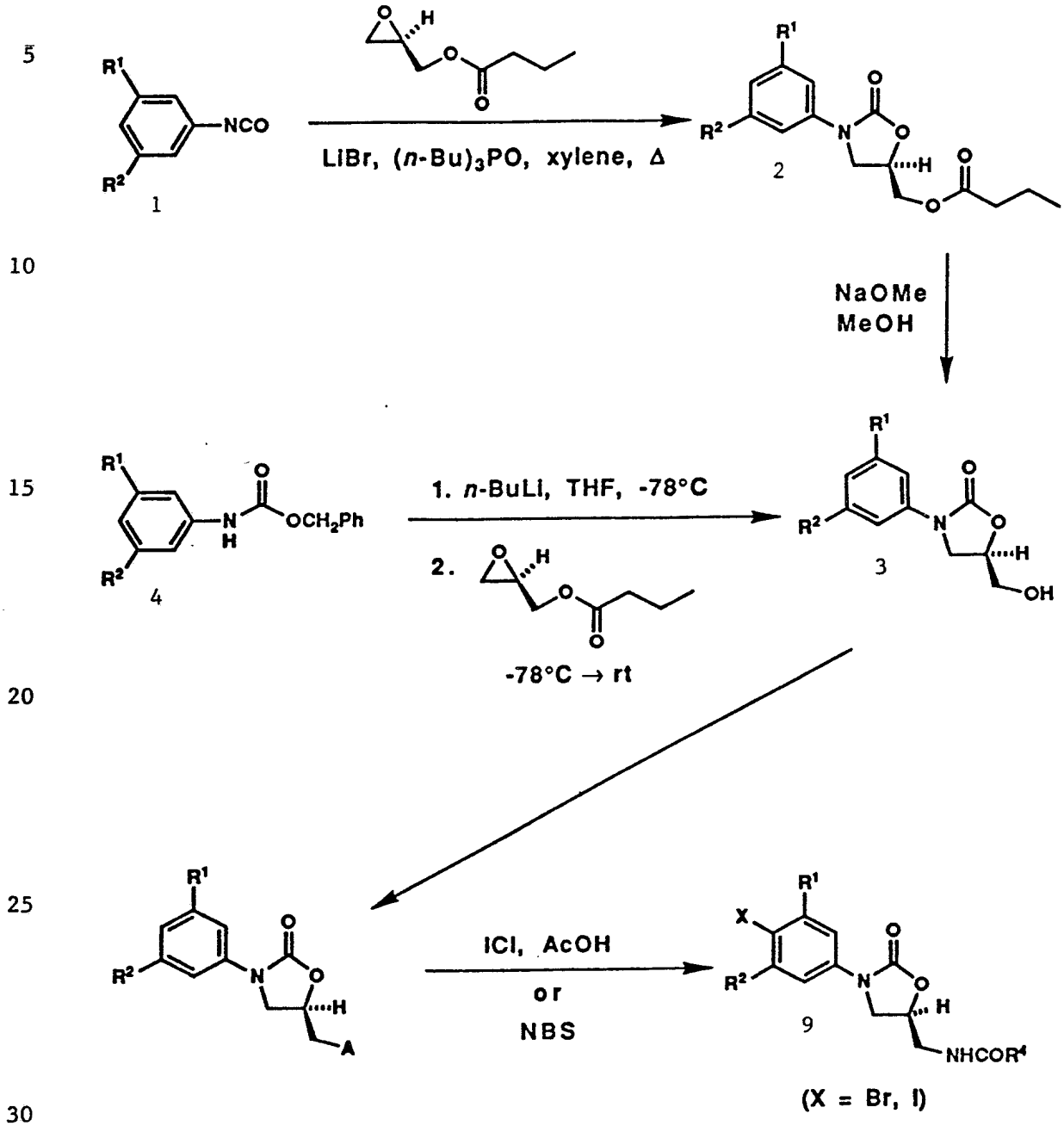


(ee) 1,2,3-triazolyl



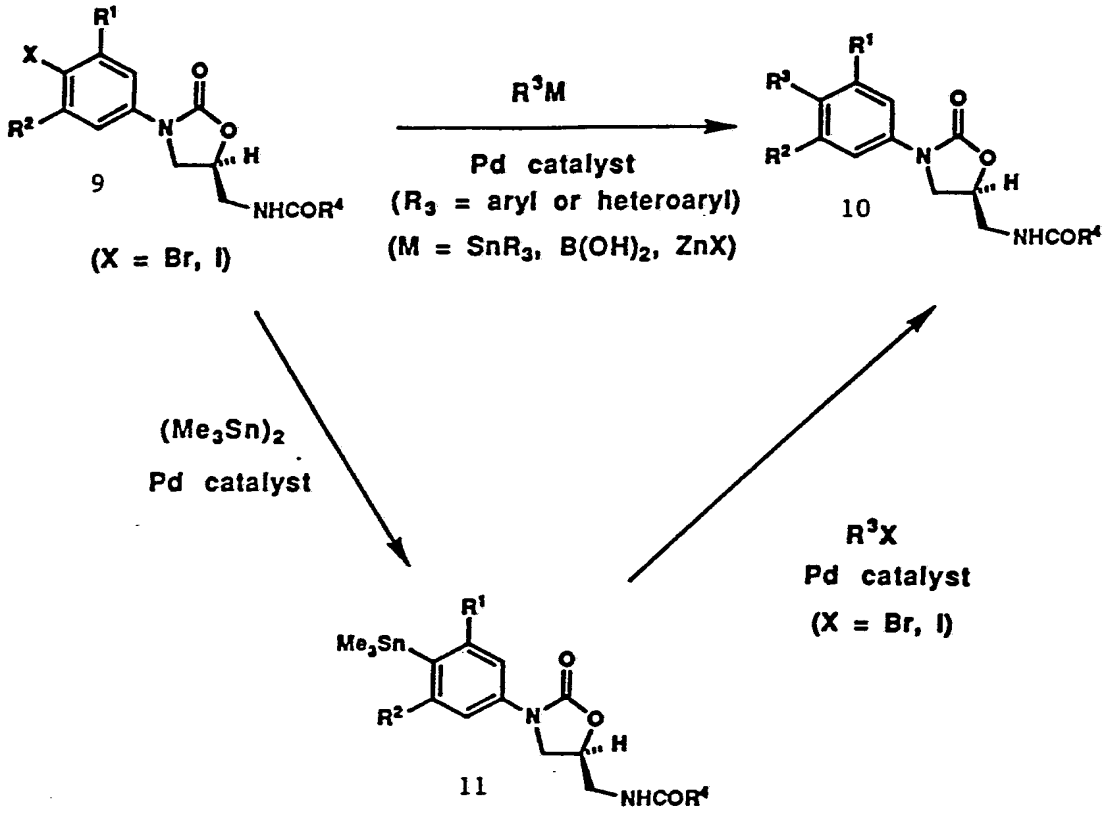
(ff) 1,2,4-triazolyl

CHART D




5: A = OTs or OMs
6: A = $N_3$
7: A = $NH_2$
8: A = $NHCOR^4$

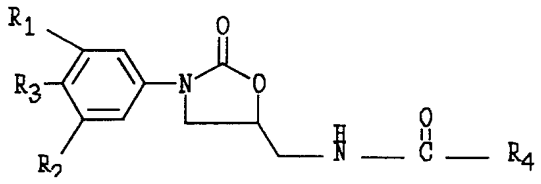
CHART E


R1
X
R2
O
N
O
H
NHCOR4
9
(X = Br, I)
R3M
Pd catalyst
(R3 = aryl or heteroaryl)
(M = SnR3, B(OH)2, ZnX)
R1
R3
R2
10
(Me3Sn)2
Pd catalyst
R3X
Pd catalyst
(X = Br, I)
Me3Sn
11

## CLAIMS

We claim:

1. A substituted aryl- and heteroaryl-phenyl oxazolidinone of Formula (XII)



(XII)

where

(I) $R_1$ and $R_2$ are the same or different and are selected from the group consisting of

(a) -H,

(b) -F,

(c) -Cl,

(d) $-CF_3$, and

(f) $-OCH_3$, provided that only one of $R_1$ or $R_2$ may be hydrogen;

(II) $R_3$ is selected from the group consisting of

(a) phenyl,

(b) pyridyl,

(c) pyrazinyl, (d) pyridazinyl, (e) pyrimidinyl,

(f) 1,2,3-, (g) 1,2,4-, (h) 1,2,5-triazinyl,

(i) quinolinyl, (j) isoquinolinyl,

(k) quinoxalinyl, (l) quinazolinyl, (m) phthalazinyl, (n) cinnolinyl,

(o) naphthyridinyl,

(p) indolyl having nitrogen optionally substituted with $R_{5-1}$ where $R_{5-1}$ is

-H,

$C_1$-$C_4$ alkyl optionally substituted with one or more halogens,

$C_3$-$C_6$ cycloalkyl, or

$-C(O)R_{5-2}$ where $R_{5-2}$ is

-H,

$C_1$-$C_4$ alkyl optionally substituted with one or more halogens, or

phenyl optionally substituted with one or more halogens,

(q) pyrrolopyridinyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above, (r) furanopyridinyl, (s) thienopyridinyl,

(t) benzothiazolyl, (u) benzoxazolyl,

(v) imidazolyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

(w) pyrazolyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

(x) thiazolyl, (y) isothiazolyl,

(z) oxazolyl, (aa) isoxazolyl,

(bb) pyrroyl having nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

(cc) furanyl, (dd) thiophenyl,

wherein substituents (a)-(dd) are optionally substituted with X and Y,

(ee) 1,2,3-, (ff) 1,2,4-triazolyl having the saturated nitrogen substituted with $R_{5-1}$ where $R_{5-1}$ is as defined above,

wherein substituents (ee) and (ff) are optionally substituted with X;

(III) each occurrence of Y is independently selected from

(a) -H,

(b) -Fl, (c) -Cl, (d) -Br, (e) -I,

(f) $-R_{3-1}$, (g) $-OR_{3-1}$ where $R_{3-1}$ is H or $C_1$-$C_4$ alkyl, or

(h) $-NO_2$;

(IV) each occurrence of X is independently selected from

(a) -H,

(b) $C_1$-$C_8$ alkyl optionally substituted with

one or more halogens,

-OH,

=O other than at alpha position,

$-S(O)_nR_{3-2}$ where $R_{3-2}$ is $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl, or

$-NR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are the same or different and are -H, $C_1$-$C_8$ alkyl, $C_3$-$C_8$ cycloalkyl, $-(CH_2)_tCHOR_{3-5}$, $-(CH_2)_tNR_{3-6}R_{3-7}$, or taken together are $-(CH_2)O(CH_2)-$,

$-(CH_2)_tCH(CO)R_{3-8}$, or $-(CH_2)N(R_{3-8})(CH_2)_2-$ where

$R_{3-5}$ is -H or $C_1$-$C_4$ alkyl, or

$R_{3-6}$ and $R_{3-7}$ are the same or different and are -H, $C_1$-$C_4$ alkyl or taken together are $-(CH_2)_r-$,

(c) $C_2$-$C_5$ alkenyl,

(d) $C_3$-$C_8$ cycloalkyl,

(e) $-OR_{3-3}$ where $R_{3-3}$ is as defined above,

(f) -CN,

(g) -S-$(O)_n$-$R_{3-8}$ where $R_{3-8}$ is

$C_1$-$C_4$ alkyl optionally substituted with

one or more halogens,

-OH,

-CN,

-$NR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

-$CO_2R_{3-5}$ where $R_{3-5}$ is as defined above,

$C_2$-$C_4$ alkenyl,

-$NR_{3-9}R_{3-10}$ where $R_{3-9}$ is -H, $C_1$-$C_4$ alkyl, or $C_3$-$C_8$ cycloalkyl and $R_{3-10}$ is -H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkenyl, $C_3$-$C_4$ cycloalkyl, -$OR_{3-5}$, or -$NR_{3-6}R_{3-7}$ where $R_{3-5}$, $R_{3-6}$, and $R_{3-7}$ are as defined above,

-$N_3$,

-NHC(O)$R_{3-11}$ where $R_{3-11}$ is $C_1$-$C_4$ alkyl optionally substituted with one or more halogens,

(h) -$S(O)_2$-N=$S(O)_pR_{3-14}R_{3-15}$ where $R_{3-14}$ and $R_{3-15}$ are the same or different and are $C_1$-$C_2$ alkyl, or taken together are -$(CH_2)_q$-,

(i) -S-C(O)-$R_{3-11}$ where $R_{3-11}$ is as defined above,

(j) tetrazoly,

(k) -$NR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

(l) -$N(R_{3-3})COR_{3-11}$ where $R_{3-3}$ and $R_{3-11}$ are as defined above,

(m) -$N(R_{3-3})S(O)_nR_{3-11}$ where $R_{3-3}$ and $R_{3-11}$ are as defined above,

(n) -$CONR_{3-3}R_{3-4}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

(o) -C(O)$R_{3-16}$ where $R_{3-16}$ is

-H,

$C_1$-$C_8$ alkyl optionally substituted with one or more halogens,

$C_1$-$C_4$ alkyl optionally substituted with

-$OR_{3-5}$,

-OC(O)$R_{3-5}$,

-$NR_{3-3}R_{3-4}$,

-$S(O)_nR_{3-17}$,

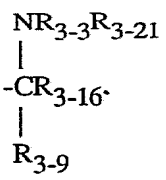
$C_3$-$C_8$ cycloalkyl, or

$C_2$-$C_5$ alkenyl optionally substituted with -CHO or -$CO_2R_{3-5}$, where $R_{3-3}$, $R_{3-4}$, and $R_{3-5}$ are as defined above and $R_{3-17}$ is $C_1$-$C_4$ alkyl or $C_3$-$C_8$ cycloalkyl,

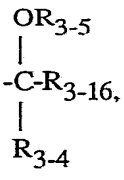
(p) -C(=$NR_{3-18}$)$R_{3-16}$ where $R_{3-16}$ is as defined above and $R_{3-18}$ is -$NR_{3-3}R_{3-4}$, -$OR_{3-3}$, or -NHC(O)$R_{3-3}$ where $R_{3-3}$ and $R_{3-4}$ are as defined above,

(q) -$CR_{3-16}(OR_{3-19})OR_{3-20}$ where $R_{3-16}$ is as defined above and $R_{3-19}$ and

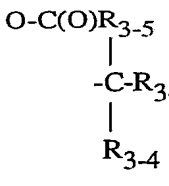
$R_{3-20}$ are the same or different and are $C_1$-$C_4$ alkyl, or taken together are $-(CH_2)_m-$,



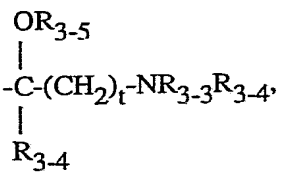
(r)



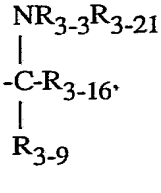
(s)



(t)



(u)



(v)

where $R_{3-3}$, $R_{3-4}$, $R_{3-5}$, $R_{3-9}$, and $R_{3-16}$ are as defined above and $R_{3-21}$ is $R_{3-4}$ or $-NR_{3-4}R_{3-5}$ where $R_{3-4}$ and $R_{3-5}$ are as defined above,

m is 2 or 3;

n is 0, 1, or 2;

p is 0 or 1;

q is 3, 4 or 5;

t is 1, 2 or 3;

(V) $R_4$ is selected from the group consisting of

(a) -H,

(b) $C_1$-$C_{12}$ alkyl optionally substituted with 1-3 Cl,

(c) $C_3$-$C_{12}$ cycloalkyl,

(d) $C_5$-$C_{12}$ alkenyl containing one double bond,

(e) phenyl optionally substituted with 1-3 -OH, $-OCH_3$, $-OC_2H_5$, $-NO_2$, -F, -Cl, -Br, -COOH and $-SO_3H$, $-N(R_{4-1})(R_{4-2})$ where $R_{4-1}$ and $R_{4-2}$ are the same or different and are -H and $C_1$-$C_5$ alkyl,

(f) furanyl,

(g) tetrahydrofuranyl,

(h) 2-thiophene,

(i) pyrrolidinyl,

(j) pyridinyl,

(k) $-O-R_{4-3}$ where $R_{4-3}$ is $C_1$-$C_4$ alkyl,

(l) $-NH_2$,

(m) -$NHR_{4-4}$ where $R_{4-4}$ is $C_1$-$C_3$ alkyl or -ϕ,

(n) -$NR_{4-4}R_{4-5}$ where $R_{4-4}$ is as defined above and $R_{4-5}$ is $C_1$-$C_3$ alkyl, or taken together with the attached nitrogen atom to form a saturated mono-nitrogen $C_5$-$C_7$ heterocyclic ring including -O- (morpholine),

(o) -$CH_2$-OH,

(p) -$CH_2$-$OR_{4-6}$ where $R_{4-6}$ is $C_1$-$C_4$ alkyl or -CO-$R_{4-7}$ where $R_{4-7}$ is $C_1$-$C_4$ alkyl or -ϕ;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 where one of $R_1$ or $R_2$ are hydrogen.

3. A compound according to claim 2 where $R_3$ is phenyl optionally substituted with X and Y.

4. A compound according to claim which is

(±)-5-(acetamidomethyl)-3-(4-phenyl-3-fluorophenyl)-2-oxazolidinone,

(S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

(±)-5-(acetamidomethyl)-3-(4-phenyl-3-chlorophenyl)-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-phenyl-3-(trifluoromethyl)phenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-(4-phenyl-3-methoxyphenyl)-2-oxazolidinone, and

(±)-5-(acetamidomethyl)-3-[4-(4-(dimethylamino)phenyl)-3-fluorophenyl]-2-oxazolidinone.

5. A compound according to claim 2 where $R_3$ is pyridyl optionally substituted with X and Y.

6. A compound according to claim 5 which is

(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-fluorophenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-chlorophenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-(trifluoromethyl)phenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3-methoxyphenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-fluorophenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-chlorophenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-(trifluoromethyl)phenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3-methoxyphenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(2,6-dimethylpyridin-4-yl)-3-fluorophenyl]-2-

oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(2-methylpyridin-4-yl)-3-fluorophenyl]-2-oxazolidinone, and

(±)-5-(acetamidomethyl)-3-[4-(2-ethylpyridin-4-yl)-3-fluorophenyl]-2-oxazolidinone.

7. A compound according to claim 2 where $R_3$ is quinolinyl or isoquinolinyl optionally substituted with X and Y.

8. A compound according to claim 7 which is

(±)-5-(acetamidomethyl)-3-[4-(3-quinolyl)-3-fluorophenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(4-quinolyl)-3-fluorophenyl]-2-oxazolidinone,

(±)-5-(acetamidomethyl)-3-[4-(6-quinolyl)-3-fluorophenyl]-2-oxazolidinone, and

(±)-5-(acetamidomethyl)-3-[4-(4-isoquinolyl)-3-fluorophenyl]-2-oxazolidinone.

9. A compound according to claim 2 where $R_3$ is indolyl having nitrogen optionally substituted with $R_5$-1 and optionally substituted with X and Y.

10. A compound according to claim 9 which is

(±)-5-(acetamidomethyl)-3-[4-(5-indolyl)-3-fluorophenyl]-2-oxazolidinone, and

(±)-5-(acetamidomethyl)-3-[4-(1-methyl-5-indolyl)-3-fluorophenyl]-2-oxazolidinone.

11. A compound according to claim 2 where $R_3$ is benzothiazolyl or benzoxazolyl optionally substituted with X and Y.

12. A compound according to claim 11 which is

(±)-5-(acetamidomethyl)-3-[4-(6-benzothiazolyl)-3-fluorophenyl]-2-oxazolidinone, and

(±)-5-(acetamidomethyl)-3-[4-(6-benzoxazolyl)-3-fluorophenyl]-2-oxazolidinone.

13. A compound according to claim 2 where $R_3$ is thiazolyl or oxazolyl optionally substituted with X and Y.

14. A compound according to claim 13 which is

(±)-5-(acetamidomethyl)-3-[4-(2-amino-4-thiazolyl)-3-fluorophenyl]-2-oxazolidinone, and

(±)-5-(acetamidomethyl)-3-[4-(2-amino-4-oxazolyl)-3-fluorophenyl]-2-oxazolidinone.

15. A compound according to claim 1 where $R_1$ and $R_2$ are other than hydrogen.

16. A compound according to claim 15 where $R_3$ is phenyl optionally substituted with X and Y.

17. A compound according to claim 16 which is
(±)-5-(acetamidomethyl)-3-(4-phenyl-3,5-difluorophenyl)-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-(4-phenyl-3,5-dichlorophenyl)-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-phenyl-3,5-bis(trifluoromethyl)phenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-(4-phenyl-3,5-dimethoxyphenyl)-2-oxazolidinone, and
(±)-5-(acetamidomethyl)-3-[4-(4-(dimethylamino)phenyl)-3,5-difluorophenyl]-2-oxazolidinone.

18. A compound according to claim 15 where $R_3$ is pyridyl optionally substituted with X and Y.

19. A compound according to claim 18 which is
(±)-5-(acetamidomethyl)3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethy)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone, methanesulfonic acid salt,
(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-dichlorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-bis(trifluoromethyl)phenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-dimethoxyphenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)3-[4-(4-pyridyl)]-3,5-difluorophenyl-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3,5-dichlorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(4-pyridyl)-3,5-bis(trifluoromethyl)phenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(4-pyridinyl)-3,5-dimethoxyphenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(2,6-dimethylpyridin-4-yl)-3,5-difluorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(2-methylpyridin-4-yl)-3,5-difluorophenyl]-2-oxazolidinone, and
(±)-5-(acetamidomethyl)-3-[4-(2-ethylpyridin-4-yl)-3,5-difluorophenyl]-2-oxazolidinone.

20. A compound according to claim 15 where $R_3$ is quinolinyl or isoquinolinyl optionally

substituted with X and Y.

21. A compound according to claim 20 which is
(±)-5-(acetamidomethyl)-3-[4-(3-quinolyl)-3,5-difluorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(4-quinolyl)-3,5-difluorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(6-quinolyl)-3,5-difluorophenyl]-2-oxazolidinone, and
(±)-5-(acetamidomethyl)-3-[4-(4-isoquinolyl)-3,5-difluorophenyl]-2-oxazolidinone.

22. A compound according to claim 15 where $R_3$ is indolyl having nitrogen optionally substituted with $R_{5-1}$ and optionally substituted with X and Y.

23. A compound according to claim 22 which is
(±)-5-(acetamidomethyl)-3-[4-(5-indolyl)-3,5-difluorophenyl]-2-oxazolidinone, and
(±)-5-(acetamidomethyl)-3-[4-(1-methyl-5-indolyl)-3,5-difluorophenyl]-2-oxazolidinone.

24. A compound according to claim 15 where $R_3$ is benzothiazolyl or benzoxazolyl optionally substituted with X and Y.

25. A compound according to claim 24 which is
(±)-5-(acetamidomethyl)-3-[4-(6-benzothiazolyl)-3,5-difluorophenyl]-2-oxazolidinone,
and
(±)-5-(acetamidomethyl)-3-[4-(6-benzoxazolyl)-3,5-difluorophenyl]-2-oxazolidinone.

26. A compound according to claim 15 where $R_3$ is thiazolyl or oxazolyl optionally substituted with X and Y.

27. A compound according to claim 26 which is
(±)-5-(acetamidomethyl)-3-[4-(2-dimethylamino)-4-thiazolyl)-3,5-difluorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(2-amino-4-thiazolyl)-3,5-difluorophenyl]-2-oxazolidinone,
(±)-5-(acetamidomethyl)-3-[4-(2-(dimethylamino)-4-oxazolyl)-3,5-difluorophenyl]-2-oxazolidinone, and
(±)-5-(acetamidomethyl)-3-[4-(2-amino-4-oxazolyl)-3,5-difluorophenyl]-2-oxazolidinone.

28. A process for making a compound of formula (XII) comprising:
(a) converting a substituted aniline to a stabase derivative,

(b) treating the stabase derivative to form an aryl- or heteroaryl-substituted aniline, and

(c) converting the aryl- or heteroaryl-substituted aniline to a aryl- or heteroaryl-substituted phenyloxazolidinone.

29. A process for making an oxazolidinone iodide comprising reacting a carbobenzyloxy allyl compound in the presence of an excess of pyridine and iodine, said excess being of equal amounts of 2-20 molar equivalents.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08267

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D263/20; C07D413/10; C07D417/10; A61K31/42
A61K31/44; A61K31/47; A61K31/425

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0 352 781 (E.I. DU PONT DE NEMOURS AND COMPANY) 31 January 1990 cited in the application see claims | 1 |
| X | EP,A,0 316 594 (E.I. DU PONT DE NEMOURS AND COMPANY) 24 May 1989 cited in the application see claims | 1 |
| X | EP,A,0 127 902 (E.I. DU PONT DE NEMOURS AND COMPANY) 12 December 1984 cited in the application see claims | 1 |

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 04 DECEMBER 1992 | 23. 12. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | HENRY J.C. |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| X | JOURNAL OF MEDICINAL CHEMISTRY<br>vol. 33, no. 9, September 1990, WASHINGTON<br>US<br>pages 2569 - 2578<br>WALTER A.GREGORY ET AL<br>'Antibacterials.Synthesis and<br>structure-activity studies of<br>3-aryl-2-oxooxazolidines.2The A group'<br>cited in the application<br>see the whole document | 1 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/08267

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The formulation of claim 1 is so complicated because of the distinct combinations of the meanings of the variable parts that it does not comply with Art 6 PCT prescribing that the claims shall be clean and concise. For these reasons the search has been limited to the examples

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9208267 SA 65261

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/12/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0352781 | 31-01-90 | US-A- | 4948801 | 14-08-90 |
| | | AU-B- | 622465 | 09-04-92 |
| | | AU-A- | 3911589 | 01-02-90 |
| | | JP-A- | 2124877 | 14-05-90 |
| | | US-A- | 5130316 | 14-07-92 |
| | | US-A- | 5043443 | 27-08-91 |
| EP-A-0316594 | 24-05-89 | AU-A- | 2404388 | 27-04-89 |
| | | JP-A- | 1135777 | 29-05-89 |
| | | US-A- | 4977173 | 11-12-90 |
| EP-A-0127902 | 12-12-84 | AU-B- | 583250 | 27-04-89 |
| | | AU-A- | 2909984 | 13-12-84 |
| | | CA-A- | 1254213 | 16-05-89 |
| | | CA-A- | 1275652 | 30-10-90 |
| | | DE-A- | 3485162 | 21-11-91 |
| | | JP-A- | 60008277 | 17-01-85 |
| | | SU-A- | 1505442 | 30-08-89 |
| | | SU-A- | 1426451 | 23-09-88 |
| | | US-A- | 4705799 | 10-11-87 |

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 263/20, A61K 31/42
C07D 413/12

A1

(11) International Publication Number: WO 93/23384

(43) International Publication Date: 25 November 1993 (25.11.93)

(21) International Application Number: PCT/US93/03570

(22) International Filing Date: 21 April 1993 (21.04.93)

(30) Priority data:
07/880,432 8 May 1992 (08.05.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 07/880,432 (CON)
Filed on 8 May 1992 (08.05.92)

(71) Applicant *(for all designated States except US)*: THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

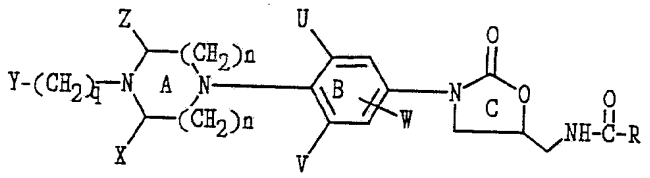
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : HUTCHINSON, Douglas, K. [US/US]; 109 East Candlewyck, Apt. 613, Kalamazoo, MI 49002 (US). BRICKNER, Steven, Joseph [US/US]; 1304 Dogwood Drive, Portage, MI 49002 (US). BARBACHYN, Michael, Robert [US/US]; 1216 Miles Avenue, Kalamazoo, MI 49001 (US). GAMMILL, Ronald, B. [US/US]; 6704 Pleasantview Drive, Portage, MI 49002 (US). PATEL, Mahest, V. [US/US]; 6367 Maple Leaf Avenue, Kalamazoo, MI 49009 (US).

(74) Agent: CORNEGLIO, Donald, L.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: OXAZOLIDINONES CONTAINING A SUBSTITUTED DIAZINE MOIETY AND THEIR USE AS ANTIMICROBIALS




(I)

(57) Abstract

A compound of structural formula (I) or pharmaceutically acceptable salts thereof wherein: Y is chosen from a-n as defined herein; wherein each occurrence of said $C_{1-6}$ alkyl may be substituted with one or more F, Cl, Br, I, $OR^1$, $CO_2R^1$, CN, $SR^1$, or $R^1$ (where $R^1$ is a hydrogen or $C_{1-4}$ alkyl); X and Z are independently $C_{1-6}$ alkyl, $C_{3-12}$ cycloalkyl or hydrogen, or X and Z form a $C_{0-3}$ bridging group, preferably X and Z are hydrogen; U, V and W are independently $C_{1-6}$ alkyl, F, Cl, Br, hydrogen or a $C_{1-6}$ alkyl substituted with one or more of F, Cl, Br or I, preferably U and V are F and W is hydrogen; R is hydrogen, $C_{1-12}$ alkyl, $C_{3-12}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl substituted with one or more F, Cl, Br, I or OH; and q is 0 to 4 inclusive. Oxazolidinone derivatives possessing a substituted diazine moiety bonded to the N-aryl ring are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including multiply-resistant *staphylococci* and *streptococci*, as well as anaerobic organisms such as *bacteroides* and *clostridia* species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| AT | Austria | FR | France | MR | Mauritania |
| AU | Australia | GA | Gabon | MW | Malawi |
| BB | Barbados | GB | United Kingdom | NL | Netherlands |
| BE | Belgium | GN | Guinea | NO | Norway |
| BF | Burkina Faso | GR | Greece | NZ | New Zealand |
| BG | Bulgaria | HU | Hungary | PL | Poland |
| BJ | Benin | IE | Ireland | PT | Portugal |
| BR | Brazil | IT | Italy | RO | Romania |
| CA | Canada | JP | Japan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | | | SE | Sweden |
| CH | Switzerland | KR | Republic of Korea | SK | Slovak Republic |
| CI | Côte d'Ivoire | KZ | Kazakhstan | SN | Senegal |
| CM | Cameroon | LI | Liechtenstein | SU | Soviet Union |
| CS | Czechoslovakia | LK | Sri Lanka | TD | Chad |
| CZ | Czech Republic | LU | Luxembourg | TG | Togo |
| DE | Germany | MC | Monaco | UA | Ukraine |
| DK | Denmark | MG | Madagascar | US | United States of America |
| ES | Spain | ML | Mali | VN | Viet Nam |
| FI | Finland | MN | Mongolia | | |

# OXAZOLIDINONES CONTAINING A SUBSTITUTED DIAZINE MOIETY AND THEIR USE AS ANTIMICROBIALS

## Background of the Invention

The subject invention discloses oxazolidinone derivatives possessing a substituted diazine moiety bonded to an N-aryl ring. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including multiply-resistant *staphylococci* and *streptococci*, as well as anaerobic organisms such as *bacteroides* and *clostridia* species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. The compounds are particularly useful because they are effective against the latter organisms which are known to be responsible for infection in persons with AIDS.

## Information Disclosure Statement

PCT/US89/03548 application discloses 5'indolinyl-5ß-amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5ß-amidomethyloxazolidinones, and 3-(nitrogen substituted)-phenyl-5ß-amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patent 4,801,600, 4,921,869, Gregory W. A., et al., J. Med. Chem., 32, 1673-81 (1989); Gregory W. A., et al., J. Med. Chem., 33, 2569-78 (1990); Wang C., et al., Tetrahedron, 45, 1323-26 (1989); and Brittelli, et al., J. Med. Chem., 35, 1156 (1992).

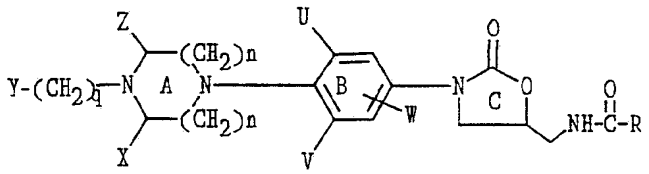
European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones.

European Patent Publication 316,594 discloses 3-substituted styryl oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and pyridinylmethyl substituted phenyl oxazolidinones.

## Summary of the Invention

In one aspect the subject invention is a compound of structural Formula I:



or pharmaceutically acceptable salts thereof wherein:

Y is a) -hydrogen,

b) $-C_{1-6}$ alkyl or -aryl,

c) -OH, $-O-C_{1-6}$ alkyl, -O-vinyl, -O-phenyl, $-O-C(O)-C_{1-6}$ alkyl, -O-C(O)-phenyl (phenyl can be substituted with one to three F, Cl, $-OCH_3$, -OH, $NH_2$ or

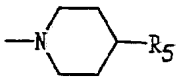
$C_{1-4}$ alkyl) or -O-C(O)-O-$CH_3$,

d) -S-$C_{1-6}$ alkyl,

e) -$SO_2$-$C_{1-6}$ alkyl, -$SO_2$-N($R^3$)$_2$ (where $R^3$ is independently hydrogen, $C_{1-4}$ alkyl or phenyl which can be substituted with one to three F, Cl, $OCH_3$, OH, $NH_2$, or $C_{1-4}$ alkyl),

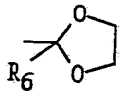
f) -C(O)-$C_{1-6}$ alkyl, -C(O)-O-$C_{1-6}$ alkyl, -C(O)-N($R^3$)$_2$, -C(O)-CH($R^4$)N($R^3$)$_2$, or -C(O)-CH($R^4$)NH-C(NH)-$NH_2$ where ($R^4$ is an amino acid side chain),

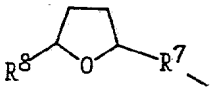
g) -N($R^3$)$_2$, -N($CH_2$)$_m$ (where m is 2-6 and forms a cyclic structure with the nitrogen atom and where one or more carbon atoms can be replaced with S, O or N$R^3$), or

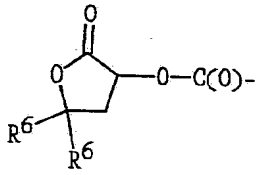


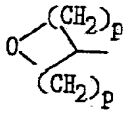
(where $R^5$ is OH, $OCH_3$, $CH_2OH$, $CH_2OCH_3$, $CO_2CH_3$ or $CO_2C_2H_5$),

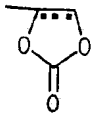
h) -C($CH_3$)=N-OR,

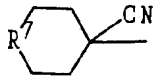
i)  (where $R^6$ is $CH_3$ or hydrogen),

j)  (where $R^7$ is $CH_2$ or C(O) and $R^8$ is -H or =O),

k)  ,

l)  (where p is 1 or 2),

m) 

n)  (where $R^7$ is O, S, S(O), $SO_2$, $CH_2$, NH, $NCH_3$, $NC_2H_5$, NCHO, $NCOCH_3$ or $NCO_2CH_3$);

wherein each occurrence of said $C_{1-6}$ alkyl may be substituted with one or more F, Cl, Br, I, $OR^1$, $CO_2R^1$, CN, $SR^1$, or $R^1$ (where $R^1$ is a hydrogen or $C_{1-4}$ alkyl);

X and Z are independently $C_{1-6}$ alkyl, $C_{3-12}$ cycloalkyl or hydrogen, or X and Z form a $C_{0-3}$ bridging group, preferably X and Z are hydrogen;

U, V and W are independently $C_{1-6}$ alkyl, F, Cl, Br, hydrogen or a $C_{1-6}$ alkyl substituted with one or more of F, Cl, Br or I, preferably U and V are F and W is hydrogen;

R is hydrogen, $C_{1-12}$ alkyl, $C_{3-12}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl substituted with one or more F, Cl, Br, I or OH; and

q is 0 to 4 inclusive.

Preferably, in the above Formula I, U and V are F and W is hydrogen; or U is F and V and W is hydrogen. Preferred forms of Y are selected from the group consisting of H, methyl, ethyl, isopropyl, tert-butyl, benzyl, phenyl, pyridyl, acetyl, difluoroacetyl, hydroxyacetyl, benzoyl, methoxy carbonyl, ethoxy carbonyl, 2-chloroethoxy carbonyl, 2-hydroxyethoxy carbonyl, 2-benzoloxyethoxy carbonyl, 2-methoxyethoxy carbonyl, 2,2,2-trifluoroethoxy carbonyl, cyanomethyl, 2-cyanoethyl, carbomethoxymethyl, 2-carbomethoxyethyl, 2-fluoroethoxy carbonyl, benzyloxy carbonyl, tertary-butoxy carbonyl, methyl sulfonyl, phenyl sulfonyl or para-toluenesulfonyl, more preferred, are methoxy carbonyl or cyanomethyl. Also preferred is where R is methyl, H, methoxy, or $CHCl_2$ and n is one. It is also preferred that the compounds of Formula I are optically pure enantiomers having the *S*- configuration at C5 of the oxazolidinone ring.

Preferred compounds of the subject invention are

(a) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester;

(b) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester;

(c) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester;

(d) N-((2-oxo-3-(4-(4-(phenylcarbonyl)-1-piperazinyl)phenyl)-5-oxazolidinyl)methyl)-acetamide;

(e) N-((3-(4-(3-Fluoro-4-(4-(2-Cyanoethyl)-1-piperazinyl))phenyl)-2-oxo-5-

oxazolidinyl)methyl)-acetamide;

(f) N-((3-(4-(3-Fluoro-4-(4-(2-hydroxyethyl)carbonyl-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

(g) N-((3-(4-(3-Fluoro-4-((phenylcarbonyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

(h) 4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 2-methoxyethyl ester;

(i) 4-[4-[5(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazineacetonitrile;

(j) (+/-)-N-[[3-[4-[4-(1,4-Dioxopentyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl)-acetamide;

(k) (*S*)-N-[[3-[3-fluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; or

(l) (*S*)-N-[[3-[3,5-difluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

More preferred are compounds (a) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester; and

(i) 4-[4-[5(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazineacetonitrile.

In another aspect, the subject invention is directed toward a method for treating microbial infections in warm blooded animals by administering to a warm blooded animal in need thereof an effective amount of a compound of Formula I as described above. Preferably, the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

Detailed Description of the Invention

The present invention discloses diazinyl oxazolidinones of structural Formula I as defined above. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including multiply-resistant *staphylococci* and *streptococci*, as well as anaerobic organisms such as *bacteroides* and *clostridia* species, and acid-fast bacteria such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

With respect to the above definition, $C_{1-6}$ or $C_{1-12}$ alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, etc. and isomeric forms thereof.

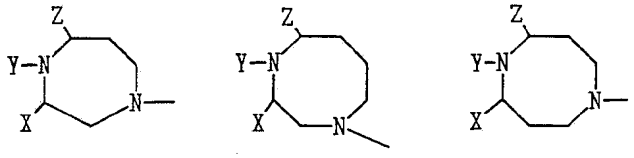
Cycloalkyl are three to twelve carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. and isomeric forms thereof.

Alkoxy are one to six carbons attached to an oxygen forming such groups as methoxy, ethyloxy, butyloxy, etc. and isomeric forms thereof. Further in some instances, groups are described as an alkoxy carbonyl which are named in the compound's nomenclature as an alkyl-ester (such as, methoxy carbonyl and methyl ester).

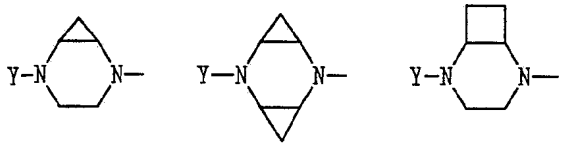
Aryl is defined as a phenyl, pyridyl or napthyl moiety which can be optionally substituted with one or more F, Cl, Br, I, $OR^1$, $CO_2R^1$, CN, $SR^1$, or $R^1$ (where $R^1$ is a hydrogen or $C_{1-4}$ alkyl).

Pharmaceutically acceptable salts means salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

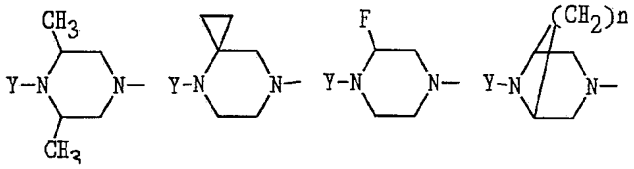
Ring A may be 6-8 atoms in size, and in the larger rings may have either two or three carbons between each nitrogen atom, for example:



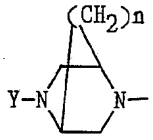
In the larger ring cases, the ring may be bridged to form a bicyclic system as shown in the examples below:



When ring A is 6 atoms in size, then the ring may be optionally substituted at positions X and Z with alkyl groups, cycloalkyl groups, fluoro groups, or bridging alkyl groups, as shown in the following examples below:



In addition to the above examples, the alternative bicyclic system shown below would also serve as another example:



Ring B, in addition to being unsubstituted, can be substituted with one or more halogen

atoms in the series fluorine, chlorine or bromine. Thus, the groups U, V, and W on ring B can be independently either hydrogen atoms or halogen atoms in a variety of substitution patterns.

The group Y on the nitrogen atom of ring A can be introduced by standard synthetic methods (described later) from commercially available reagents. Preferably, Y is selected from the group consisting of H, methyl, ethyl, isopropyl, tert-butyl, benzyl, phenyl, pyridyl, acetyl, difluoroacetyl, hydroxyacetyl, benzoyl, methoxy carbonyl, ethoxy carbonyl, 2-chloroethoxy carbonyl, 2-hydroxyethoxy carbonyl, 2-benzoloxyethoxy carbonyl, 2-methoxyethoxy carbonyl, 2,2,2-trifluoroethoxy carbonyl, cyanomethyl, 2-cyanoethyl, carbomethoxymethyl, 2-carbomethoxyethyl, 2-fluoroethoxy carbonyl, benzyloxy carbonyl, tertary-butoxy carbonyl, methyl sulfonyl, phenyl sulfonyl or para-toluenesulfonyl, more preferred, are methoxy carbonyl or cyanomethyl.

The R substituent is preferably methyl, but may be H, methoxy, or $CHCl_2$.

The most preferred compounds of the series would be prepared as the optically pure enantiomers having the (*S*)-configuration at C5 of the oxazolidinone ring.

Optically pure material could be obtained either by one of a number of asymmetric syntheses or alternatively by resolution from a racemic mixture by selective crystallization of a salt from, for example, intermediate amine 12 (as described in Example 1 and shown in Scheme 1) with an appropriate optically active acid such as dibenzoyl tartrate or 10-camphorsulfonic acid, followed by treatment with base to afford the optically pure amine.

Another route for the preparation of optically pure material would take a different route from those described in the Schemes. Treatment of commercially available 3-fluorophenylisocyanate with commercially available (*R*)-glycidyl butyrate under the conditions of Herweh and Kauffmann (*Tetrahedron Letters* **1971**, 809) would afford the corresponding oxazolidinone in optically pure form with the requisite (*S*)-configuration at the 5-position of the oxazolidinone ring. Removal of the butyrate group by treatment with potassium carbonate in methanol or sodium methoxide in methanol would give the corresponding alcohol which would be derivatized by standard methods as the mesylate followed by displacement with sodium azide to give the azidomethyl oxazolidinone. Reduction of the azide by hydrogenation followed by acylation of the resultant amine by treatment with acetic anhydride and pyridine would afford the key optically active acetylaminomethyl oxazolidinone. With the acetylaminomethyl oxazolidinone in hand, elaboration of the piperazine moiety would be necessary. Nitration of the fluorooxazolidinone derivative would proceed giving predominantly the nitro group in the position *para-* to the nitrogen atom of the oxazolidinone ring, and *ortho-* to the ring fluorine atom. Reduction of the nitro group by hydrogenation would afford the corresponding aniline derivative which upon treatment with bis(2-chloroethyl)amine hydrochloride in the presence of potassium carbonate in refluxing diglyme would afford the optically active piperazine derivative

N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl-2-oxo-5-oxazolidinyl)methyl)-acetamide (22) which can be used to prepare several of the examples in this disclosure.

These compounds are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration. Of the Formula I compounds, 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23) and 4-[4-[5(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazineacetonitrile are most active, and therefore preferred. These are examples of general formula I where ring A is the piperazine moiety.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula I of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound of Formula I according to this invention.

The quantity of active component, that is the compound of Formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements

of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula I according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound according to Formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of Formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

Antimicrobial activity was tested in vivo using the Murine Assay procedure. Groups of female mice (six mice of 18-20 grams each) were injected intraperitoneally with bacteria which were thawed just prior to use and suspended in brain heart infusion with 4% brewers yeast (*Staphylococcus aureus*) or brain heart infusion (Streptococcus species). Antibiotic treatment at six dose levels per drug was administered one hour and five hours after infection by either oral intubation or subcutaneous routes. Survival was observed daily for six days. $ED_{50}$ values based on mortality ratios were calculated using probit analysis. The subject compounds were compared against well-known antimicrobial as controls. The data are shown in Table 1.

Table 1

In Vivo Activity of Examples 1-5

| Organism | UC # | $ED_{50}$, PO (mg/kg) | Control, $ED_{50}$, SC (mg/kg) |
|---|---|---|---|
| *S. aureus* | 9213 | Example 1 3.8 | Vancomycin 1.8 |
| | | Example 3 10.4 | Vancomycin 1.8 |
| | | Example 5 10.0 | Vancomycin 4.2 |
| | | Example 6 12.0 | Vancomycin 2.5 |
| | | Example 7 12.0 | Vancomycin 0.9 |
| | | Example 10 9.4 | Vancomycin 1.9 |
| | | Example 36 7.9 | Vancomycin 1.7 |
| | | Example 37 12.6 | Vancomycin 1.9 |
| *S. aureus* | 9271 | Example 1 4.0 | Vancomycin 5.9 |
| *S. aureus* | 6625 | Example 1 4.0 | Ciprofloxacin 6.6 |
| *S. pyogenes* | 152 | Example 1 2.3 | Clindamycin 2.6 |

In Table 1 the compounds of each of the Examples shown are as follows:

Example 1: 4-(4-(5-((Acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23);

Example 3: 4-(4-(5-((Acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester;

Example 5: N-((3-(4-(3-Fluoro-4-(4-(2-Cyanoethyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

Example 6: 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, 2-hydroxyethyl ester;

Example 7: N-((3-(4-(3-Fluoro-4-((phenylcarbonyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

Example 10: (+/-)-N-[[3-[4-[4-(1,4-Dioxopentyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl)-acetamide;

Example 36: (*S*)-N-[[3-[3-fluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

Example 37: (*S*)-N-[[3-[3,5-difluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide.

The general method for the synthesis of 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23) and 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester (24) is described in Example 1 and 2, respectively, as well as being structurally represented in Schemes 1 and 2, below. (The compounds used are identified by chemical name followed by a numeral designation from the Schemes for simplicity.) Commercially available difluoronitrobenzene (2) is treated with excess piperazine to afford displacement product 3. After protection as the tert-butoxy carbonyl (BOC) derivative affording 4, reduction of the nitro group with the ammonium formate-Pd/C reagent system afforded aniline derivative 5. Protection of 5 afforded benzyloxy carbonyl (CBZ) derivative 6 which was allylated as shown to produce 7. Osmylation of 7 using the method of Kelly and VanRheenen, Tetrahedron Letters, 1973 (1976), gave diol 8 which cyclized upon treatment with potassium carbonate in refluxing acetonitrile to afford oxazolidinone 9. Mesylation of 9 under classical conditions afforded mesylate 10 which undergoes smooth displacement with sodium azide to form azide 11. Reduction of azide 11 by hydrogenation over Pd/C gave amine 12 which was acylated *in situ* with acetic anhydride and pyridine to afforded BOC-protected oxazolidinone intermediate 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (21).

Deprotection with trifluoroacetic acid afforded the key intermediate for analog preparation, N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22). Treatment of (22) with either methyl chloroformate or ethyl chloroformate under preferably Schotten-Baumann conditions ($NaHCO_3$/acetone-water) afforded 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23) and 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester (24), respectively.

Although the route explained above and described in Example 1 can be used to prepare all of the subject compounds, a less efficient route may be used to prepare intermediates leading to other of the subject compounds such as N-((2-oxo-3-(4-(4-((phenylcarbonyl)-1-piperazinyl)phenyl)-5-oxazolidinyl)methyl acetamide (20) and 4-(4-(5((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester (19). For instance, diol 13, prepared from piperazine and *p*-fluoronitrobenzene in a manner identical to that described for diol 8 in Scheme I, is treated with one equivalent of either mesyl chloride or tosyl chloride to afford the mono-derivatized material 14, along with unchanged starting material and bis-derivatized material. After chromatographic isolation of mesylate 14a or tosylate 14b, treatment of either material with sodium azide afforded the azido alcohol 15. Treatment of 15 with base

effected cyclization to afford the oxazolidinone 16, which in turn can be converted to acetamide derivative 17 by the one-pot reduction-acylation procedure described in Example 1. As shown, solvolytic deprotection of 17 afforded N-((2-oxo-3-(4-(1-piperazinyl)phenyl)-5-oxazolidinyl)methyl)-acetamide (18), which can then be acylated to form the two non-fluorinated analogs, 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester (19) and N-((2-oxo-3-(4-(4-(phenylcarbonyl)-1-piperazinyl)phenyl)-5-oxazolidinyl)methyl)-acetamide (20).

Preparation of analogs of 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23) and 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester (24) can be envisioned simply by substitution of other cyclic amines for piperazine, other nitrobenzene derivatives for 2, or by treatment of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22) (or its analogs) with other acylating or alkylating agents.

EXAMPLE 1: 4-(4-(5-((Acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23)

(a) Preparation of 1-(2-Fluoro-4-nitrophenyl)piperazine (3):

A solution of 12.0 g (75.42 mmol) of 3,4-difluoronitrobenzene (2) in 150 mL of acetonitrile was treated with 16.24 g (188.6 mmol) of piperazine, followed by warming at reflux for 3 hours. The solution was cooled to ambient temperature and was concentrated *in vacuo*. The residue was diluted with 200 mL of water and was extracted with ethyl acetate (3 X 250 mL). The combined organic layers were extracted with water (200 mL) and saturated NaCl solution (200 mL), followed by drying ($Na_2SO_4$). The solution was concentrated *in vacuo* to afford an orange oil which was chromatographed over 450 g of 230-400 mesh silica gel eluting initially with dichloromethane until the least polar fractions had eluted and then elution was continued with 2% (v/v) methanol-chloroform and then with 10% (v/v) methanol-chloroform. These procedures afforded 13.83 g (81%) of the desired piperazine derivative 3, mp= 68.5-71°C.

(b) Preparation of 1-(*tert*-Butoxycarbonyl)-4-(2-fluoro-4-nitrophenyl)piperazine (4):

A solution of 12.0 g (53.29 mmol) of nitro derivative 3 in 110 mL tetrahydrofuran was treated dropwise with a solution of 14.53 g (66.61 mmol) of di-*tert*-butyldicarbonate in 110 mL of tetrahydrofuran. After addition, the solution was stirred at ambient temperature for 24 hours. The solution was concentrated *in vacuo* and the residue was chromatographed over 450 g of 230-400 mesh silica gel eluting with 20% (v/v) ethyl acetate in hexane, 30% (v/v) ethyl acetate in hexane and finally with 50% (v/v) ethyl acetate in hexane. These procedures afforded 16.6 g (96%) of BOC derivative 4 as a yellow solid, mp= 151-153.5°C.

(c) Preparation of 1-(*tert*-Butoxycarbonyl)-4-(2-fluoro-4-aminophenyl)piperazine (5):

A solution of 1.73 g (5.32 mmol) of nitro compound 4 in 30 mL methanol and 20 mL tetrahydrofuran and 10 mL ethyl acetate was treated with 1.68 g (26.59 mmol) of ammonium formate and 200 mg of 10% palladium on carbon. Gas evolution became immediately apparent, and subsided after *ca.* 30 minutes. The mixture was stirred overnight and was then filtered through celite, washing the filter cake with methanol. The filtrate was concentrated *in vacuo*, dissolved in 50 mL ethyl acetate and extracted with water (2 x 30 mL) and saturated NaCl solution (30 mL). Drying ($Na_2SO_4$) and concentration *in vacuo* afforded 1.6 g (*ca.* 100%) of amine 5 as a brown solid, sufficiently pure for use in the next step.

(d) Preparation of 1-(*tert*-Butoxycarbonyl)-4-(2-fluoro-4-benzyloxycarbonylamino)piperazine (6):

A solution of 1.57 g (5.32 mmol) of amine 5 and 806 mg (0.84 mL, 6.65 mmol) of dimethylaniline in 25 mL of tetrahydrofuran at -20°C was treated dropwise with 1.0 g (0.84 mL, 5.85 mmol) of benzyl chloroformate. The solution was stirred at -20°C for 30 minutes, followed by warming to ambient temperature. The mixture was diluted with 125 mL ethyl acetate and was extracted with water (2 x 50 mL) and saturated NaCl solution (50 mL). Drying ($Na_2SO_4$) and concentration *in vacuo* afforded and inhomogeneous material which was adsorbed on silica gel and chromatographed over 115 g of 230-400 mesh silica gel, eluting with 18% (v/v) ethyl acetate in hexane and then with 25% (v/v) ethyl acetate in hexane, and finally with 30% (v/v) ethyl acetate in hexane. These procedures afforded 1.15 g (50%) of the CBZ derivative 6 as a white solid, mp= 150-153°C.

(e) Preparation of 1-(*tert*-Butoxycarbonyl)-4-(2-fluoro-4-benzyloxycarbonylallylamino) piperazine (7):

A solution of 1.15 g (2.68 mmol) of the CBZ derivative 6 in 10.2 mL dimethylformamide was treated portionwise with 77 mg (129 mg of 60% in oil, 3.21 mmol) of sodium hydride followed by stirring at ambient temperature for 20 minutes. The solution was treated with 356 mg (0.26 mL, 2.95 mmol) of allyl bromide followed by stirring at ambient temperature for 18 hours. The solution was cautiously treated with 75 mL water and was extracted with diethyl ether (3 x 100 mL). The combined organic layers were extracted with saturated sodium chloride solution (100 mL) and dried ($Na_2SO_4$). Concentration *in vacuo* afforded an inhomogeneous material which was dissolved in dichloromethane and dried ($Na_2SO_4$). Concentration *in vacuo* afforded an amber oil which was chromatographed over 60 g 230-400 mesh silica gel eluting with 25% (v/v) ethyl acetate in hexane. These procedures afforded 1.12 g (90%) of the allyl derivative 7 as an oil.

(f) Preparation of 1-(*tert*-butoxycarbonyl)-4-[2-fluoro-4-benzyloxycarbonyl(2,3-dihydroxyprop-1-yl)aminophenyl]piperazine (8):

A solution of 2.18 g (4.64 mmol) of allyl compound 7 and 3.26 g (27.86 mmol) of N-methylmorpholine N-oxide in 21 mL acetone and 6.4 mL water was treated with 5 mL of a 2.5% (w/v) solution of osmium tetroxide in *tert*-butyl alcohol. The resulting solution was stirred at ambient temperature for 24 hours. The solution was cooled to 0°C and 25 mL of saturated $NaHSO_3$ solution was added, followed by stirring at 0°C for 15 minutes and then warming to ambient temperature for 2 hours. The mixture was diluted with 50 mL water and 50 mL saturated NaCl solution, followed by extraction with ethyl acetate (5 x 100 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a brown oil. This material was chromatographed over 150 g of 230-400 mesh silica gel, eluting with 10% (v/v) methanol in chloroform. These procedures afforded 2.0 g (86%) of the diol 8 as an off-white hygroscopic rigid foam.

(g) Preparation of 3-[3-fluoro-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone (9):

A solution of 2.0 g (4.01 mmol) of diol 8 in 20 mL acetonitrile was treated with 1.1 g (8.02 mmol) of potassium carbonate followed by warming at reflux for 3 hours. The solution was cooled and concentrated *in vacuo*. The residue was dissolved in 100 mL ethyl acetate and the resulting solution was extracted with water (2 x 50 mL) and with saturated NaCl solution (50 mL). Drying ($Na_2SO_4$) and concentration *in vacuo* afforded an oil which was chromatographed over 80 g of 230-400 mesh silica gel eluting with 20% (v/v) acetone in dichloromethane. These procedures afforded 1.6 g (100%) of oxazolidinone 9 as a white solid, mp= 144-146.5°C.

(h) Preparation of 3-[3-Fluoro-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl]-5-methanesulfonyloxymethyl-2-oxazolidinone (10):

A solution of 375 mg (0.95 mmol) of oxazolidinone 9 and 144 mg (0.20 mL, 1.42 mmol) triethylamine in 3.8 mL dichloromethane at 0°C was treated dropwise with 130 mg (0.09 mL, 1.14 mmol) of methanesulfonyl chloride followed by stirring at 0°C for 1 hour. The solution was diluted with 30 mL dichloromethane and was extracted with water (2 x 25 mL) and with saturated $NaHCO_3$ (25 mL). Drying ($Na_2SO_4$) and concentration *in vacuo* afforded 440 mg (98%) of mesylate 10 as a white solid, sufficiently pure for use in the next step.

(i) Preparation of 3-[3-Fluoro-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl]-5-azidomethyl-2-oxazolidinone (11):

A solution of 440 mg (0.93 mmol) of mesylate 10 in 22 mL acetone was treated with a solution of 604 mg (9.29 mmol) of sodium azide in 6.4 mL water. The mixture was warmed at reflux for 18 hours. The mixture was cooled and a solution of 600 mg of sodium azide in 6 mL water was added followed by warming at reflux for an additional 18 hours. The mixture was cooled and a solution of 1.2 g of sodium azide in 12 mL water was added followed by warming at reflux for 24 hours. The mixture was cooled and diluted with 60 mL water and extracted with ethyl acetate (3 x 75). The combined organic layers were extracted with 100 mL saturated NaCl solution followed by drying ($Na_2SO_4$). Concentration *in vacuo* afforded 358 mg (92%) of azide 11 as a white solid, mp= 130.5°C-132.5°C, sufficiently pure for use in the next step.

(j) Preparation of 3-(3-Fluoro-4-(4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl)-5-aminomethyl-2-oxazolidinone (12) and 3-[3-fluoro-4-*tert*-butoxycarbonylpiperazin-1-yl)phenyl]-5-acetylaminomethyl-2-oxazolidinone (21):

A solution of 1.42 g (3.38 mmol) of the azide 11 in 200 mL ethyl acetate was treated with 400 mg of 10% Palladium on carbon followed by hydrogenation at atmospheric pressure for 48 hours. The resulting ethyl acetate solution of 12 was treated with 1.34 g (1.37 mL, 16.9 mmol) of pyridine and 870 mg (0.80 mL, 8.5 mmol) of acetic anhydride followed by stirring at ambient temperature for 48 hours. The solution was treated with 1.37 mL pyridine and 0.8 mL acetic anhydride followed by stirring at ambient temperature for another 48 hours. The solution was filtered through celite, washing the filter cake with ethyl acetate. The filtrate was washed with water (4 x 50mL), 1.0 *M* $CuSO_4$ solution (50 mL), and again with water (50 mL). Drying ($Na_2SO_4$) and concentration *in vacuo* afforded a foam which was diluted with dichloromethane and stirred for 1 hour with saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane and the combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford an amber oil which was chromatographed over 74 g of 230-400 mesh silica gel, eluting with 2% (v/v) methanol in dichloromethane and then with 5% (v/v) methanol in dichloromethane. These procedures afforded 1.19 g (81%) of 3-(3-fluoro-4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-5-acetylaminomethyl-2-oxazolidinone (21) as a rigid off-white foam, mp= 162-164°C.

(k) Preparation of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22):

A solution of 1.19 g (2.73 mmol) of BOC derivative 3-(3-fluoro-4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-5-acetylaminomethyl-2-oxazolidinone (21) in 40 mL dichloromethane at 0°C was treated with 15 mL trifluoroacetic acid. The solution was stirred at 0°C for 30 minutes followed by warming to ambient temperature, at which point the reaction

was complete. The solution was concentrated *in vacuo* and the residue was diluted with ethyl acetate and saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate, and it became evident that a large part of the product remained in the aqueous layer. The aqueous layer was adjusted to pH 14 by addition of 50% NaOH solution. Extraction with ethyl acetate followed by drying ($Na_2SO_4$) and concentration *in vacuo* afforded 179 mg of an amber oil. This material was subjected to radial chromatography on a 2 mm plate eluting with 10% (v/v) methanol in chloroform and then with 15% (v/v) methanol in chloroform. These procedures afforded 125 mg (79%) of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22) as an off-white rigid foam.

(l) Preparation of 4-(4-(5-((Acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23):

A solution of 120 mg (0.36 mmol) of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide and 60 mg (0.71 mmol) of solid $NaHCO_3$ in 1.5 mL acetone and 0.7 mL water at 0°C was treated with 37 mg (30 µL, 0.39 mmol) of methyl chloroformate. The solution was stirred at 0°C for 1 hour, followed by dilution with 20 mL water. The mixture was extracted with 30 mL ethyl acetate and the organic layer was then extracted with water (2 x 10 mL) and saturated $NaHCO_3$ (10 mL). The solution was then dried ($Na_2SO_4$) and concentrated *in vacuo* to afford 95 mg of crude product. This material was subjected to radial chromatography using a 2 mm plate eluting with 33% (v/v) acetone in dichloromethane and then with 50% (v/v) acetone in dichloromethane. These procedures afforded 81 mg (57%) of 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester (23) as a white solid, mp= 177-179°C.

EXAMPLE 2: 4-(4-(5-((Acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester (24)

The same procedure as followed in Example 1, steps a-k, were followed. Then a solution of 100 mg (0.30 mmol) of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (23) (the product from step k above) and 50 mg (0.59 mmol) of solid $NaHCO_3$ in 2 mL acetone and 1 mL water at 0°C was treated with 35 mg (31 µL, 0.33 mmol) of ethyl chloroformate. The solution was stirred at 0°C for 2 hours, followed by warming to ambient temperature for 18 hours. The solution was diluted with 30 mL water and was extracted with 40 mL ethyl acetate. The organic layer was washed with 30 mL water and 30 mL saturated $NaHCO_3$ solution. Drying ($Na_2SO_4$) and concentration *in vacuo* afforded a white solid. This material was subjected to radial chromatography on a 2 mm plate, eluting with 2% (v/v) methanol in chloroform. These procedures afforded 70 mg (58%) of 4-(4-(5-

((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester (24) as a white solid, mp= 224-226°C.

EXAMPLE 3: 4-(4-(5-((Acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester

Following the procedure of Example 1 the subject compound was prepared by substituting 4-fluoronitrobenzene for the starting material 3,4-difluoronitrobenzene (2).

EXAMPLE 4: N-((2-Oxo-3-(4-(4-(phenylcarbonyl)-1-piperazinyl)phenyl)-5-oxazolidinyl)methyl)-acetamide

Following the procedure of Example 2 the subject compound was prepared by substituting 4-fluoronitrobenzene for the starting material 3,4-difluoronitrobenzene (2).

EXAMPLE 5: N-((3-(4-(3-Fluoro-4-(4-(2-Cyanoethyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide

A solution of 75 mg (0.22 mmol) of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22) (Ex. 1, Part k.) in 5mL methanol was treated with 13 mg (17 µL, 0.25 mmol) of acrylonitrile followed by warming at reflux for 3 hours. The solution was cooled and concentrated *in vacuo*. The residue was subjected to radial chromatography on a 4mm plate eluting with 5% (v/v) methanol in chloroform. These procedures afforded 84 mg (97%) of the desired nitrile, N-((3-(4-(3-Fluoro-4-(4-(2-Cyanoethyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide, as a white solid, mp= 125-130°C.

EXAMPLE 6: 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, 2-hydroxyethyl ester

A solution of 208 mg (0.25 mmol) of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22) (Ex. 1, Part k.) in 3 mL acetone and 2 mL water was treated with 21 mg (0.25 mmol) of sodium bicarbonate followed by cooling to 0°C. The mixture was treated with a solution of 54 mg (0.25 mmol) of 2-benzyloxyethyl chloroformate in 2 mL of acetone. The solution was allowed to warm to ambient temperature over 22 hours, followed by dilution with 30 mL ethyl acetate and extraction with water (3 x 30 mL) and saturated sodium bicarbonate solution (20 mL). The solution was dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a white solid. This material was subjected to radial chromatography on a 4 mm plate eluting with 20% (v/v) acetone in dichloromethane. These procedures afforded 113 mg (*ca.* 100%) of the chloroformate, 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, 2-hydroxyethyl ester, as a

white solid, mp= 121-123°C. A solution of this material in 5 ml methanol was treated with 35 mg 10% palladium on carbon followed by hydrogenolysis at 1 atmosphere for 1 hour. The mixture was filtered through celite, washing the filter cake with methanol. The filtrate was concentrated *in vacuo* to afford a white solid. This material was subjected to radial chromatography on a 2 mm plate, eluting with 5% (v/v) methanol in chloroform, and then with 10% (v/v) methanol in chloroform. These procedures afforded 76 mg (82%) of the hydroxyethyl chloroformate 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl) -1-piperazinecarboxylic acid, 2-hydroxyethyl ester as a white solid, mp= 203-206°C.

EXAMPLE 7: N-((3-(4-(3-Fluoro-4-((phenylcarbonyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide

Following the procedure of Example 1, the subject compound, was prepared from 100 mg (0.297 mmol) of N-((3-(4-(3-fluoro-4-(1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide (22) (Ex. 1, Part k.) substituting benzoyl chloride for the starting material methyl chloroformate. These procedures afforded 73 mg (56%) of N-((3-(4-(3-Fluoro-4-((phenylcarbonyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide as a fine white powder, mp= 184-187°C.

EXAMPLE 8: 4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 2-methoxyethyl ester

A solution of 75 mg (0.22 mmol) of piperazine derivative **22** in 4 mL acetone and 2 mL water was treated with 21 mg (0.25 mmol) sodium bicarbonate followed by cooling to 0°C and addition of a solution of 35 mg (0.25 mmol) of 2-methoxyethyl chloroformate in 0.5 mL tetrahydrofuran. The mixture was warmed to ambient temperature for 22 hours. The mixture was diluted with 30 mL ethyl acetate and was extracted with water (3 x 20 mL) and saturated sodium bicarbonate solution (20 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a white solid. This material was subjected to radial chromatography on a 4 mm plate eluting initially with 20% (v/v) acetone in dichloromethane and then with 30% (v/v) acetone in dichloromethane. These procedures afforded 92 mg (96%) of the desired compound as a white solid.

EXAMPLE 9: 4-[4-[5(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazineacetonitrile

A solution of 75 mg (0.22 mmol) of piperazine derivative **22** in 4 mL acetone and 2 mL water was treated with 21 mg (0.25 mmol) sodium bicarbonate, followed by cooling to 0°C.

The mixture was treated with 226 mg (190 µL, 3.0 mmol) of freshly distilled chloroacetonitrile followed by warming to ambient temperature for 60 hours. The solution was diluted with 35 mL ethyl acetate and extracted with water (3 x 20 mL) and saturated sodium bicarbonate solution (20 mL). The combined aqueous layers were extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a white solid. This material was subjected to radial chromatography on a 4 mm plate eluting with 5% (v/v) methanol in chloroform. These procedures afforded 80 mg (96%) of the desired nitrile as a shiny white solid.

EXAMPLE 10: (+/-)-N-[[3-[4-[4-(1,4-Dioxopentyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl) Acetamide (Y= $MeCO(CH_2)_2CO$-, monoF, racemic)

The compound of Ex. 1(k), above, (0.104 g) was treated with 0.041 g of levulinic acid, 0.083 g of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, and 0.005 g of N,N-dimethylaminopyridine in 2 mL of pyridine, and the mixture stirred for 2 days at 20°C. Following aqueous extractive workup using methylene chloride, 0.139 g of residue was obtained. This was purified using medium pressure liquid chromatography on silica gel, 5% methanol in ethyl acetate (v/v), to give 0.118 g of a white solid, mp 148-150°C.

EXAMPLE 11: N-[[3-[4-[4-(1,4-Dioxopentyl)-1-piperazinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl) Acetamide, (S)- (Y= same as above, diF, optically active)

Using the same general procedure as in the above procedure to make Example 10, but starting with the trifluoroacetate salt of piperazine U-99472, prepared as directly below, 0.291 g of the salt gave after medium pressure liquid chromatography followed by preparative TLC (1000 µm, 20% acetone/methylene chloride, v/v) to give 0.103 g of a foamy white solid, mp 52-56 °C.

EXAMPLE 12: (+/-)-N-[[3-[4-[4-[(1-Oxo-6-oxa-7-phenyl)heptyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl) Acetamide (Y=$PhCH_2O(CH_2)_4CO$-).

Following the general procedure of above for Example 10, but substituting 5-benzyloxyvaleric acid (0.074 g) for the levulinic acid, 0.101 g of the compound of Ex. 1k, above, gave after medium pressure liquid chromatography (10% methanol in ethyl acetate) 0.130 g of the title compound, tlc $R_f$ = 0.24 (10% methanol in ethyl acetate, v/v).

EXAMPLE 13: (+/-)-N-[[3-[4-[4-(1-Oxo-5-hydroxypentyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl) Acetamide (Y=$HO(CH_2)_4CO$-).

The compound of Example 12, (66 mg) was dissolved in 5 mL of methanol, and the flask evacuated and filled with nitrogen 3 times. To the mixture was added 0.034 g of palladium black, and the flask evacuated and filled with hydrogen from a balloon 3 times. The mixture was stirred under hydrogen for 3 hr, then filtered through diatomaceous earth and washed with methanol, and the filtrate was evaporated. This residue was triturated with chloroform and and a white solid precipitated, this was collected to give the titled compound, tlc $R_f$ = 0.07 (10% methanol in ethyl acetate, v/v), 171-172 C m.p.

EXAMPLE 14: N-[[3-[3,5-Difluoro-4-[4-[5-R,S-methyl-[(1,3-dioxa-2-oxo)cyclopentyl]]]-1-piperazinyl]phenyl)-2-oxo-5-oxazolidinyl]methyl] Acetamide , -(5S) (Y = cyclic carbonate, optically active at oxazolidinone, but has racemate at cyclic carbonate, diF)

A BOC-piperazine, diF, optically active compound (0.094 g) was treated with 1.0 mL of trifluoroacetic acid in 1.5 mL of methylene chloride at 0°C for 50 min, then allowed to warm to 20°C, and the volatiles removed in vacuo to give a red oil (trifluoroacetate of U-99472). To this was added 0.036 g of chloromethylethylene carbonate and 0.069 g of potassium carbonate in acetonitrile, and the mixture heatd at reflux for one day. The mixture was filtered and evaporated in vacuo to give a yellow oil. The residue was purified by medium pressure liquid chromatography on silica gel (gradient elution with 5%-10% methanol in methylene chloride (v/v), followed by prepative TLC (7% methanol in methylene chloride) to give 0.022 g of a white solid, mp 106-111°C.

EXAMPLE 15: N-[[3-[3,5-Difluoro-4-[4-(1-oxo-2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] Acetamide, (S)- (Y = $MeOCH_2CO$-optically active, diF)

To a solution of the trifluoroacetate salt of piperazine (0.192 g) in 3 mL of methylene chloride and 1.0 mL of triethylamine under nitrogen at 0°C was added 0.071 g of methoxyacetyl chloride. The mixture was stirred at 0°C , then worked up by aqueous extraction using methylene chloride. The organic layer was dried ($MgSO^4$) and concentrated to 5-10 mL, and cooled, the solids were collected and recrystallized from ethyl acetate to give 44 mg of a white solid, mp 239-241°C.

EXAMPLE 16: (+/-)-N-[[3-[4-[4-(N-carbobenzyloxy)-2-amino-1-oxo-ethyl)-1-piperazinyl]]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl] Acetamide (Y= $PhCH_2O_2CNHCH_2CO$- racemic,

monoF)

To the compound of Ex. 1k (0.115 g) was added 0.085 g of N-carbobenzyloxyglycine in 4 mL of tetrahydrofuran and 2 mL of water, then the pH was adjusted to about 4 with the addition of 3N hydrochloric acid, the 0.203 g of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide was added. The mixture was stirred at 20°c for 1 hr, then additional 0.101 g of N-carbobenzyloxyglycine and 0.225 g of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide were added, and the pJ was adjusted from 3 to between 4 and 5 with the addition of 2 N sodium hydroxide, and the mixture stirred overnight. After extractive aqueous workup with ethyl acetate, the organic layers were concentrated and the residue was purified by concentration from methylene chloride and methanol, then trituration with methanol to give 0.042 mg of a white solid, mp=189-191°C.

EXAMPLE 17: (S)-N-[[3-[4-[4-(cyanomethyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl-acetamide: (U-97665)

The following steps demostrate the preparation of a mono-F substituted product of the invention.

(a) (S)-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (2):

A solution of 7.5g(17.5mmol) of the CBz derivative 1 in 240ml of tetrahydrofuran at -78°C was treated with 12.0mL (1.6M, 19.25mmol) of n-butyllithium in hexane dropwise over *ca.* 3 min. The solution was stirred at -78°C for 30min, followed by addition of 2.78g(2.73mL, 19.25mmol) of neat R-(-)-glycidyl butyrate dropwise over *ca.* 5 min followed by warming of the solution to 0°C and then eventually to ambient temperature for 18h. The mixture was diluted with dichloromethane and extracted with water and saturated aqueous sodium chloride solution. The organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a gummy residue. This material was recrystallized from hot ethyl acetate with some hexane added, to afford 6.4g(93%) of the desired product, mp 130.5-133°C.

(b) (S)-4-[4-[5-(methanesulfonyloxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (3):

A solution of 2.88g(7.28mmol) of the alcohol 2 in 32mL dichloromethane at 0°C was treated with 1.29g(1.77mL, 12.7mmol) of triethylamine followed by addition of 1.04g(0.70mL, 9.10mmol) of methanesulfonylchloride. The solution was stirred at 0°C for 15min, followed by dilution with dichloromethane and extraction with water. The solution was dried ($Na_2SO_4$) and concentrated *in vacuo* to afford 3.4g(98%) of the mesylate 3 as a light pink solid (high resolution mass spectrum: calcd for $C^{20}H^{28}FN^3O^7S$: 473.1632. found: 473.1631), sufficiently

pure for use in the next step.

(c) (S)-4-[4-[5-(azidomethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (4):

A solution of the 16.8g(35.5mmol) of the mesylate 3 in 400mL of dimethylformamide was treated with 11.5g(177.5mmol) of sodium azide followed by warming at 60°C for 16h. The solution was diluted with ethyl acetate and extracted with water. The organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo* to afford 14.9g(100%) of the azide 4 as a light yellow solid, mp 101-104°C, sufficiently pure for further use.

(d) (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (5):

A solution of 14.92g(35.5mmol) of the azide 4 in 2000mL of ethyl acetate was treated with 2g of 10% palladium on carbon followed by hydrogenation at one atmosphere for 24h. The flask was flushed with nitrogen, followed by sequential addition of 14.0g(14.4ml, 177.5mmol) of pyridine and 9.1g(8.4mL, 88.8mmol) of acetic anhydride. The mixture was stirred at ambient temperature for 72h, followed by filtration through celite. The filtrate was extracted with water, 1N copper sulfate solution, dried and concentrated *in vacuo* to afford a tan solid. This material was purified by silica gel chromatography to afford 12.7g(82%) of the product 5 as a powdery white solid, mp 153-159°C.

(e) (S)-N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazoldinyl]methyl]-acetamide:

35mL of trifluoroacetic acid at 0°C was treated with 5.0g(11.46mmol) of the Boc-derivative followed by warming to ambient temperature over 1h. The solution was concentrated *in vacuo* to afford a residue which was dissolved in water and stirred with 125mL of AG1-X8 ($OH^-$ form) ion exchange resin for 2.5h. The resin was removed by filtration, washed with water, and the combined filtrates were freeze-dried to afford 2.7g(69%) of the desired title compound as a white fluffy solid, mp 73-76°C.

(f) (S)-N-[[3-[4-[4-(cyanomethyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl-acetamide:

A solution of 2.42g(7.2mmol) of the above compound (e) in 242mL acetone and 74mL water was cooled to 0°C and treated with 1.20g(14.4mmol) of sodium bicarbonate, followed by addition of 26.2g(22.0mL, 0.35mol) of chloroacetonitrile. The solution was then warmed to ambient temperature for 36h. The mixture was then diluted with ethyl acetate and extracted with water and saturated sodium chloride solution. Drying ($Na_2SO_4$) and concentration *in vacuo*

afforded and off-white solid which was purified by silica gel chromatography eluting with a methanol-chloroform solvent system. These procedures afforded 2.2g(82%) of the title compound as a fluffy white solid, mp 166-167°C.

EXAMPLE 18: (S)-N-[[3-[4-[4-(cyanomethyl)-1-piperazinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl-acetamide:

Following the procedure for preparation of Example 17, substituting difluoro piperazine derivative ((S)-N-[[3-[3,5-difluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-5oxazolidinyl]methyl-acetamide) for monofluoro derivative Ex. 17(e), the title compound was obtained as a white powder, mp 150-154°C.

EXAMPLE 19: (±)-N-[[3-[4-[4-(2-cyanoethyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide:

A solution of 75mg(0.22mmol) of a racemic of Ex. 17(e) in 5mL methanol was treated with 13mg(17µL, 0.25mmol) of acrylonitrile followed by warming at reflux for 3h. The solution was concentrated *in vacuo*. The residue was subjected to radial chromatography eluting with 5%(v/v) methanol in chloroform. These procedures afforded 84mg(97%) of the title compound as a white solid, mp 125-130°C.

EXAMPLE 20: (±)-N-[[3-[4-[4-(2-cyano-2-propyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl-acetamide:

A solution of 75mg(0.22mmol) of racemic Ex. 17(e) in 1mL dry acetonitrile was treated sequentially with 5mg(0.03mmol) anhydrous zinc chloride, 26mg(33µL, 0.45mmol) dry acetone, and 44mg(59µL, 0.45mmol) trimethylsilylcyanide. The solution was warmed at reflux for 18h, followed by dilution with ethyl acetate and extraction with water. Drying ($Na_2SO_4$) and concentration *in vacuo* afforded a tan solid which was subjected to radial chromatography eluting with 5%(v/v) methanol in dichloromethane. These procedures afforded 36mg(40%) of the title compound as a white solid, mp 139-143°C.

EXAMPLE 21: (S)-N-[[3-[4-[4-(4-cyanotetrahydropyran-4-yl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl-acetamide:

A solution of 50mg(0.15mmol) of Ex. 17(e) in 2mL dry acetonitrile was treated sequentially with 3mg(0.02mmol) anhydrous zinc chloride, 30mg(28µL, 0.30mmol) tetrahydropyran-4-one, and 29mg(40µL, 0.30mmol) trimethylsilylcyanide. The solution was warmed at reflux for 30h, followed by dilution with ethyl acetate and extraction with water. Drying ($Na_2SO_4$) and concentration *in vacuo* afforded a light yellow solid. This material was

subjected to radial chromatography eluting with a methanol-dichloromethane solvent system. These procedures afforded 24mg(36%) of the title compound as a white solid, mp 134-137°C.

EXAMPLE 22: (±)-N-[[3-[3-fluoro-4-(4-formyl-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-Acetamide:

A solution of 0.250g(0.267mmol) of racemice Ex. 17(e) in 4mL THF and 2mL water was treated with 11mg(9μL, 0.243mmol) of formic acid and adjusted to pH4.5 using 0.1N aqueous hydrochloric acid. The mixture was then added at once to 153mg(0.80mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in 1mL water with stirring at ambient temperature and the mixture adjusted to pH 4.5 using 2N sodium hydroxide and 0.1N hydrochloric acid. After stirring about 1 hour, additional carbodiimide(100mg,0.53mmol) and formic acid(30mg,0.80mmol) were added with stirring at ambient temperature for 16h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was subsequently extracted with saturated sodium bicarbonate and saturated sodium chloride solutions, dried($Na_2SO_4$) and concentrated *in vacuo* to afford a white solid. This material was subjected to silica gel chromatography eluting with a methanol-methylene chloride system to afford 0.094g(97%) of the title compound as a white solid, mp 190-193.5°C.

EXAMPLE 23: (S)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidine)]-2-fluorophenyl]-1-piperazinecarboxylic acid methyl ester:

A solution of Ex. 17(e) in 22mL acetone and 11mL water was treated with 150mg(1.80mmol) of sodium bicarbonate and cooled to 0°C followed by addition of 0.170g(0.14mL,1.80mmol) of methyl chloroformate. After 2h, the mixture was diluted with ethyl acetate and extracted with water and saturated sodium chloride solution. Drying ($Na_2SO_4$) and concentration *in vacuo* afforded a white solid which was purified by silica gel chromatography eluting with an acetone-methylene chloride system. These procedures afforded 0.494g(77%) of the title compound as a white solid, mp 179.5-182°C.

EXAMPLE 24: (S)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidine)]-2,6-difluorophenyl]-1-piperazinecarboxylic acid methyl ester:

Following the procedure for preparation of Ex. 23, substituting difluoropiperazine 7 for Ex. 17(e), the title compound was obtained as a white powder, mp 175-178°C.

EXAMPLE 25: (±)-N-[[3-[4-[3-fluoro-4-[(phenylcarbonyl)-1-piperazinyl]]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide:

Following the procedure for preparation of Ex. 23 (using racemic Ex. 17(e), and substituting benzoyl chloride for methyl chloroformate, the title compound was obtained as a white powder, mp 184-187°C.

EXAMPLE 26: (±)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidine)]-2-fluorophenyl]-1-piperazinecarboxylic acid, 2-methoxyethyl ester:

A solution of 75mg(0.22mmol) of monofluropiperazine derivative Ex. 25 in 4mL acetone and 2mL water was treated with 21mg(0.25mmol) of sodium bicarbonate followed by cooling to 0°C. The solution was the treated with a solution of 35mg(0.25mmol) of 2-methoxyethyl chloroformate in 0.5mL tetrahydrofuran. The solution was then warmed to ambient temperature for 22h. The solution was diluted with ethyl acetate and extracted with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a white solid. This material was subjected to radial chromatography eluting with an 30%(v/v) acetone-dichloromethane. These procedures afforded 92mg(96%) of the title compound as a white solid, mp 166-167°C.

EXAMPLE 27: (S)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidine)]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, 2-methoxyethyl ester:

Following the procedure for the preparation of Ex. 26, substituting difluoropiperazine 7 for Ex. 17(e), the title compound was obtained as a white solid, mp 154.5-156°C.

EXAMPLE 28: (±)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolinyl-2-fluorophenyl]-1-piperazinecarboxylic acid, 2-(phenylmethoxy)ethyl ester:

A solution of 208mg(0.25mmol) of Ex. 25 in 3mL acetone and 2mL water was treated with 21mg(0.25mmol) of sodium bicarbonate followed by cooling to 0°C. The mixture was treated with a solution of 54mg(0.25mmol) of 2-(phenylmethoxy)ethyl chloroformate in 2mL acetone. The solution was warmed to ambient temperature for 22h, followed by dilution with ethyl acetate and extraction with water and saturated sodium bicarbonate solution. Drying ($Na_2SO_4$) and concentration *in vacuo* afforded a white solid which was subjected to radial chromatography eluting with 20%(v/v) acetone in dichloromethane. These procedures afforded 113mg(100%) of the title compound as a white solid, mp 121-123°C.

EXAMPLE 29: (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolinyl-2,6-difluorophenyl]-1-piperazinecarboxylic acid, 2-(phenylmethoxy)ethyl ester:

Following the procedure for preparation of Ex. 28, substituting difluoropiperazine 7 for Ex. 17(e), the title compound was obtained as a white solid, mp 108-110°C.

EXAMPLE 30: (±)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolinyl-2,6-difluorophenyl]-1-piperazinecarboxylic acid, 2-hydroxyethyl ester:

A solution of 113mg of Ex. 28 in 5mL methanol was treated with 35mg 10% palladium on carbon followed by hyrogenation at atmospheric pressure for 1h. The mixture was filtered through celite, washing the filter cake with methanol. The filtrate was concentrated *in vacuo* to afford a white solid. This material was purified by radial chromatography eluting with a methanol-chloroform solvent system. These procedures afforded 76mg(82%) of the title compound as a white solid, mp 203-206°C.

EXAMPLE 31: [S-(R)]-N-[[3-[3,5-difluoro-4-[4-[(tetrahydro-2-furanyl)carbonyl]-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide:

A solution of 100mg(0.28mmol) of difluoropiperazine derivative ((S)-N-[[3-[3,5-difluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-5oxazolidinyl]methyl-acetamide)and 144mg(1.25mmol) of (R)-2-tetrahydorfuranoic acid in 4mL tetrahydrofuran and 2mL water was adjusted to pH 4.5 by addition of 2N NaOH solution. This solution was treated with a solution of 324mg(1.69mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in 2mL water. The solution was then maintained at pH 4.6 by addition of 2N NaOH solution while stirring at ambient temperature for 1.5h. The solution was diluted with water and extracted with ethyl acetate. The combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford a tan solid which was subjected to radial chromatography eluting with a methanol-dichloromethane solvent system. These procedures afforded 106mg(83%) of the title compound amide as a white solid, mp 198-200°C.

EXAMPLE 32: (*S*)-N-[[3-[3,5-difluoro-4-[4-[2-(1-piperidinyl)ethyl]-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The following demonstrates the preparation steps for difluorointermediates of the invention.

(a) 2,6-difluoro-4-nitrobenzene(trifluoromethane)sulfonate.

2,6-Difluoro-4-nitrophenol (31.55 g, 180.19 mmol) was combined with $CH_2Cl_2$ (300 mL) and pyridine (29.15 mL, 360.38 mmol). The resultant slurry was cooled to 0 °C in an ice bath and then treated dropwise with triflic anhydride (31.8 mL, 189.2 mmol) over a period of 45 minutes. The reaction was allowed to stir at 0 °C for two hours and then it was stored in the refrigerator (5 °C) overnight. The reaction was determined to be complete by TLC (15%

EtOAc/hexane, UV short wave). The reaction mixture was concentrated under reduced pressure, and then treated with both $H_2O$ (50 mL) and EtOAc (50 mL). This mixture was transferred to a separatory funnel with more EtOAc (100 mL) and washed with 1N HCl until the washings were acidic (2 x 100 mL). The aqueous phases were back-extracted with EtOAc (2 x 200 mL). The combined EtOAc extracts were combined and then washed again with 1N HCl (400 mL) and once with brine (400 mL). The organic phase was dried over anhydrous $Na_2SO_4$, filtered and then concentrated to yield 54.092 g of a red-gold oil. Although the oil was pure by NMR, it was combined with crude products from two other runs and chromatographed over silica gel (550 g) packed with 5% EtOAc. Elution with 2 L each of 5% EtOAc and 10% EtOAc afforded a 95% overall yield of the title compound as a pale yellow oil with HRMS ($M^+$) calcd for $C_7H_2F_5NO_5S$ 306.9574, found 306.9590.

(b) 1-(*tert*-butoxycarbonyl)-4-(2,6-difluoro-4-nitrophenyl)piperazine.

A solution of 2,6-difluoro-4-nitrobenzene(trifluoromethane)sulfonate (55 g, 179 mmol) in dry DMF (275 mL) was treated with 1-(*tert*-butoxycarbonyl)piperazine (45.71 g, 250 mmol). The resultant clear yellow solution turned orange upon the addition of N,N-diisopropylethylamine (47 mL, 269 mmol). The reaction was heated to reflux for 15 hours under $N_2$. The reaction was determined to be complete by TLC (30% EtOAc/hexane, UV short wave). The reaction mixture was concentrated to dryness and combined with the crude product of another reaction for purification. The crude material was dissolved in hot $CH_2Cl_2$ (420 mL; some solids unrelated to the product did not dissolve) and then chromatographed on three separate columns (2 columns with 750 g silica gel, packed with $CH_2Cl_2$, loaded with 180 mL material, and eluted with 1 L each of 1-5% EtOAc/$CH_2Cl_2$; one column with 250 g silica gel, packed with $CH_2Cl_2$, loaded with 60 mL compound, and eluted with 2.5 and 5% EtOAc/$CH_2Cl_2$) to give an 87% yield of the title compound as an orange solid with HRMS ($M^+$) calcd for $C_{15}H_{19}F_2N_3O_4$ 343.1343, found 343.1358.

(c) 1-(*tert*-butoxycarbonyl)-4-[2,6-difluoro-4-(benzyloxycarbonyl) aminophenyl]piperazine.

The 1-(*tert*-butoxycarbonyl)-4-(2,6-difluoro-4-nitrophenyl)piperazine (44.7 g, 130 mmol) was dissolved in 20% THF/MeOH (600 mL) in a 2 L flask. Ammonium formate (41 g, 651 mmol) was added portionwise, followed by 10% Pd-C (1.12 g, 2.5 weight %), with cooling in an ice bath. When the addition was completed the ice bath was removed. The flask became slightly warm, and the yellow color disappeared. The reaction was found to be complete by TLC (30% EtOAc/hexane, UV short wave) in 1.5 hours. The reaction mixture was filtered through Celite (washing the filter cake with 500 mL MeOH). The filtrate was concentrated under reduced pressure to give a solid which was then treated with 1 L EtOAc and 500 mL

$H_2O$. The layers were separated and then the organic layer was washed again with $H_2O$ (500 mL) and once with brine (500 mL). The aqueous portions were back-extracted with more EtOAc (2 x 300 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated to yield a yellow solid (40.8 g) which was immediately dissolved in dry DMF (500 mL) and cooled to -20 °C (ice/MeOH bath) under $N_2$. The solution was treated with N,N-dimethylaniline (20.6 mL, 163 mmol), followed by the dropwise addition of of benzyl chloroformate (21.5 mL, 143 mmol). The ice bath was allowed to dissipate overnight. The reaction was determined to be complete by TLC (30% EtOAc/hexane, UV short wave). The mixture was concentrated down to a yellow oil, dissolved in 1 L of EtOAc, and washed with $H_2O$ (500 mL) and brine (500 mL). The aqueous portions were back-extracted with more EtOAc (2 x 300 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated to yield a yellow solid. The crude material was recrystallized from hot EtOAc/hexane to afford 39.11 g (67%) of the title compound as a pale yellow crystalline solid with mp 171-172 °C.

(d) [3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol.

The 1-(*tert*-butoxycarbonyl)-4-[2,6-difluoro-4-(benzyloxycarbonyl)aminophenyl]piperazine (14.05 g, 31 mmol) was dissolved in dry THF (150 mL) and then cooled to -78 °C (dry ice/acetone). The reaction was next treated with with *n*-BuLi (21.6 mL, 35 mmol) dropwise over a 25 minute period. The reaction was allowed to stir at -78 °C for 30 minutes and then (*R*)-(-)-glycidylbutyrate (4.89 mL, 35 mmol) was added dropwise over 7 minutes. The reaction was maintained at -78 °C for an additional 15 minutes and then the bath was removed, allowing the reaction to slowly warm up to room temperature overnight. The reaction was determined to be complete by TLC (5% MeOH/$CHCl_3$, UV short wave). The reaction mixture was diluted with 500 mL $CH_2Cl_2$ and then washed with both $H_2O$ (3 x 300 mL) and brine (300 mL). The aqueous portions were back-extracted with more $CH_2Cl_2$ (3 x 400 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated to give a creamy yellow solid. The crude solid was purified by recrystallization from hot EtOAc/hexane to give 11.063 g (85%) of the title compound as a white solid with mp 164-166 °C.

(e) [[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-*p*-toluenesulfonate.

The [3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol (24.2 g, 59 mmol) was dissolved in pyridine (110 mL) and then cooled to

0 °C (ice bath). Freshly recrystalized *p*-toluenesulfonyl chloride (13.4 g, 70 mmol) of was added and the reaction was allowed to stir at 0 °C for 2.5 hours under $N_2$. The flask was then stoppered and stored in the refrigerator (5 °C) overnight. The reaction mixture became a pale pink slurry. TLC revealed that some alcohol still remained. The reaction mixture was treated with additional *p*-toluenesulfonyl chloride (1.12 g, 5.85 mmol), catalytic 4-(dimethylamino)pyridine, and 20 mL of dry $CH_2Cl_2$ to facilitate stirring. After 4 hours at 0 °C, the reaction was found to be complete by TLC (5% MeOH/$CH_2Cl_3$, UV short wave). The mixture was added to 750 mL ice water and the precipitated product isolated via suction filtration, washing it with both water (1 L) and ether (500 mL). After drying *in vacuo*, 29.921 g (90%) of the title compound was obtained as white solid with mp 150.5-151.5 °C.

(f) [[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate.

The [3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol (3.831 g, 9.27 mmol) was dissolved in $CH_2Cl_2$ (40 mL), cooled to 0 °C, and treated with triethylamine (1.74 g, 2.4 mL, 17.22 mmol) under $N_2$. Methanesulfonyl chloride (1.48 g, 1 mL, 12.92 mmol) was slowly added over 1 min. TLC analysis (20% acetone/$CH_2Cl_2$) after 0.5 h revealed the reaction to be complete. The reaction mixture was diluted with $CH_2Cl_2$ (200 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to furnish the title compound as an off-white solid with HRMS ($M^+$) calcd for $C_{20}H_{27}F_2N_3O_7S$ 491.1538, found 491.1543.

(g) [[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]azide.

The [[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-*p*-toluenesulfonate (29.661 g, 52 mmol) was dissolved in dry DMF (125 mL) and then treated with solid $NaN_3$ (10.19 g, 156 mmol) at room temperature. The reaction was heated to 60 °C for three hours and then allowed to cool to room temperature overnight under $N_2$. The reaction was found to be complete by TLC (30% EtOAc/hexane, run twice, UV short wave). The reaction mixture was concentrated *in vacuo* to give a cream colored solid. The crude product was dissolved in 600 mL EtOAc and then washed with both $H_2O$ (2 x 500 mL) and brine (500 mL). The aqueous portions were back-extracted with more EtOAc (2 x 400 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to yield 22.41 g (91%) of the title compound as a pale yellow solid with mp 115-117 °C.

Employing essentially identical conditions, the corresponding mesylate was converted to

the same azide.

(h) N-[[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The [[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]azide (22.4 g, 51 mmol) was dissolved in 1 L of EtOAc and then degassed three times with $N_2$. Next, 10% Pd-C (4.48 g, 20% by weight) was added and the solution was degassed again three times (with $N_2$) before replacing the atmosphere with $H_2$ (balloon). After 3 hours, the reaction was determined to be complete by TLC (20% MeOH/$CHCl_3$, UV short wave). At this point, pyridine (8.26 mL, 102 mmol) was added, followed by treatment with acetic anhydride (9.64 mL, 102 mmol). The reaction mixture was allowed to stir overnight at room temperature. The reaction was found to be complete by TLC (20% MeOH/$CHCl_3$, UV short wave). The reaction mixture was filtered through celite (the filter cake was washed with 500 mL EtOAc), the filtrate concentrated down to approximately 600 mL, and washed with $H_2O$ (2 x 500 mL) and brine (500 mL). The aqueous portions were back-extracted with more EtOAc (2 x 500 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated to give a yellow solid. Recrystallization of the crude product from hot $CHCl_3$ and hexane afforded 19.167 g (83%) of the title compound as a white solid with mp 177-179 °C.

(i) N-[[3-[3,5-difluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The N-[[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (1.00 g, 2.20 mmol) was dissolved in $CH_2Cl_2$ (6 mL) and cooled to 0 °C with an ice bath. Trifluoroacetic acid (20 mL) was added, the cooling bath removed, and the reaction mixture allowed to warm to ambient temperature over 1 h. The reaction mixture was then concentrated *in vacuo* and the residue dissolved in $H_2O$ (15 mL). The resultant solution was added to Bio Rad AG-1-X8 ion exchange resin (12 mL; $OH^-$ form, washed with $H_2O$ until neutral), additional $H_2O$ (5 mL) was added, and the mixture stirred for 10 min. The mixture was then filtered and the resin washed with additional $H_2O$ (3 x 5 mL). The aqueous filtrate was lyophilized to give 0.559 g (72%) of the title compound as a white solid with mp 108-112 °C (dec).

(j) (*S*)-N-[[3-[3,5-difluoro-4-[4-[2-(1-piperidinyl)ethyl]-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A mixture of (*S*)-N-[[3-[3,5-difluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.200 g, 0.565 mmol), 1-(2-chloroethyl)piperidine monohydrochloride (0.125 g, 0.678 mmol) and potassium carbonate (0.478 g, 3.39 mmol) in

acetonitrile (10 mL) was heated to reflux for 1.5 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was triturated with dichloromethane, the solids filtered off, and the filtrate concentrated *in vacuo* to furnish an off-white solid (0.248 g). This crude material was chromatographed over silica gel (5 g), eluting with 5% and then 10% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.137 g (52%) of the title compound as an off-white solid with mp 198-200 °C.

EXAMPLE 33: (*S*)-N-[[3-[3-fluoro-4-[4-[2-(1-piperidinyl)ethyl]-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A mixture of (*S*)-N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.200 g, 0.595 mmol), 1-(2-chloroethyl)piperidine monohydrochloride (0.131 g, 0.714 mmol) and potassium carbonate (0.493 g, 3.57 mmol) in acetonitrile (12 mL) was heated to reflux for 1.0 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was triturated with dichloromethane, the solids filtered off, and the filtrate concentrated *in vacuo* to give the crude product (0.308 g). This crude material was chromatographed over silica gel (5 g), eluting with 5% and then 10% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.192 g (72%) of the title compound as an off-white solid with mp 169-170 °C.

EXAMPLE 34: (*S*)-N-[[3-[3-fluoro-4-[4-[2-(4-morpholinyl)ethyl]-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A mixture of (*S*)-N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.200 g, 0.595 mmol), 4-(2-chloroethyl)morpholine hydrochloride (0.133 g, 0.714 mmol) and potassium carbonate (0.493 g, 3.57 mmol) in acetonitrile (12 mL) was heated to reflux for 1.0 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was triturated with dichloromethane, the solids filtered off, and the filtrate concentrated *in vacuo* to give an amber gum (0.201 g). This crude material was chromatographed over silica gel (5 g), eluting with 5% and then 10% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.129 g (48%) of the title compound as an off-white solid with mp 150-151.5 °C.

EXAMPLE 35: (*S*)-N-[[3-[4-[4-[2-(diethylamino)ethyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A mixture of (*S*)-N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.200 g, 0.595 mmol), 2-diethylaminoethyl chloride

hydrochloride (0.123 g, 0.714 mmol) and potassium carbonate (0.493 g, 3.57 mmol) in acetonitrile (12 mL) was heated to reflux for 1.0 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was triturated with dichloromethane, the solids filtered off, and the filtrate concentrated *in vacuo* to give an off-white gummy solid (0.241 g). This crude material was chromatographed over silica gel (5 g), eluting with 5% and then 10% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.159 g (61%) of the title compound as an off-white solid with mp 131-133 °C.

EXAMPLE 36: (*S*)-N-[[3-[3-fluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A mixture of (*S*)-N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.450 g, 1.34 mmol), 2-chloroethyl methyl ether (1.220 mL, 13.40 mmol) and potassium carbonate 1.110 g, 8.04 mmol) in acetonitrile (25 mL) was heated to reflux for 24 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was triturated with dichloromethane, the solids filtered off, and the filtrate concentrated *in vacuo* to give a yellow foamy solid (0.326 g). This crude material was chromatographed over silica gel (25 g), eluting with 1%, 3%, and then 5% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.296 g (56%) of the title compound as an off-white solid with mp 144.5-146 °C.

EXAMPLE 37: (*S*)-N-[[3-[3,5-difluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A solution of (*S*)-N-[[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.200 g, 0.441 mmol) in dichloromethane (1 mL) was treated with trifluoroacetic acid (4 mL) at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the resultant residue combined with 2-chloroethyl methyl ether (403 µL, 4.41 mmol), potassium carbonate (0.730 g, 5.28 mmol), and acetonitrile (9 mL) and the mixture heated to reflux for 15 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was triturated with dichloromethane, the solids filtered off, and the filtrate concentrated *in vacuo* to give the crude product. This crude material was chromatographed over silica gel (10 g), eluting with 1%, 3%, and then 5% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.097 g (53%) of the title compound as an off-white solid with mp 162-164 °C.

EXAMPLE 38: (*S*)-N-[[3-[3-fluoro-4-[4-(3-hydroxypropyl)-1-piperazinyl]phenyl]-2-oxo-

5-oxazolidinyl]methyl]acetamide.

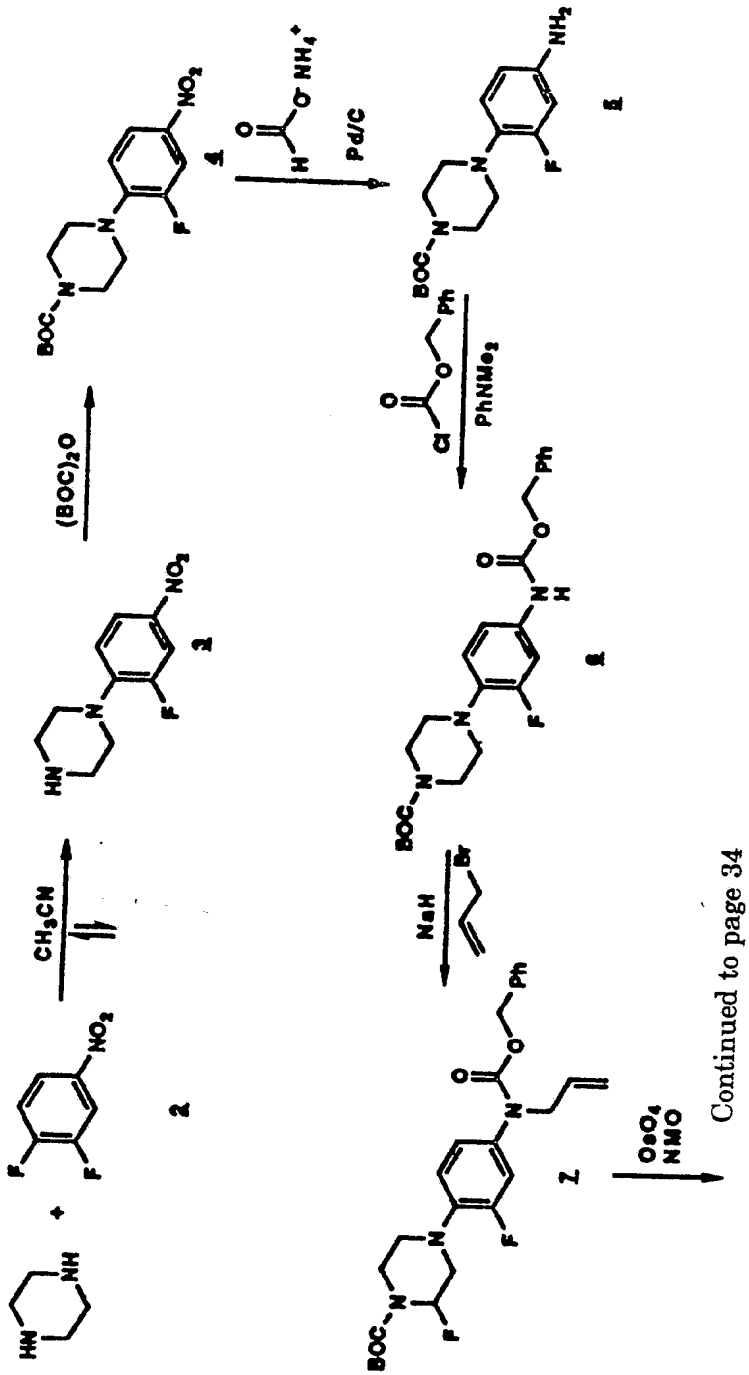
A mixture of (*S*)-N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.200 g, 0.595 mmol), 3-chloro-1-propanol (299 µL, 3.57 mmol) and potassium carbonate (0.493 g, 3.57 mmol) in acetonitrile (12 mL) was heated to reflux for 7 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude material was dissolved in 10% methanol/chloroform and absorbed onto silica gel (2 g). Chromatography of this material over silica gel (10 g), eluting with 1%, 3%, and then 6% methanol/chloroform, afforded, after concentration of appropriate fractions, 0.096 g (41%) of the title compound as a white solid with mp 154-155.5 °C.

EXAMPLE 39: (*S*)-N-[[3-[3,5-difluoro-4-[4-(2-hydroxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

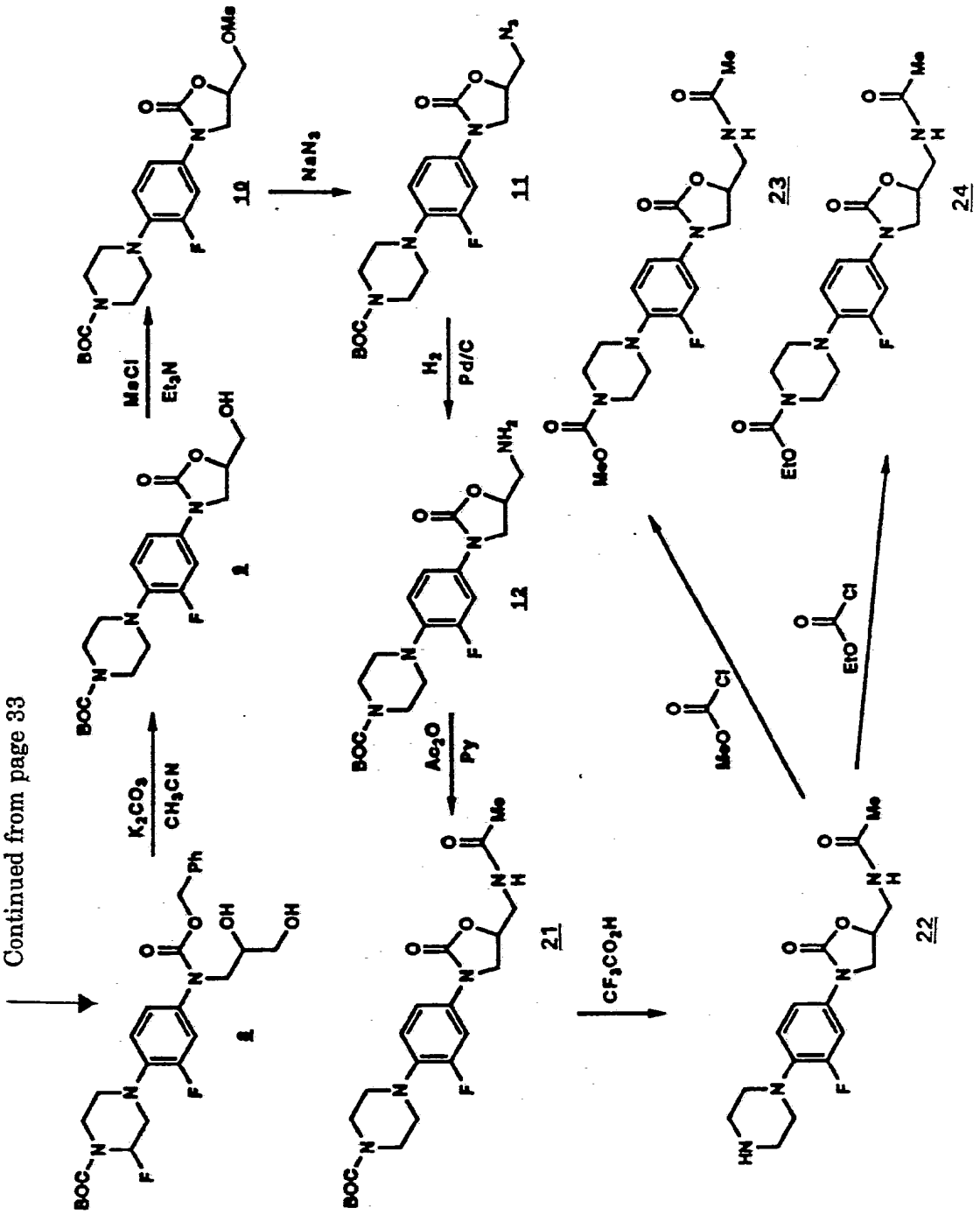
A solution of (*S*)-N-[[3-[3,5-difluoro-4-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.400 g, 0.881 mmol) in dichloromethane (3 mL) was treated with trifluoroacetic acid (7 mL) at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the resultant amber syrup combined with 2-chloroethanol (354 µL, 5.27 mmol), potassium carbonate (0.730 g, 5.27 mmol), and acetonitrile (20 mL) and the mixture heated to reflux for 24 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude product was chromatographed over silica gel (10 g), eluting with 1%, 3%, and then 6% methanol/chloroform, to afford, after concentration of appropriate fractions, 0.067 g (19%) of the title compound as an off-white solid with mp 172-174 °C.

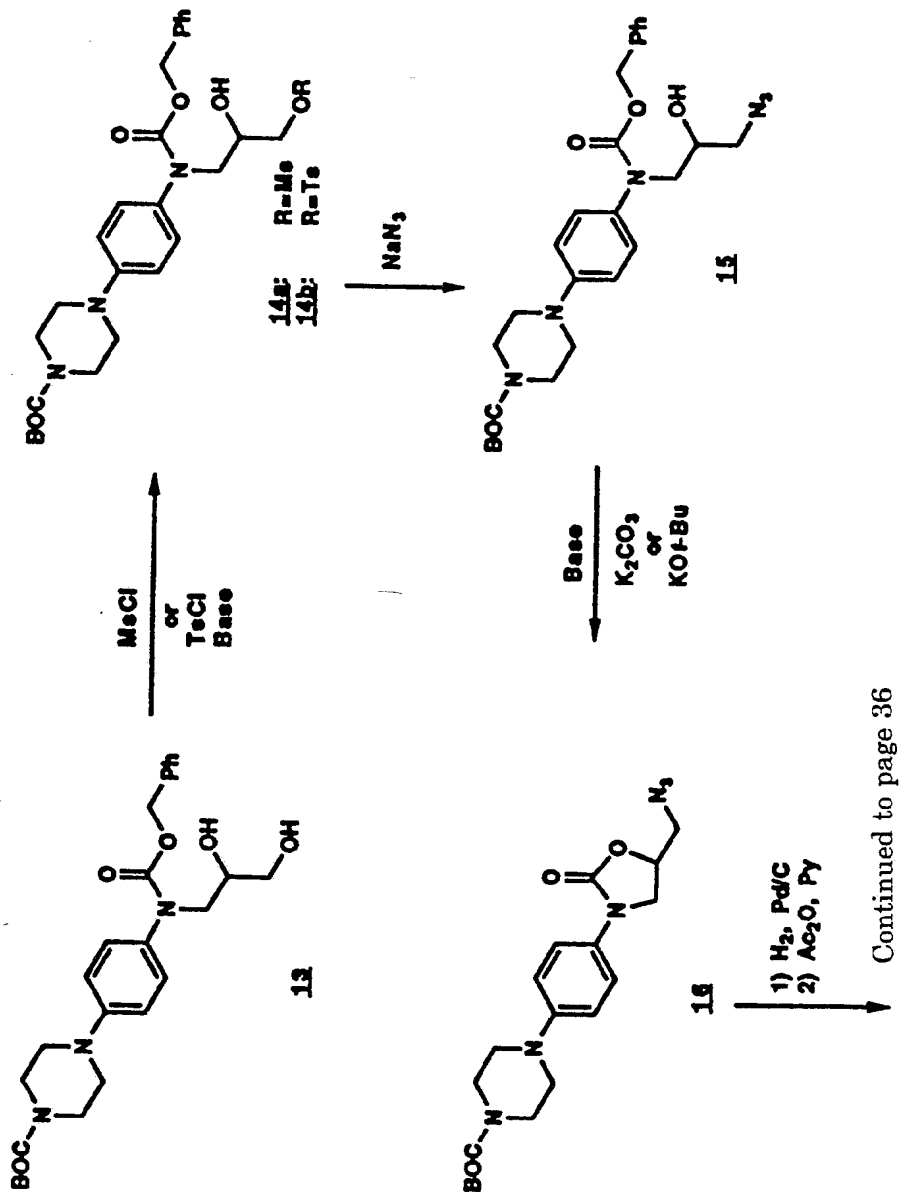
EXAMPLE 40: (*S*)-N-[[3-[3-fluoro-4-[4-[3-(4-morpholinyl)-1-oxopropyl]-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

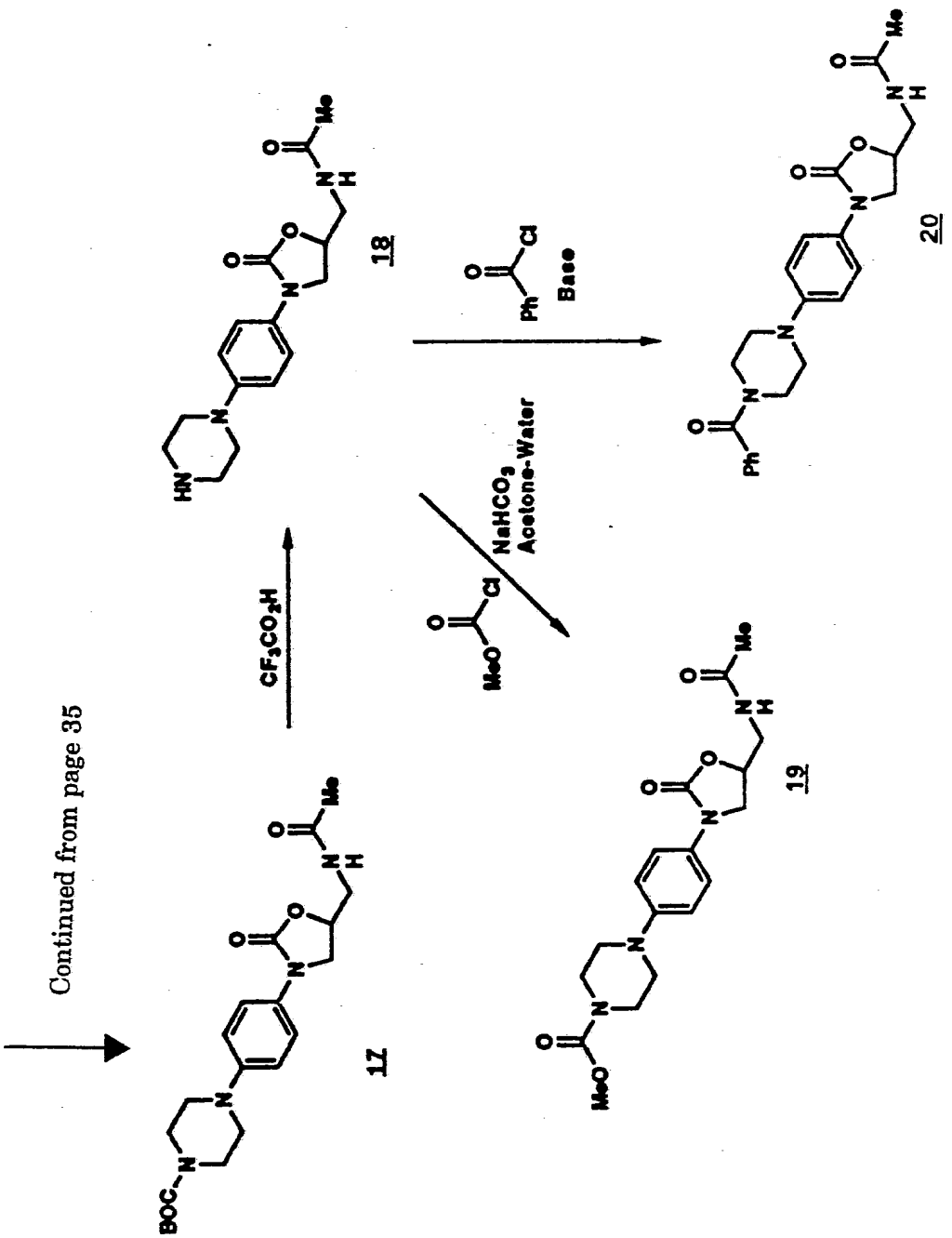
3-(4-Morpholinyl)propionic acid (0.600 g, 2.11 mmol), prepared by condensation of morpholine with ethyl acrylate (3 equivalents) in refluxing ethanol, followed by distillation, saponification (1N aqueous sodium hydroxide, tetrahydrofuran, reflux), neutralization (1N HCl) and lyophilization, was combined with 1,3-dicyclohexylcarbodiimide (0.434 g, 2.11 mmol), 4-(dimethylamino)pyridine (13 mg, 0.11 mmol), (*S*)-N-[[3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.354 g, 1.05 mmol), and 1:1 tetrahydrofuran/dichloromethane (50 mL) at room temperature. After 3 days the reaction mixture was filtered to remove the precipitated 1,3-dicyclohexylurea and the filtrate concentrated *in vacuo*. The crude product was chromatographed over silica gel (20 g), eluting with a gradient of 1-6% methanol/chloroform, to give 0.446 g (95%) of the title compound as a white solid with mp 209-210 °C.



Continued to page 34

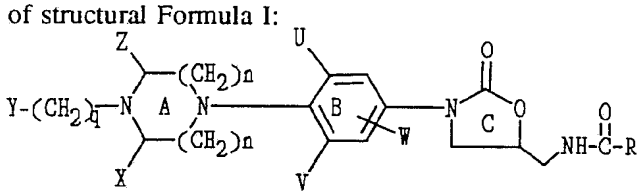

Continued from page 33
K2CO3
CH3CN
MsCl
Et3N
NaN3
H2
Pd/C
Ac2O
Py
CF3CO2H
BOC
Me
Ph
OH
OMs
N3
NH2
MeO
EtO
Cl
HN
F
9
10
11
12
21
22
23
24


Ph
OH
OR
R=Me
R=Ts
14a:
14b:
NaN3
15
MsCl
or
TsCl
Base
Base
K2CO3
or
KOt-Bu
13
16
1) H2, Pd/C
2) Ac2O, Py
Continued to page 36


Continued from page 35
17
18
19
20
$CF_3CO_2H$
$NaHCO_3$
Acetone-Water
Base

What is Claimed:

1. A compound of structural Formula I:



or pharmaceutically acceptable salts thereof wherein:

Y is a) -hydrogen,

b) -$C_{1-6}$ alkyl or -aryl,

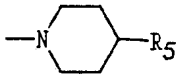
c) -OH, -O-$C_{1-6}$ alkyl, -O-vinyl, -O-phenyl, -O-C(O)-$C_{1-6}$ alkyl, -O-C(O)-phenyl (phenyl can be substituted with one to three F, Cl, -$OCH_3$, -OH, $NH_2$ or $C_{1-4}$ alkyl) or -O-C(O)-O-$CH_3$,

d) -S-$C_{1-6}$ alkyl,

e) -$SO_2$-$C_{1-6}$ alkyl, -$SO_2$-N($R^3$)$_2$ (where $R^3$ is independently hydrogen, $C_{1-4}$ alkyl or phenyl which can be substituted with one to three F, Cl, $OCH_3$, OH, $NH_2$, or $C_{1-4}$ alkyl),

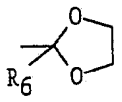
f) -C(O)-$C_{1-6}$ alkyl, -C(O)-O-$C_{1-6}$ alkyl, -C(O)-N($R^3$)$_2$, -C(O)-CH($R^4$)N($R^3$)$_2$, or -C(O)-CH($R^4$)NH-C(NH)-$NH_2$ where ($R^4$ is an amino acid side chain),

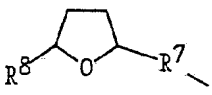
g) -N($R^3$)$_2$, -N($CH_2$)$_m$ (where m is 2-6 and forms a cyclic structure with the nitrogen atom and where one or more carbon atoms can be replaced with S, O or N$R^3$), or

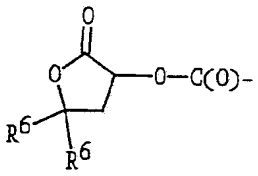


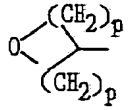
(where $R^5$ is OH, $OCH_3$, $CH_2OH$, $CH_2OCH_3$, $CO_2CH_3$ or $CO_2C_2H_5$),

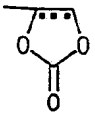
h) -C($CH_3$)=N-OR,

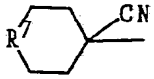
i)  (where $R^6$ is $CH_3$ or hydrogen),

j)  (where $R^7$ is $CH_2$ or C(O) and $R^8$ is -H or =O),

k) 

l)  (where p is 1 or 2),

m) 

n)  (where $R^7$ is O, S, S(O), $SO_2$, $CH_2$, NH, $NCH_3$, $NC_2H_5$, NCHO, $NCOCH_3$ or $NCO_2CH_3$);

wherein each occurrence of said $C_{1-6}$ alkyl may be substituted with one or more F, Cl, Br, I, $OR^1$, $CO_2R^1$, CN, $SR^1$, or $R^1$ (where $R^1$ is a hydrogen or $C_{1-4}$ alkyl);

X and Z are independently $C_{1-6}$ alkyl, $C_{3-12}$ cycloalkyl or hydrogen, or X and Z form a $C_{0-3}$ bridging group, preferably X and Z are hydrogen;

U, V and W are independently $C_{1-6}$ alkyl, F, Cl, Br, hydrogen or a $C_{1-6}$ alkyl substituted with one or more of F, Cl, Br or I, preferably U and V are F and W is hydrogen;

R is hydrogen, $C_{1-12}$ alkyl, $C_{3-12}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl substituted with one or more F, Cl, Br, I or OH; and

q is 0 to 4 inclusive.

2. The compound of Claim 1 wherein X and Z are hydrogen.

3. The compound of Claim 1 wherein U and V are F and W is hydrogen.

4. The compound of Claim 1 wherein U is F and V and W is hydrogen.

5. The compound of Claim 1 wherein Y is selected from the group consisting of H, methyl, ethyl, isopropyl, tert-butyl, benzyl, phenyl, pyridyl, acetyl, difluoroacetyl, hydroxyacetyl, benzoyl, methoxy carbonyl, ethoxy carbonyl, 2-chloroethoxy carbonyl, 2-hydroxyethoxy

carbonyl, 2-benzoloxyethoxy carbonyl, 2-methoxyethoxy carbonyl, 2,2,2-trifluoroethoxy carbonyl, cyanomethyl, 2-cyanoethyl, carbomethoxymethyl, 2-carbomethoxyethyl, 2-fluoroethoxy carbonyl, benzyloxy carbonyl, tertiary-butoxy carbonyl, methyl sulfonyl, phenyl sulfonyl or para-toluenesulfonyl.

6. The compound of Claim 4 wherein Y is methoxy carbonyl or cyanomethyl.

7. The compound of Claim 1 wherein R is methyl, H, methoxy, or $CHCl_2$.

8. The compound of Claim 1 which is an optically pure enantiomer having the *S*-configuration at C5 of the oxazolidinone ring.

9. The compound of Claim 1 wherein n is 1.

10. The compound of Claim 1 which is:

(a) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, methyl ester;

(b) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester;

(c) 4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester;

(d) N-((2-oxo-3-(4-(4-(phenylcarbonyl)-1-piperazinyl)phenyl)-5-oxazolidinyl)methyl)-acetamide;

(e) N-((3-(4-(3-Fluoro-4-(4-(2-Cyanoethyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

(f) N-((3-(4-(3-Fluoro-4-(4-(2-hydroxyethyl)carbonyl-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

(g) N-((3-(4-(3-Fluoro-4-((phenylcarbonyl)-1-piperazinyl))phenyl)-2-oxo-5-oxazolidinyl)methyl)-acetamide;

(h) 4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, 2-methoxyethyl ester;

(i) 4-[4-[5(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazineacetonitrile;

(j) (+/-)-N-[[3-[4-[4-(1,4-Dioxopentyl)-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl)-acetamide;

(k) (*S*)-N-[[3-[3-fluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide; or

(l) (*S*)-N-[[3-[3,5-difluoro-4-[4-(2-methoxyethyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

11. A method for treating microbial infections in warm blooded animals comprising: administering to a warm blooded animal in need thereof an effective amount of a compound of Formula I as shown in Claim 1.

12. The method of Claim 11 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

13. The method of Claim 12 wherein said compound is administered in an amount of from about 3.0 to about 50 mg/kg of body weight/day.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/03570

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D263/20; A61K31/42; C07D413/12

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| A | EP,A,0 311 090 (E.I. DU PONT DE NEMOURS AND COMPANY) 12 April 1989 cited in the application see claims | 1,11-13 |
| A | EP,A,0 352 781 (E.I. DU PONT DE NEMOURS AND COMPANY) 31 January 1990 cited in the application see page 45 - page 51; claims | 1,11-13 |
| A | EP,A,0 312 000 (E.I. DU PONT DE NEMOURS AND COMPANY) 19 April 1989 cited in the application see page 15 - page 16; claims | 1,11-13 |

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 09 JULY 1993 | 14. 07. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | HENRY J.C. |

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

ırnational application No.

PCT/US 93/03570

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-13 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9303570
SA 73323

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 09/07/93

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0311090 | 12-04-89 | US-A- | 4801600 | 31-01-89 |
| | | AU-A- | 2350788 | 13-04-89 |
| | | JP-A- | 1132569 | 25-05-89 |
| | | SU-A- | 1616518 | 23-12-90 |
| | | US-A- | 4921869 | 01-05-90 |
| | | US-A- | 4985429 | 15-01-91 |
| | | US-A- | 5032605 | 16-07-91 |
| | | US-A- | 4965268 | 23-10-90 |
| | | US-A- | 5036092 | 30-07-91 |
| EP-A-0352781 | 31-01-90 | US-A- | 4948801 | 14-08-90 |
| | | AU-B- | 622465 | 09-04-92 |
| | | AU-A- | 3911589 | 01-02-90 |
| | | JP-A- | 2124877 | 14-05-90 |
| | | US-A- | 5130316 | 14-07-92 |
| | | US-A- | 5043443 | 27-08-91 |
| EP-A-0312000 | 19-04-89 | AU-A- | 2396288 | 20-04-89 |
| | | DE-A- | 3869310 | 23-04-92 |
| | | JP-A- | 1132570 | 25-05-89 |
| | | SU-A- | 1616517 | 23-12-90 |
| | | US-A- | 4942183 | 17-07-90 |

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 623 615 A1**

(12) # EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: **94106049.3**

(22) Anmeldetag: **19.04.94**

(51) Int. Cl.5: **C07D 413/06**, C07D 263/20, A61K 31/42, A61K 31/495, C07D 491/10, //(C07D491/10, 307:00,221:00)

(30) Priorität: **01.05.93 DE 4314378**
**22.02.94 DE 4405633**

(43) Veröffentlichungstag der Anmeldung:
**09.11.94 Patentblatt 94/45**

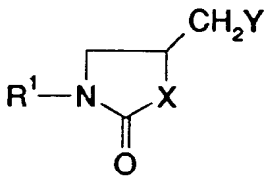
(84) Benannte Vertragsstaaten:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE**

(71) Anmelder: **MERCK PATENT GmbH**
**Frankfurter Strasse 250**
**D-64293 Darmstadt (DE)**

(72) Erfinder: **Raddatz, Peter, Dr.**
**Akazienweg 8a**
**D-64342 Seeheim-Jugenheim (DE)**
Erfinder: **Gante, Joachim, Prof.**
**Stormstrasse 4**
**D-64291 Darmstadt (DE)**
Erfinder: **Juraszyk, Horst, Dr.**
**Kleiner Ring 14**
**D-63342 Seeheim (DE)**
Erfinder: **Wurziger, Hanns, Dr.**
**Greinstrasse 7b**
**D-64291 Darmstadt (DE)**
Erfinder: **Prücher, Helmut**
**Königsbergerstrasse 9**
**D-64646 Heppenheim (DE)**
Erfinder: **Bernotat-Danielowski, Sabine, Dr.**
**Liebigstrasse 5**
**D-61231 Bad Naumheim (DE)**
Erfinder: **Melzer, Guido**
**Mörikestrasse 6**
**D-65719 Hofheim/Ts. (DE)**

(54) **Adhäsionsrezeptor -Antagonisten.**

(57) Neue Verbindungen der Formel I

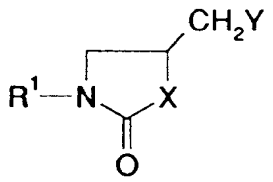


I

worin
$R^1$, X und Y die in Patentanspruch 1 angegebenen Bedeutungen haben, sowie deren Salze hemmen die Bindung von Fibrinogen an den Fibrinogenrezeptor und können zur Behandlung von Thrombosen, Apoplexie, Herzinfarkt, Entzündungen, Arteriosklerose, Osteoporose sowie von Tumoren verwendet werden.

EP 0 623 615 A1

Die Erfindung betrifft neue Verbindungen der Formel I



I

worin

| | |
|---|---|
| X | O, S, NH oder NA, |
| Y | einen unsubstituierten oder einen einfach durch $R^2$ substituierten Aziridino-, Azetidino-, Pyrrolidino-, Piperidino-, 1 -Oxa-8-azaspiro[4,5]decan-8-yl-, Hexahydroazepino- oder 4-$R^4$-piperazino-rest, der zusätzlich durch eine Gruppe OZ, SZ oder $N(Z)_2$ und/oder durch Carbonylsauerstoff substituiert sein kann, |
| Z | jeweils H, A, Phenyl-$C_kH_{2k}$- oder Ac, |
| $R^1$ | einen einfach durch CN, $H_2N$-$CH_2$-, $(A)_2N$-$CH_2$-, $H_2N$-C(=NH)-, $H_2N$-C(=NH)-NH-, $H_2N$-C(=NH)-NH-$CH_2$-, HO-NH-C(=NH)- oder HO-NH-C(=NH)-NH substituierten Phenylrest, |
| $R^2$ | -$C_mH_{2m}$-$COOR^3$ oder -$C_nH_{2n}$-O-$C_pH_{2p}$-$COOR^3$, |
| $R^3$ | H, A oder Benzyl, |
| $R^4$ | H, A, Benzyl oder -$C_mH_{2m}$-$COOR^3$, |
| A | jeweils Alkyl mit 1-6 C-Atomen, |
| Ac | Acyl mit 1-11 C-Atomen, |
| k und m | jeweils 0, 1, 2 oder 3, |
| n | 0, 1 oder 2, und |
| p | 1, 2 oder 3 bedeuten, |

sowie deren Salze.

Ähnliche Verbindungen sind aus der EP-A1-0 381 033 bekannt.

Der Erfindung lag die Aufgabe zugrunde, neue Verbindungen mit wertvollen Eigenschaften aufzufinden, insbesondere solche, die zur Herstellung von Arzneimitteln verwendet werden können.

Diese Aufgabe wurde durch die Erfindung gelöst. Es wurde gefunden, daß die Verbindungen der Formel I sowie ihre Solvate und Salze bei guter Verträglichkeit wertvolle pharmakologische Eigenschaften besitzen. Insbesondere hemmen sie die Bindung von Fibrinogen, Fibronectin und des von-Willebrand-Faktorsan den Fibrinogenrezeptor der Blutplättchen (Glykoprotein IIb/IIIa) als auch die Bindung derselben und weiterer adhäsiver Proteine, wie Vitronectin, Kollagen und Laminin, an die entsprechenden Rezeptoren auf der Oberfläche verschiedener Zelltypen. Die Verbindungen beeinflussen somit Zell-Zell- und Zell-Matrix-Wechselwirkungen. Sie verhindern insbesondere die Entstehung von Blutplättchenthromben und können daher zur Behandlung von Thrombosen, Apoplexie, Herzinfarkt, Entzündungen, Arteriosklerose verwendet werden. Ferner haben die Verbindungen einen Effekt auf Tumorzellen, indem sie deren Metastasierung hemmen. Somit können sie auch als Anti-Tumor-Mittel eingesetzt werden.

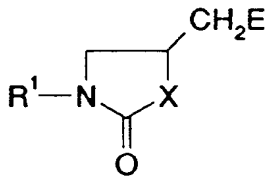
Die Verbindungen eignen sich zudem als antimikrobielle Wirkstoffe, die Infektionen, wie sie beispielsweise durch Bakterien, Pilze oder Hefen ausgelöst werden, verhindern können. DieSubstanzen können daher vorzugsweise als begleitende antimikrobielle Wirkstoffe gegeben werden, wenn Eingriffe an Organismen vorgenommen werden, bei denen körperfremde Stoffe, wie z.B. Biomaterialien, Implantate, Katheter oder Herzschrittmacher, eingesetzt werden. Sie wirken als Antiseptika.

Die Eigenschaften der Verbindungen können nach Methoden nachgewiesen werden, die in der EP-A1-0 462 960 beschrieben sind. Die Hemmung Fibrinogenbindung an den Fibrinogenrezeptor kann nach der Methode nachgewiesen werden, die in der EP-A1-0 381 033 angegeben ist. Die thrombozytenaggregationshemmende Wirkung läßt sich in vitro nach der Methode von Born (Nature 4832, 927-929, 1962) nachweisen.

Gegenstand der Erfindung ist ferner ein Verfahren zur Herstellung einer Verbindung der angegebenen Formel I sowie von deren Salzen, dadurch gekennzeichnet, daß man

(a) eine Verbindung der Formel I aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt, oder daß man

(b) eine Verbindung der Formel II



II

worin
E Cl, Br, I oder eine reaktionsfähig veresterte OH-Gruppe
bedeutet, und
$R^1$ und X die oben angegebenen Bedeutungen haben
mit einer Aminoverbindung der Formel III

H-Y III

worin
Y die oben angegebene Bedeutung hat,
umsetzt, oder daß man
(c) eine Verbindung der Formel IV

$R^1$-NH-$CH_2$-CH(XH)-$CH_2$-Y IV

worin
$R^1$, X und Y die oben angegebenen Bedeutungen haben, oder eines ihrer reaktionsfähigen Derivate
mit einem reaktiven Derivat der Kohlensäure umsetzt, oder daß man
(d) zur Herstellung einer Guanidinoverbindung der Formel I ($R^1$ = einfach durch $H_2N$-C(=NH)-NH-substituierter Phenylrest) eine Aminoverbindung entsprechend der Formel I, die jedoch an Stelle des Restes $R^1$ eine Aminophenylgruppe enthält, mit einem amidinierenden Mittel behandelt,
und/oder daß man in einer Verbindung der Formel I einen oder beide Reste $R^1$ und/oder Y in (einen) andere(n) Rest(e) $R^1$ und/oder Y umwandelt und/oder eine Verbindung der Formel I durch Behandeln mit einer Säure oder einer Base in eines ihrer Salze überführt.

Die Verbindungen der Formel I besitzen mindestens ein chirales Zentrum und können daher in mehreren enantiomeren Formen auftreten. Alle diese Formen (z.B. D- und L-Formen) und deren Gemische (z.B. die DL-Formen) sind in der Formel I eingeschlossen.

Vor- und nachstehend haben die Reste bzw. Parameter X, Y, Z, $R^1$ bis $R^4$, A, Ac, k, m, n, p und E die bei den Formeln I oder II angegebenen Bedeutungen, falls nicht ausdrücklich etwas anderes angegeben ist. Falls mehrere Gruppen A und/oder Z im Molekül I, II und/oder III vorhanden sind, können sie gleich oder voneinander verschieden sein.

In den vorstehenden Formeln hat die Gruppe A 1-6, vorzugsweise 1,2, 3 oder 4 C-Atome. Im einzelnen bedeutet A vorzugsweise Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, sek.-Butyl oder tert.-Butyl, ferner auch Pentyl, 1-, 2- oder 3-Methylbutyl, 1,1-, 1,2- oder 2,2-Dimethylpropyl, 1-Ethylpropyl, Hexyl, 1-, 2-, 3- oder 4-Methylpentyl.

X ist vorzugsweise O, aber auch S, NH oder NA, z.B. N-$CH_3$.

Y ist vorzugsweise 3-($R^3$OOC)-azetidino, 3-($R^3$OOC-$CH_2$-O-)-azetidino, 2-($R^3$OOC-)pyrrolidino, 3-($R^3$OOC-)-pyrrolidino, 2-($R^3$OOC-)-piperidino, 3-($R^3$OOC-)-piperidino, 4-($R^3$OOC-)-piperidino, 2-($R^3$OOC-$CH_2$-)-piperidino, 3-($R^3$OOC-$CH_2$-)-piperidino, 4-($R^3$OOC-$CH_2$-)-piperidino, 4-($R^3$OOC-$CH_2CH_2$-)-piperidino, 4-Hydroxy-4-($R^3$OOC)-piperidino, 4-Hydroxy-4-($R^3$OOC-$CH_2$-)-piperidino, 4-Amino-4-($R^3$OOC)-piperidino, 4-Amino-4-($R^3$OOC-$CH_2$)-piperidino, 3-Oxo-4-($R^3$OOC-$CH_2$-)-piperidino, 2-($R^3$OOC-$CH_2$-O-)-piperidino, 3-($R^3$OOC-$CH_2$-O-)-piperidino, 4-($R^3$OOC-$CH_2$-O-)-piperidino, 1-Oxa-2-oxo-8-azaspiro[4,5]-decan-8-yl, 2-, 3- oder 4-($R^3$OOC)-hexahydroazepino, 4-($R^3$OOC-$CH_2$-)-piperazino, 4-($R^3$OOC-$CH_2CH_2$-)-piperazino, 2-($R^3$OOC)-piperazino, 3-($R^3$OOC)-piperazino, 4-Benzyl-3-($R^3$OOC)-piperazino.

Z ist vorzugsweise H, ferner bevorzugt A wie Methyl oder Ethyl, Phenyl, Benzyl, Acetyl oder Benzoyl.

$R^1$ ist vorzugsweise ein in 4-Stellung, aber auch in 2- oder 3-Stellung wie angegeben substituierter Phenylrest, im einzelnen bevorzugt 2-, 3- oder (insbesondere) 4-Cyanphenyl, 2-, 3- oder (insbesondere) 4-Aminomethylphenyl, 2-, 3- oder (insbesondere) 4-Dimethylaminomethylphenyl, 2-,3- oder (insbesondere) 4-Amidinophenyl, 2-, 3- oder 4-Guanidinophenyl, 2-, 3- oder 4-Guanidinomethylphenyl, 2-, 3- oder (insbeson-

dere) 4-Hydroxyamidinophenyl.

$R^2$ ist vorzugsweise $-COOR^3$, $-CH_2COOR^3$ oder $-O-CH_2COOR^3$.

$R^3$ ist vorzugsweise H, Methyl, Ethyl, tert.-Butyl oder Benzyl.

$R^4$ ist vorzugsweise H, Methyl, Ethyl, Benzyl oder $CH_2COOR^3$.

Ac ist vorzugsweise Alkanoyl mit 1-6 C-Atomen wie Formyl, Acetyl, Propionyl, Butyryl, Isobutyryl, Valeryl oder Capronyl, ferner Benzoyl, Toluyl, 1- oder 2-Naphthoyl oder Phenylacetyl.

Die Parameter k und m sind vorzugsweise 0 oder 1. Der Parameter n ist vorzugsweise 0. Der Parameter p ist vorzugsweise 1.

Unter den Verbindungen der Formel I sind diejenigen bevorzugt, in denen mindestens einer der angegebenen Reste, Gruppen und/oder Parameter eine der angegebenen bevorzugten Bedeutungen hat. Einige Gruppen von bevorzugten Verbindungen sind diejenigen der Formeln Ia bis Id, die der Formel I entsprechen, worin jedoch

in Ia

X O bedeutet;

in Ib

X O und

$R^1$ Cyanphenyl bedeutet;

in Ic

X O und

$R^1$ Aminomethylphenyl bedeutet;

in Id

X O und

$R^1$ Amidinophenyl bedeutet.

Weiterhin sind bevorzugt Verbindungen der Formeln Ie sowie Iae, Ibe, Ice und Ide, die den Formeln I, Ia, Ib, Ic und Id entsprechen, worin jedoch zusätzlich

Y 3-$R^2$-azetidino, 2-$R^2$-pyrrolidino, 2-$R^2$-piperidino, 3-$R^2$-piperidino, 4-$R^2$-piperidino, 4-$R^2$-piperazino oder 3-$R^2$-4-$R^4$-piperazino,

$R^2$ $-COOR^3$, $-CH_2COOR^3$ oder $-OCH_2COOR^3$ und

$R^4$ $-CH_2COOR^3$ bedeutet.

Kleinere ausgewählte Gruppen von Verbindungen sind diejenigen der Formeln If und Ig. Sie entsprechen der Formel I, wobei jedoch

in If

X O,

Y 3-($R^3OOC-CH_2-O-$)-azetidino, 2-($R^3OOC-$)-pyrrolidino, 2-, 3- oder 4-($R^3OOC-$)-piperidino, 4-($R^3OOC-CH_2-$)-piperidino, 3- oder 4-($R^3OOC-CH_2O-$)-piperidino, 4-($R^3OOC-CH_2$)-piperazino oder 3-($R^3OOC-$)-4-$R^4$-piperazino,

$R^1$ 4-Cyanphenyl, 4-Aminomethylphenyl, 4-Amidinophenyl, oder 4-Guanidinomethylphenyl,

$R^3$ H, C1-C4-Alkyl oder Benzyl und

$R^4$ H oder Benzyl bedeuten, und

in Ig

X O,

Y 4-($R^3OOC-$)-piperidino oder 4-($R^3OOC-CH_2O-$)-piperidino,

$R^1$ 4-Cyanphenyl, 4-Aminomethylphenyl oder 4-Amidinophenyl und

$R^3$ H, $C_1$-$C_4$-Alkyl oder Benzyl bedeuten.

Die Verbindungen der Formel I und auch die Ausgangsstoffe zu ihrer Herstellung werden im übrigen nach an sich bekannten Methoden hergestellt, wie sie in der Literatur (z.B. in den Standardwerken wie Houben-Weyl, Methoden der organischen Chemie, Georg-Thieme-Verlag, Stuttgart; ferner EP-A1-0381033, EP-A1-0462960) beschrieben sind, und zwar unter Reaktionsbedingungen, die für die genannten Umsetzungen bekannt und geeignet sind. Dabei kann man auch von an sich bekannten, hier nicht näher erwähnten Varianten Gebrauch machen.

Die Ausgangsstoffe können, falls erwünscht, auch in situ gebildet werden, so daß man sie aus dem Reaktionsgemisch nicht isoliert, sondern sofort weiter zu den Verbindungen der Formel I umsetzt.

Die Verbindungen der Formel I können erhalten werden, indem man sie aus ihren funktionellen Derivaten durch Solvolyse, insbesondere Hydrolyse, oder durch Hydrogenolyse in Freiheit setzt.

Bevorzugte Ausgangsstoffe für die Solvolyse bzw. Hydrogenolyse sind solche, die sonst der Formel I entsprechen, aber an Stelle einer oder mehrerer freier Amino- und/oder Hydroxygruppen entsprechende geschützte Amino- und/oder Hydroxygruppen enthalten, vorzugsweise solche, die an Stelle eines H-Atoms, das mit einem N-Atom verbunden ist, eine Aminoschutzgruppe tragen, insbesondere solche, die an Stelle

einer HN-Gruppe eine R'-N-Gruppe tragen, worin R' eine Aminoschutzgruppe bedeutet, und/oder solche, die an Stelle des H-Atoms einer Hydroxygruppe eine Hydroxyschutzgruppe tragen, z.B. solche, die der Formel I entsprechen, jedoch an Stelle einer Gruppe -COOH eine Gruppe -COOR" tragen, worin R" eine Hydroxyschutzgruppe bedeutet.

Es können auch mehrere - gleiche oder verschiedene - geschützte Amino- und/oder Hydroxygruppen im Molekül des Ausgangsstoffes vorhanden sein. Falls die vorhandenen Schutzgruppen voneinander verschieden sind, können sie in vielen Fällen selektiv abgespalten werden.

Der Ausdruck "Aminoschutzgruppe" ist allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Aminogruppe vor chemischen Umsetzungen zu schützen (zu blockieren), die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an einer anderen Stelle des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind insbesondere unsubstituierte oder substituierte Acyl-, Aryl- (z.B. 2,4-Dinitrophenyl (DNP)), Aralkoxymethyl- (z.B. Benzyloxymethyl (BOM)) oder Aralkylgruppen (z.B. Benzyl, 4-Nitrobenzyl, Triphenylmethyl). Da die Aminoschutzgruppen nach der gewünschten Reaktion (oder Reaktionsfolge) entfernt werden, ist ihre Art und Größe im übrigen nicht kritisch; bevorzugt werden jedoch solche mit 1-20, insbesondere 1-8 C-Atomen. Der Ausdruck "Acylgruppe" ist im Zusammenhang mit dem vorliegenden Verfahren im weitesten Sinne aufzufassen. Er umschließt von aliphatischen, araliphatischen, aromatischen oder heterocyclischen Carbonsäuren oder Sulfonsäuren abgeleitete Acylgruppen sowie insbesondere Alkoxycarbonyl-, Aryloxycarbonyl- und vor allem Aralkoxycarbonylgruppen. Beispiele für derartige Acylgruppen sind Alkanoyl wie Acetyl, Propionyl, Butyryl; Aralkanoyl wie Phenylacetyl; Aroyl wie Benzoyl oder Toluyl; Aryloxyalkanoyl wie Phenoxyacetyl; Alkoxycarbonyl wie Methoxycarbonyl, Ethoxycarbonyl, 2,2,2-Trichlorethoxycarbonyl, Isopropoxycarbonyl, tert.-Butoxycarbonyl (BOC), 2-Jodethoxycarbonyl; Aralkyloxycarbonyl wie Benzyloxycarbonyl (CBZ), 4-Methoxybenzyloxycarbonyl, 9-Fluorenylmethoxycarbonyl (FMOC). Bevorzugte Aminoschutzgruppen sind BOC, DNP und BOM, ferner CBZ, Benzyl und Acetyl.

Der Ausdruck "Hydroxyschutzgruppe" ist ebenfalls allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Hydroxygruppe vor chemischen Umsetzungen zu schützen, die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an einer anderen Stelle des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind die oben genannten unsubstituierten oder substituierten Aryl-, Aralkyl- oder Acylgruppen, ferner auch Alkylgruppen. Die Natur und Größe der Hydroxyschutzgruppen ist nicht kritisch, da sie nach der gewünschten chemischen Reaktion oder Reaktionsfolge wieder entfernt werden; bevorzugt sind Gruppen mit 1-20, insbesondere 1-10 C-Atomen. Beispiele für Hydroxyschutzgruppen sind u.a. tert.-Butyl, Benzyl, p-Nitrobenzoyl, p-Toluolsulfonyl und Acetyl, wobei Benzyl und Acetyl besonders bevorzugt sind.

Die als Ausgangsstoffe zu verwendenden funktionellen Derivate der Verbindungen der Formel I können nach üblichen Methoden hergestellt werden, wie sie z.B. in den genannten Standardwerken und Patentanmeldungen beschrieben sind, z.B. durch Umsetzung von Verbindungen, die den Formeln II und III entsprechen, wobei jedoch mindestens eine dieser Verbindungen eine Schutzgruppe an Stelle eines H-Atoms enthält.

Das In-Freiheit-Setzen der Verbindungen der Formel I aus ihren funktionellen Derivaten gelingt - je nach der benutzten Schutzgruppe - z.B. mit starken Säuren, zweckmäßig mit Trifluoressigsäure oder Perchlorsäure, aber auch mit anderen starken anorganischen Säuren wie Salzsäure oder Schwefelsäure, starken organischen Carbonsäuren wie Trichloressigsäure oder Sulfonsäuren wie Benzol- oder p-Toluolsulfonsäure. Die Anwesenheit eines zusätzlichen inerten Lösungsmittels ist möglich, aber nicht immer erforderlich.

Als inerte Lösungsmittel eignen sich vorzugsweise organische, beispielsweise Carbonsäuren wie Essigsäure, Ether wie Tetrahydrofuran oder Dioxan, Amide wie Dimethylformamid (DMF), halogenierte Kohlenwasserstoffe wie Dichlormethan, Sulfoxide wie Dimethylsulfoxid (DMSO), ferner auch Alkohole wie Methanol, Ethanol oder Isopropanol sowie Wasser. Ferner kommen Gemische der vorgenannten Lösungsmittel in Frage. Trifluoressigsäure wird vorzugsweise im Überschuß ohne Zusatz eines weiteren Lösungsmittels verwendet, Perchlorsäure in Form eines Gemisches aus Essigsäure und 70%iger Perchlorsäure im Verhältnis 9:1. Die Reaktionstemperaturen für die Spaltung liegen zweckmäßig zwischen etwa 0 und etwa 50°; vorzugsweise arbeitet man zwischen 15 und 30° (Raumtemperatur).

Die BOC-Gruppe kann z.B. bevorzugt mit 40%iger Trifluoressigsäure in Dichlormethan oder mit etwa 3 bis 5 n HCl in Dioxan bei 15-60° abgespalten weden, die FMOC-Gruppe mit einer etwa 5-20%igen Lösung von Dimethylamin, Diethylamin oder Piperidin in DMF bei 15-50°. Eine Abspaltung der DNP-Gruppe gelingt z.B. auch mit einer etwa 3-10%igen Lösung von 2-Mercaptoethanol in DMF/Wasser bei 15-30°.

Hydrogenolytisch entfernbare Schutzgruppen (z.B. BOM, CBZ oder Benzyl) können z.B. durch Behandeln mit Wasserstoff in Gegenwart eines Katalysators (z.B. eines Edelmetallkatalysators wie Palladium, zweckmäßig auf einem Träger wie Kohle) abgespalten werden. Als Lösungsmittel eignen sich dabei die

oben angegebenen, insbesondere z.B. Alkohole wie Methanol oder Ethanol oder Amide wie DMF. Die Hydrogenolyse wird in der Regel bei Temperaturen zwischen etwa 0 und 100 ° und Drucken zwischen etwa 1 und 200 bar, bevorzugt bei 20-30 ° und 1-10 bar durchgeführt. Eine Hydrogenolyse der CBZ-Gruppe gelingt z.B. gut an 5-10%igem Pd-C in Methanol bei 20-30 °.

Verbindungen der Formel I können bevorzugt auch durch Reaktion einer Verbindung der Formel II mit einer Base der Formel III erhalten werden. Dabei bedient man sich zweckmäßig der an sich bekannten Methoden der N-Alkylierung.

Die Fluchtgruppe E bedeutet vorzugsweise Cl, Br, I, $C_1$-$C_6$-Alkylsulfonyloxy wie Methan- oder Ethansulfonyloxy oder $C_6$-$C_{10}$-Arylsulfonyloxy wie Benzol-, p-Toluol- oder 1- oder 2-Naphthalinsulfonyloxy.

Die Reaktion gelingt vorzugsweise in Gegenwart einer zusätzlichen Base, z.B. eines Alkali- oder Erdalkalimetall-hydroxids oder carbonats wie Natrium-, Kalium- oder Calciumhydroxid, Natrium-, Kalium- oder Calciumcarbonat, in einem inerten Lösungsmittel, z.B. einem halogenierten Kohlenwasserstoff wie Dichlormethan, einem Ether wie THF oder Dioxan, einem Amid wie DMF oder Dimethylacetamid, einem Nitril wie Acetonitril, bei Temperaturen zwischen etwa -10 und 200, vorzugsweise zwischen 0 und 120 °. Falls die Fluchtgruppe E von I verschieden ist, empfiehlt sich ein Zusatz eines Iodids wie Kaliumiodid.

Die Ausgangsstoffe der Formel II sind in der Regel neu. Sie können z.B. hergestellt werden durch Reaktion eines substituierten Anilins der Formel $R^1$-$NH_2$ mit einer Verbindung der Formel $R^5CH_2$-$CHR^6$-$CH_2OH$ (worin $R^5$ E, $R^6$ $XR^7$, $R^7$ eine Schutzgruppe, $R^5$ und $R^6$ zusammen auch O bedeuten) zu einer Verbindung der Formel $R^1$-NH-$CH_2$-$CHR^8$-$CH_2OH$ (worin $R^8$ $XR^7$ oder OH bedeutet), gegebenenfalls Abspaltung der Schutzgruppe $R^7$ zu Verbindungen der Formel $R^1$-NH-$CH_2$-CH(XH)-$CH_2OH$, Reaktion mit einem Derivat der Kohlensäure wie Diethylcarbonat zu 3-$R^1$-5-hydroxymethyl-2-oxazolidinonen und Umwandlung der Hydroxymethylgruppe in eine $CH_2E$-Gruppe, z.B. mit $SOCl_2$, $SOBr_2$, Methansulfonylchlorid oder p-Toluolsulfonylchlorid. Die Verbindungen der Formel H-Y (III) sind in der Regel bekannt oder in Analogie zu bekannten Verbindungen herstellbar.

Verbindungen der Formel I können ferner erhalten werden durch Reaktion einer Verbindung der Formel IV (oder eines reaktionsfähigen Derivats davon) mit einem reaktiven Derivat der Kohlensäure.

Als Kohlensäurederivate eignen sich insbesondere Dialkylcarbonate wie Diethylcarbonat, ferner auch Chlorameisensäurealkylester wie Ethyl-chlorformiat. Bevorzugt dient das Kohlensäurederivat, das zweckmäßig im Überschuß eingesetzt wird, auch als Lösungs- bzw. Suspensionsmittel. Es kann aber auch eines der angegebenen Lösungsmittel anwesend sein, sofern es bei dieser Umsetzung inert ist. Weiterhin empfiehlt sich der Zusatz einer Base, insbesondere eines Alkalimetallalkoholats wie Kalium-tert.-butylat. Man arbeitet zweckmäßig bei Reaktionstemperaturen zwischen 0 und 150 °, vorzugsweise zwischen 70 und 120 °.

Die Ausgangsstoffe der Formel IV sind in der Regel neu. Sie sind z.B. erhältlich durch Funktionalisierung der oben genannten Verbindungen der Formel $R^1$-NH-$CH_2$-CH(XH)-$CH_2OH$ zu Verbindungen der Formel $R^1$-NH-$CH_2$-CH(XH)-$CH_2$-Eund Reaktion mit Verbindungen der Formel H-Y (III).

Zur Herstellung von Verbindungen der Formel I, worin $R^1$ eine Guanidinophenylgruppe bedeutet, kann man eine entsprechende Aminophenylverbindung mit einem amidinierenden Mittel behandeln. Als amidinierendes Mittel ist 1-Amidino-3,5-dimethylpyrazol bevorzugt, das insbesondere in Form seines Nitrats eingesetzt wird. Man arbeitet zweckmäßig unter Zusatz einer Base wie Triethylamin oder Ethyl-diisopropylamin in einem inerten Lösungsmittel oder Lösungsmittelgemisch, z.B. Wasser/Dioxan bei Temperaturen zwischen 0 und 120 °, vorzugsweise 60 und 120 °.

Weiterhin ist es möglich, in einer Verbindung der Formel I einen oder beide der Reste $R^1$ und/oder Y in (einen) andere(n) Rest(e) $R^1$ und/oder Y umzuwandeln.

Insbesondere kann man Cyangruppen zu Aminomethylgruppen reduzieren oder in Amidinogruppen oder Hydroxyamidinogruppen umwandeln, Carboxylgruppen verestern, Estergruppen spalten, Benzylgruppen hydrogenolytisch entfernen, Aminomethylgruppen in Guanidinomethylgruppen überführen.

Eine Reduktion von Cyangruppen zu Aminomethylgruppen gelingt zweckmäßigerweise durch katalytische Hydrierung, z.B. an Raney-Nickel bei Temperaturen zwischen 0 und 100 °, vorzugsweise 10 und 30 °, und Drucken zwischen 1 und 200 bar, vorzugsweise bei Normaldruck, in einem inerten Lösungsmittel, z.B. einem niederen Alkohol wie Methanol oder Ethanol, zweckmäßig in Gegenwart von Ammoniak. Arbeitet man z.B. bei etwa 20 ° und 1 bar, so bleiben im Ausgangsmaterial vorhandene Benzylester- oder N-Benzylgruppen erhalten. Will man diese hydrogenolytisch spalten, so verwendet man zweckmäßig einen Edelmetallkatalysator, vorzugsweise Pd-Kohle, wobei man der Lösung eine Säure wie Essigsäure sowie auch Wasser zusetzen kann.

Zur Herstellung eines Amidins der Formel I ($R^1$ = Amidinophenyl) kann man an ein Nitril der Formel I ($R^1$ = Cyanphenyl) Ammoniak anlagern. Die Anlagerung erfolgt bevorzugt mehrstufig, indem man in an sich bekannter Weise a) das Nitril mit $H_2S$ in ein Thioamid umwandelt, das mit einem Alkylierungsmittel, z.B. $CH_3I$, in den entsprechenden S-Alkyl-imidothioester übergeführt wird, welcher seinerseits mit $NH_3$ zum

Amidin reagiert, b) das Nitril mit einem Alkohol, z.B. Ethanol in Gegenwart von HCl in den entsprechenden Imidoester umwandelt und diesen mit Ammoniak behandelt, oder c) das Nitril mit Lithiumbis-(trimethylsilyl)-amid umsetzt und das Produkt anschließend hydrolysiert.

Analog sind die entsprechenden N-Hydroxy-amidine der Formel I ($R^1$ = durch HO-NH-C(=NH)-substituiertes Phenyl) aus den Nitrilen erhältlich, wenn man nach a) oder b), aber mit Hydroxylamin an Stelle von Ammoniak arbeitet.

Zur Veresterung kann man eine Säure der Formel I ($R^3$ = H) mit einem Überschuß eines Alkohols der Formel $R^3$-OH ($R^3$ = A oder Benzyl) behandeln, zweckmäßig in Gegenwart einer starken Säure wie Salzsäure oder Schwefelsäure bei Temperaturen zwischen 0 und 100, vorzugsweise 20 und 50°.

Umgekehrt kann ein Ester der Formel I ($R^3$ = A oder Benzyl), in die entsprechende Säure der Formel I ($R^3$ = H) umgewandelt werden, zweckmäßig durch Solvolyse nach einer der oben angegebenen Methoden, z.B. mit NaOH oder KOH in Wasser-Dioxan bei Temperaturen zwischen 0 und 40°, vorzugsweise 10 und 30°.

Eine Base der Formel I kann mit einer Säure in das zugehörige Säureadditionssalz übergeführt werden. Für diese Umsetzung kommen insbesondere Säuren in Frage, die physiologisch unbedenkliche Salze liefern, So können anorganische Säuren verwendet werden, z.B. Schwefelsäure, Salpetersäure, Halogenwasserstoffsäuren wie Chlorwasserstoffsäure oder Bromwasserstoffsäure, Phosphorsäuren wie Orthophosphorsäure, Sulfaminsäure, ferner organische Säuren, insbesondere aliphatische, alicyclische, araliphatische, aromatische oder heterocyclische ein- oder mehrbasige Carbon-, Sulfon- oder Schwefelsäuren, z.B. Ameisensäure, Essigsäure, Trifluoressigsäure, Propionsäure, Pivalinsäure, Diethylessigsäure, Malonsäure, Bernsteinsäure, Pimelinsäure, Fumarsäure, Maleinsäure, Milchsäure, Weinsäure, Äpfelsäure, Citronensäure, Gluconsäure, Ascorbinsäure, Nicotinsäure, Isonicotinsäure, Methan- oder Ethansulfonsäure, Ethandisulfonsäure, 2-Hydroxyethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Naphthalin-mono- und -disulfonsäuren, Laurylschwefelsäure. Salze mit physiologisch nicht unbedenklichen Säuren, z.B. Pikrate, können zur Isolierung und/oder Aufreinigung der Verbindungen der Formel I verwendet werden.

Die freien Basen der Formel I können, falls gewünscht, aus ihren Salzen durch Behandlung mit starken Basen wie Natrium- oder Kaliumhydroxid, Natrium- oder Kaliumcarbonat in Freiheit gesetzt werden.

Es ist auch möglich, Carbonsäuren der Formel I ($R^3$ = H) durch Umsetzung mit entsprechenden Basen in ihre Metall- oder Ammoniumsalze umzuwandeln, z.B. ihre Natrium-, Kalium- oder Calciumsalze.

Die Verbindungen der Formel I enthalten ein oder mehrere chirale Zentren und können daher in racemischer oder in optisch-aktiver Form vorliegen. Erhaltene Racemate können nach an sich bekannten Methoden mechanisch oder chemisch in die Enantiomeren getrennt werden. Vorzugsweise werden aus dem racemischen Gemisch durch Umsetzung mit einem optisch-aktiven Trennmittel Diastereomere gebildet. Als Trennmittel eignen sich z.B. optisch aktive Säuren, wie die D- und L-Formen von Weinsäure, Diacetylweinsäure, Dibenzoylweinsäure, Mandelsäure, Äpfelsäure, Milchsäure oder die verschiedenen optisch-aktiven Camphersulfonsäuren wie β-Camphersulfonsäure. Vorteilhaft ist auch eine Enantiomerentrennung mit Hilfe einer mit einem optisch aktiven Trennmittel (z.B. Dinitrobenzoyl-phenyl-glycin) gefüllten Säule; als Laufmittel eignet sich z.B. ein Gemisch Hexan/Isopropanol/ Acetonitril, z.B. im Volumenverhältnis 82:15:3.

Natürlich ist es auch möglich, optisch-aktive Verbindungen der Formel I nach den oben beschriebenen Methoden zu erhalten, indem man Ausgangsstoffe (z.B. solche der Formel II) verwendet, die bereits optisch-aktiv sind.

Die neuen Verbindungen der Formel I und ihre physiologisch unbedenklichen Salze können zur Herstellung pharmazeutischer Präparate verwendet werden, indem man sie zusammen mit mindestens einem Träger- oder Hilfsstoff und, falls erwünscht, zusammen mit einem oder mehreren weiteren Wirkstoff-(en) in eine geeignete Dosierungsform bringt. Die so erhaltenen Zubereitungen können als Arzneimittel in der Human- oder Veterinärmedizin eingesetzt werden. Als Trägersubstanzen kommen organische oder anorganische Stoffe in Frage, die sich für die enterale (z.B. orale oder rektale) oder parenterale Applikation oder für eine Applikation in Form eines Inhalations-Sprays eignen und mit den neuen Verbindungen nicht reagieren, beispielsweise Wasser, pflanzliche Öle, Benzylalkohole, Polyethylenglykole, Glycerintriacetat und andere Fettsäureglyceride, Gelatine, Sojalecithin, Kohlehydrate wie Lactose oder Stärke, Magnesiumstearat, Talk, Cellulose. Zur oralen Anwendung dienen insbesondere Tabletten, Dragees, Kapseln, Sirupe, Säfte oder Tropfen; von Interesse sind speziell Lacktabletten und Kapseln mit magensaftresistenten Überzügen bzw. Kapselhüllen. Zur rektalen Anwendung dienen Suppositorien, zur parenteralen Applikation Lösungen, vorzugsweise ölige oder wässerige Lösungen, ferner Suspensionen, Emulsionen oder Implantate.

Für die Applikation als Inhalations-Spray können Sprays verwendet werden, die den Wirkstoff entweder gelöst oder suspendiert in einem Treibgasgemisch enthalten. Zweckmäßig verwendet man den Wirkstoff dabei in mikronisierter Form, wobei ein oder mehrere zusätzliche physiologisch verträgliche Lösungsmittel zugegen sein können, z.B. Ethanol. Inhalationslösungen können mit Hilfe üblicher Inhalatoren verabfolgt

werden. Die neuen Verbindungen können auch lyophilisiert und die erhaltenen Lyophilisate z.B. zur Herstellung von Injektionspräparaten verwendet werden. Die angegebenen Zubereitungen können sterilisiert sein und/oder Hilfsstoffe wie Konservierungs-, Stabilisierungs- und/oder Netzmittel, Emulgatoren, Salze zur Beeinflussung des osmotischen Druckes, Puffersubstanzen, Farbund/oder Aromastoffe enthalten. Sie können, falls erwünscht, auch einen oder mehrere weitere Wirkstoffe enthalten, z.B. ein oder mehrere Vitamine.

Die erfindungsgemäßen Substanzen werden in der Regel in Analogie zu anderen bekannten, im Handel befindlichen Pharmaka, insbesondere aber in Analogie zu den in der EP-A-459256 beschriebenen Verbindungen verabreicht, vorzugsweise in Dosierungen zwischen etwa 5 mg und 1 g, insbesondere zwischen 50 und 500 mg pro Dosierungseinheit. Die tägliche Dosierung liegt vorzugsweise zwischen etwa 0,1 und 20 mg/kg, insbesondere 1 und 10 mg/kg Körpergewicht. Die spezielle Dosis für jeden bestimmten Patienten hängt jedoch von den verschiedensten Faktoren ab, beispielsweise von der Wirksamkeit der eingesetzten speziellen Verbindung, vom Alter, Körpergewicht, allgemeinen Gesundheitszustand, Geschlecht, von der Kost, vom Verabfolgungszeitpunkt und -weg, von der Ausscheidungsgeschwindigkeit, Arzneistoffkombination und Schwere der jeweiligen Erkrankung, welcher die Therapie gilt. Die orale Applikation ist bevorzugt.

Vor- und nachstehend sind alle Temperaturen in °C angegeben. In den nachfolgenden Beispielen bedeutet "übliche Aufarbeitung": Man gibt, falls erforderlich, Wasser hinzu, stellt je nach Konstitution des Endprodukts auf pH-Werte zwischen 2 und 8 ein, extrahiert mit Ethylacetat oder Dichlormethan, trennt ab, trocknet die organische Phase über Natriumsulfat, dampft ein und reinigt durch Chromatographie an Kieselgel und/oder Kristallisation. FAB = ($M^+$ + 1 )-Peak im Massenspektrum, erhalten nach der "Fast Atom Bombardment"-Methode.

Beispiel 1

Eine Lösung von 1 g 1-tert.-Butoxycarbonyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäureethylester (erhältlich durch Reaktion von 3-(4-Cyanphenyl)-5-brommethyl-2-oxazolidinon mit 1-tert.-Butoxycarbonyl-piperazin-2-carbonsäureethylester nach der in Beispiel 3 beschriebenen Methode) in 12 ml Dichlormethan und 12 ml Trifluoressigsäure wird 1 Std. bei 20° stehengelassen und eingedampft. Man erhält 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-3-carbonsäureethylester, FAB 359.

Analog erhält man aus 1-tert.-Butoxycarbonyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure bzw. aus deren Benzylester die 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-3-carbonsäure bzw. deren Benzylester.

Beispiel 2

Eine Lösung von 1 g 1-(3-(4-Benzyloxycarbonylaminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäure-tert.-butylester (erhältlich aus 3-(4-Benzyloxycarbonylaminomethylphenyl)-5-chlormethyl-2-oxazolidinon und Piperidin-4-oxyessigsäure-tert.-butylester nach der in Beispiel 3 beschriebenen Methode) in einem Gemisch von 38 ml Methanol, 6 ml Wasser und 6 ml Essigsäure wird an 0,6 g 5%ig. Pd-Kohle bei 20° und 1 bar bis zum Ende der $H_2$-Aufnahme hydriert. Man filtriert, dampft das Filtrat ein und erhält 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäure-tert.-butylester, F. 95-96°, FAB 420.

Beispiel 3

Ein Gemisch von 2,96 g 3-(4-Cyanphenyl)-5-methansulfonyloxymethyl-2-oxazolidinon (F. 162-163°; erhältlich durch Reaktion von 4-Aminobenzonitril mit 2,3-Epoxypropanol zu 4-(2,3-Dihydroxypropyl-amino)-benzonitril (ölig), Umsetzung mit Diethylcarbonat/K-tert.-butylat bei 110° zu 3-(4-Cyanphenyl)-5-hydroxymethyl-2-oxazolidinon (F. 130-131°) und Veresterung mit Methansulfonylchlorid), 1,69 g Piperidin-4-carbonsäureethylester, 70 ml Acetonitril, 1,38 g Kaliumcarbonat und 1,65 g Kaliumiodid wird 25 Std. gekocht. Nach üblicher Aufarbeitung erhält man 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäureethylester ("IA"), FAB 358.

Analog erhält man:

mit Piperidin-4-carbonsäurebenzylester:

1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäurebenzylester, F. 96°, FAB 420;

mit Piperidin-4-carbonsäure-tert.-butylester:

1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester;

mit Piperidin-3-carbonsäureethylester:

1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-carbonsäureethylester;

mit Piperidin-3-carbonsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-carbonsäurebenzylester, FAB 420;
mit Piperidin-3-carbonsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-carbonsäure-tert.-butylester;
mit Piperidin-2-carbonsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-2-carbonsäureethylester;
mit Piperidin-2-carbonsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-2-carbonsäurebenzylester, FAB 420;
mit Piperidin-2-carbonsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-2-carbonsäure-tert.-butylester;
mit Pyrrolidin-2-carbonsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidin-2-carbonsäureethylester;
mit Pyrrolidin-2-carbonsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidin-2-carbonsäurebenzylester;
mit Pyrrolidin-2-carbonsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidin-2-carbonsäure-tert.-butylester;
mit Piperidin-4-essigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-essigsäureethylester;
mit Piperidin-4-essigsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-essigsäurebenzylester;
mit Piperidin-4-essigsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-essigsäure-tert.-butylester;
mit Piperidin-4-oxyessigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäureethylester;
mit Piperidin-4-oxyessigsäurebenzylester: 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyes
sigsäurebenzylester;
mit Piperidin-4-oxyessigsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäure-tert.-butylester, F. 88-89°; FAB 416;
mit Piperidin-3-oxyessigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-oxyessigsäureethylester;
mit Piperidin-3-oxyessigsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-oxyessigsäurebenzylester;
mit Piperidin-3-oxyessigsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-oxyessigsäure-tert.-butylester;
mit Piperazin-1-essigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-4-essigsäureethylester;
mit Piperazin-1-essigsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-4-essigsäurebenzylester;
mit Piperazin-1-essigsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-4-essigsäure-tert.-butylester;
mit Azetidin-3-oxyessigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-azetidin-3-oxyessigsäureethylester;
mit Azetidin-3-oxyessigsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-azetidin-3-oxyessigsäurebenzylester;
mit Azetidin-3-oxyessigsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-azetidin-3-oxyessigsäure-tert.-butylester;
mit 1-Benzylpiperazin-2-carbonsäureethylester:
1-Benzyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäureethylester;
mit 1-Benzylpiperazin-2-carbonsäurebenzylester:
1-Benzyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäurebenzylester;
mit 1-Benzylpiperazin-2-carbonsäure-tert.-butylester:
1-Benzyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure-tert.-butylester.

Analog erhält man aus 3-(4-Cyanphenyl)-5S-methansulfonyloxymethyl-2-oxazolidinon (F. 141-142°; $[\alpha]_D^{20}$ +75,3° (c = 3,9 mg/ml in Methanol); erhältlich durch Reaktion von 4-Aminobenzonitril mit 2R-2,3-Epoxypropanol zu 4-(2S,3-Dihydroxypropylamino)-benzonitril, Umsetzung mit Diethylcarbonat/K-tert.-butylat zu 3-(4-Cyanphenyl)-5S-hydroxymethyl-2-oxazolidinon und Veresterung mit Methansulfonylchlorid) mit Pipe-

ridin-4carbonsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäurebenzylester, F. 87-88°, $[\alpha]_D^{20}$ 43,0° (c = 9,8 mg/ml in Methanol).

Analog erhält man

mit Piperidin-4-carbonsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäureethylester;

mit Piperidin-4-carbonsäure-tert.-butylester:
1-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester.

Analog erhält man aus 3-(4-Cyanphenyl)-5R-methansulfonyloxymethyl-2-oxazolidinon (erhältlich aus 2S-2,3-Epoxypropanol über 4-(2R,3-Dihydroxypropylamino)-benzonitril und 3-(4-Cyanphenyl)-5R-hydroxymethyl-2-oxazolidinon) den 1-(3-(4Cyanphenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidin-4-carbonsäurebenzylester sowie den entsprechenden Ethylester und den entsprechenden tert.-Butylester.

Beispiel 4

Analog Beispiel 3 erhält man aus 3-(4-Dimethylaminomethylphenyl)-5-brommethyl-2-oxazolidinon (erhältlich durch Reaktion von 4-Dimethylaminomethylanilin mit 2,3-Epoxypropanol zu 3-(4-Dimethylaminomethylphenylamino)-1,2-propandiol, Umsetzung mit Diethylcarbonat/K-tert.-butylat zu 3-(4-Dimethylaminomethylphenyl)-5-hydroxymethyl-2-oxazolidinon und Reaktion mit $SOBr_2$) mit Piperidin-4-carbonsäure-tert.-butylester den 1-(3-(4-Dimethylaminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester, FAB 432.

Beispiel 5

Ein Gemisch von 3,31 g 1-(3-(4-Cyanphenyl)-2-hydroxy-propyl)-piperidin-4-carbonsäureethylester (erhältlich durch Reaktion von 3-(4-Cyanphenyl)-1,2-propandiol-1-methansulfonat mit Piperidin-4-carbonsäureethylester), 15 ml Diethylcarbonat und 0,1 g Kalium-tert.-butylat wird 2 Std. bei 110° Badtemperatur gerührt. Man dampft ein, arbeitet wie üblich auf und erhält "IA", FAB 358.

Beispiel 6

Eine Lösung von 201 mg 1-Amidino-3,5-dimethylpyrazol-nitrat in 17 ml Dioxan und 5 ml Wasser wird mit 0,17 ml Ethyl-diisopropylamin versetzt und 15 Min. gerührt. Man gibt dann 375 mg 1-(3-(4-Aminophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester (erhältlich durch Reaktion von 4-Amino-acetanilid mit 2,3-Epoxypropanol zu 4-(2,3-Dihydroxypropylamino)-acetanilid, Umsetzung mit Diethylcarbonat zu 3-(4-Acetamidophenyl)-5-hydroxymethyl-2-oxazolidinon, Umwandlung in das Methansulfonat und Reaktion mit Piperidin-4-carbonsäure-tert.-butylester) hinzu, kocht das Gemisch 45 Std., dampft ein, arbeitet wie üblich auf und erhält 1-(3-(4-Guanidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester.

Analog erhält man aus 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester mit 1-Amidino-3,5-dimethylpyrazol-nitrat den 1-(3-(4-Guanidinomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester, FAB 432.

Beispiel 7

Eine Lösung von 1 g "IA" in 40 ml 10%iger methanolischer $NH_3$-Lösung wird an 0,6 g Raney-Ni bei 20° und 1 bar bis zum Ende der $H_2$-Aufnahme hydriert. Nach Filtrieren und Eindampfen erhält man 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäureethylester, FAB 362.

Analog erhält man durch Hydrierung der entsprechenden Nitrile die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidine:

-4-carbonsäure-tert.-butylester
-3-carbonsäure-ethylester
-3-carbonsäure-tert.-butylester
-2-carbonsäure-ethylester
-2-carbonsäure-tert.-butylester
-4-essigsäureethylester
-4-essigsäure-tert.-butylester
-4-oxyessigsäureethylester

-4-oxyessigsäure-tert.-butylester, F. 95-96°, FAB 420
-3-oxyessigsäureethylester
-3-oxyessigsäure-tert.-butylester;
die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidine:
-2-carbonsäureethylester
-2-carbonsäure-tert.-butylester;
die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazine:
-4-essigsäureethylester
-4-essigsäure-tert.-butylester;
die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-azetidine:
-3-oxyessigsäureethylester
-3-oxyessigsäure-tert.-butylester;
die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-4-benzylpiperazine:
-3-carbonsäureethylester
-3-carbonsäure-tert.-butylester;
die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidine:
-4-carbonsäureethylester
-4-carbonsäure-tert.-butylester;
die folgenden 1-(3-(4-Aminomethylphenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidine:
-4-carbonsäureethylester
-4-carbonsäure-tert.-butylester.

Beispiel 8

In eine Lösung von 3,57 g "IA" in 50 ml Pyridin und 6,6 ml Triethylamin wird bei -10° $H_2S$ eingeleitet (45 Min.). Anschließend rührt man 14 Std. bei 20°, dampft ein, löst den Rückstand in 50 ml Aceton und versetzt mit 9 ml Methyliodid. Nach 6stündigem Rühren bei 20° filtriert man ab, wäscht den Rückstand mit wenig Aceton, löst in 30 ml Methanol, gibt 4,6 g Ammoniumacetat hinzu und rührt 30 Std. bei 20°. Der erhaltene 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäureethylester wird abfiltriert und an Kieselgel chromatographiert (Dichlormethan/Methanol/Essigsäure 70:30:2); F. 200° (Zers.); FAB 375.

Analog erhält man aus den ensprechenden Nitrilen die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidine:
-4-carbonsäurebenzylester, F. 204° (Zers.); FAB 437; Dihydrochlorid, F. 182°
-4-carbonsäure-tert.-butylester
-3-carbonsäureethylester
-3-carbonsäurebenzylester, Acetat, FAB 437
-3-carbonsäure-tert.-butylester
-2-carbonsäureethylester
-2-carbonsäurebenzylester, FAB 437
-2-carbonsäure-tert.-butylester
-4-essigsäureethylester
-4-essigsäurebenzylester, Acetat, F. 206°
-4-essigsäure-tert.-butylester
-4-oxyessigsäureethylester
-4-oxyessigsäurebenzylester
-4-oxyessigsäure-tert.-butylester, F. 187° (Zers.); FAB 433
-3-oxyessigsäureethylester
-3-oxyessigsäurebenzyleser
-3-oxyessigsäure-tert.-butylester;
die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidine:
-2-carbonsäureethylester
-2-carbonsäurebenzylester
-2-carbonsäure-tert.-butylester;
die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperazine:
-4-essigsäureethylester
-4-essigsäurebenzylester, FAB 452
-4-essigsäure-tert.-butylester;

die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-azetidine:
-3-oxyessigsäureethylester
-3-oxyessigsäurebenzylester
-3-oxyessigsäure-tert.-butylester;
die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-benzylpiperazine:
-3-carbonsäureethylester
-3-carbonsäurebenzylester
-3-carbonsäure-tert.-butylester;
die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidine:
-4-carbonsäureethylester
-4-carbonsäurebenzylester
-4-carbonsäure-tert.-butylester;
die folgenden 1-(3-(4-Amidinophenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidine:
-4-carbonsäureethylester
-4-carbonsäurebenzylester
-4-carbonsäure-tert.-butylester.

Beispiel 9

Analog Beispiel 8, aber mit einer äquivalenten Menge Hydroxylammoniumacetat an Stelle von Ammoniumacetat, erhält man aus "IA" den 1-(3-(4-Hydroxyamidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäureethylester.

Beispiel 10

Man löst 1 g 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure-tert.-butylester in 12 ml Dichlormethan, gibt 12 ml Trifluoressigsäure hinzu, läßt 5 Min. stehen, dampft ein, arbeitet wie üblich auf und erhält 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure, FAB 330.

Analog erhält man aus den entsprechenden tert.-Butylestern die folgenden Säuren:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-carbonsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-2-carbonsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidin-2-carbonsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-essigsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-oxyessigsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-4-essigsäure
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-azetidin-3-oxyessigsäure
1-Benzyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure, F. 190 ° (Zers.); FAB 334
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-carbonsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-2-carbonsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidin-2-carbonsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-essigsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäure, F. 135 °; FAB 364
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-oxyessigsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-4-essigsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethy)-azetidin-3-oxyessigsäure
1-Benzyl-4-(3-(4-aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure, F. 265 ° (Zers.); FAB 347; Dihydrochlorid, F. 142 °
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-carbonsäure
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-2-carbonsäure, F. 198 °; FAB 347
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-pyrrolidin-2-carbonsäure
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-essigsäure, F. 256 °
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-oxyessigsäure, Öl, FAB 377
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-oxyessigsäure, F. 167-168 °
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-4-essigsäure, FAB 362
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-azetidin-3-oxyessigsäure

1-Benzyl-4-(3-(4-amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure
1-(3-(4-Guanidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Guanidinomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure, FAB 376
1-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Cyanphenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Aminomethylphenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Amidinomethylphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Amidinomethylphenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidin-4-carbonsäure
1-(3-(4-Dimethylaminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-cabonsäure.

Beispiel 11

Eine Lösung von 1 g 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-cabonsäurebenzylester in 100 ml Methanol, 17 ml Essigsäure und 17 ml Wasser wird an 0,7 g 5%ig. Pd-Kohle bei 20 ° und 1 bar bis zum Stillstand der $H_2$-Aufnahme hydriert. Man filtriert, dampft ein, verreibt mit Diethylether und erhält 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure, F. 265 °; FAB 347; Dihydrochlorid, F. 142 °.

Beispiel 12

Analog Beispiel 11 erhält man durch Hydrierung von 1-Benzyl-4-(3-(4-cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure ("IB"; oder von "IB"-benzylester) die 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-3-carbonsäure.

Die gleiche Substanz ist analog durch Hydrierung von 1-Benzyl-4-(3-(4-aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-2-carbonsäure (oder von deren Benzylester) erhältlich.

Analog erhält man aus "IB"-ethylester bzw. "IB"-tert.-butylester den 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)-piperazin-3-carbonsäureethylester bzw. den 1-(3-(4-Aminomethylphenyl)-2-oxo-5-oxazolidinylmethyl)piperazin-3-carbonsäure-tert.-butylester.

Beispiel 13

Analog Beispiel 3 erhält man aus 3-(4-Cyanphenyl)-5-methansulfonyloxymethyl-2-oxazolidinon:
mit Piperidin-3-essigsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-essigsäurebenzylester, FAB 434
mit 3-(1-Piperazinyl)-propionsäuremethylester:
3-(4-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-1-piperazinyl)-propionsäuremethylester, FAB 373
mit 3-(1-Piperazinyl)-propionsäureethylester:
3-(4-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-1-piperazinyl)-propionsäureethylester, FAB 387
mit 2-Oxopiperazin-1-essigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-3-oxo-piperazin-4-essigsäureethylester, FAB 387
mit 3-(2-Oxo-1-piperazinyl)-propionsäureethylester:
3-(4-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-2-oxo-1-piperazinyl)-propionsäureethylester, FAB 401
mit 4-Hydroxy-piperidin-4-carbonsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxy-piperidin-4-carbonsäureethylester, FAB 374
mit 4-Hydroxy-piperidin-4-esigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxy-piperidin-4-essigsäureethylester, FAB 388
mit 1-Oxa-8-azaspiro[4,5]decan-2-on (= Lacton der 3-(4-Hydroxy-4-piperidinyl)-propionsäure):
8-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-1-oxa-8-azaspiro[4,5]decan-2-on, FAB 356.

Analog erhält man aus 3-(4-Cyanphenyl)-5R- bzw. -5S-methansulfonyloxymethyl-2-oxazolidinon:
mit Piperidin-4-carbonsäurebenzylester:
1-(3-(4-Cyanphenyl)-2-oxo-5R-oxazlidinylmethyl)-piperidin-4-carbonsäurebenzylester
1-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäurebenzylester
mit Piperazin-4-essigsäureethylester:
1-(3-(4-Cyanphenyl)-2-oxo-5R-oxazolidinylmethyl)-piperazin-4-essigsäureethylester, FAB 373
1-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-piperazin-4-essigsäureethylester, FAB 373
mit 3-(1-Piperazinyl)-propionsäurebenzylester:
3-(4-(3-(4-Cyanphenyl)-2-oxo-5R-oxazolidinylmethyl)-1-piperazinyl)-propionsäurebenzylester, F. 90 °

3-(4-(3-(4-Cyanphenyl)-2-oxo-5S-oxazolidinylmethyl)-1-piperazinyl)-propionsäurebenzylester, F. 90 °.

Beispiel 14

Analog Beispiel 8 erhält man aus den entsprechenden Nitrilen (siehe Beispiel 13):
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-3-essigsäurebenzylester, Diacetat, F. 287-288 °
3-(4-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-1-piperazinyl)-propionsäureethylester, F. 206 °
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-3-oxo-piperazin-4-essigsäureethylester, F. 224 °
3-(4-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-2-oxo-1-piperazinyl)-propionsäureethylester, FAB 418
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxy-piperidin-4-carbonsäureethyelster
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxypiperidin-4-essigsäureethylester, Acetat, F. 108 °
8-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-1-oxa-8-azaspiro- [4,5]decan-2-on, FAB 373
1-(3-(4-Amidinophenyl)-2-oxo-5R-oxazolidinylmethyl)-piperidin-4-carbonsäurebenzylester, Acetat, F. 225 ° $[\alpha]_D^{20}$ +40.5 ° (c = 1, Methanol)
1-(3-(4-Amidinophenyl)-2-oxo-5S-oxazolidinylmethyl)-piperidin-4-carbonsäurebenzylester, Acetat, F. 225 °; $[\alpha]_D^{20}$ -41 ° (c = 1, Methanol)
1-(3-(4-Amidinophenyl)-2-oxo-5R-Oxazolidinylmethyl)-piperazin-4-essigsäureethylester, FAB 390
1-(3-(4-Amidinophenyl)-2-oxo-5S-oxazolidinylmethyl)-piperazin-4-essigsäureethylester, FAB 390.

Beispiel 15

Analog Beispiel 9 erhält man aus den entsprechenden Nitrilen:
1-(3-(4-Hydroxyamidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxy-piperidin-4-essigsäureethylester, Acetat, F. 178-180 °
3-(4-(3-(4-Hydroxyamidinophenyl)-2-oxo-5-oxazolidinylmethyl)-1-piperazinyl)-propionsäuremethylester, F. 202 °
3-(4-(3-(4-Hydroxyamidinophenyl)-2-oxo-5R-oxazolidinylmethyl)-1-piperazinyl)-propionsäurebenzylester, F. 159 °
3-(4-(3-(4-Hydroxyamidinophenyl)-2-oxo-5S-oxazolidinylmethyl)-1-piperazinyl)-propionsäurebenzylester, F. 159 °.

Beispiel 16

Ein Gemisch von 1 g 3-(4-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-1-piperazinyl)-propionsäureethylester, 0,2 g NaOH, 8 ml Dioxan und 2 ml Wasser wird bei 20 ° 5 Std. gerührt. Nach Ansäuern und üblicher Aufarbeitung erhält man 3-(4-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-1-piperazinyl)-propionsäure, F. 269 °.
Analog erhält man durch Verseifung der entsprechenden Ester:
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-3-oxo-piperazin-4-essigsäure, Monohydrat, F. 261 °
3-(4-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-2-oxo-1-piperazinyl)-propionsäure, FAB 390
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxy-piperidin-4-carbonsäure
1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-hydroxy-piperidin-4-essigsäure, F. 230 °
1-(3-(4-Amidinophenyl)-2-oxo-5R-oxazolidinylmethyl)-piperazin-4-essigsäure, Acetat, FAB 362; $[\alpha]_D^{20}$ -28,0 ° (c = 1, DMSO)
1-(3-(4-Amidinophenyl)-2-oxo-5S-oxazolidinylmethyl)-piperazin-4-essigsäure, Acetat, FAB 362; $[\alpha]_D^{20}$ +24,0 ° (c = 1, DMSO)

Beispiel 17

a) Man löst 1 g 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-4-methansulfonyloxy-piperidin-4-essigsäureethylester (erhältlich aus der 4-Hydroxy-verbindung (siehe Beispiel 13) mit Methansulfonylchlorid/Pyridin) in einer 2%igen $NH_3$-Lösung in 10 ml eines 1:1-Gemisches von Ethanol und THF und läßt 2 Std. bei 20 ° stehen. Man dampft ein, arbeitet wie üblich auf und erhält 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-4-amino-piperidin-4-essigsäureethylester, FAB 387.

b) Analog Beispiel 8 erhält man daraus den 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-amino-piperidin-4-essigsäureethylester, FAB 404.
c) Analog Beispiel 16 erhält man daraus durch Verseifung 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-amino-piperidin-4-essigsäure, FAB 376.

Beispiel 18

a) Analog Beispiel 17a) erhält man aus 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-4-methansulfonyloxy-piperidin-4-carbonsäureethylester (erhältlich aus der 4-Hydroxy-verbindung (siehe Beispiel 13) mit Methansulfonylchlorid/Pyridin) mit $NH_3$ den 1-(3-(4-Cyanphenyl)-2-oxo-5-oxazolidinylmethyl)-4-amino-piperidin-4-carbonsäureethylester, FAB 373.
b) Analog Beispiel 8 erhält man daraus den 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-amino-piperidin-4-carbonsäureethylester, FAB 390.
c) Analog Beispiel 16 erhält man daraus durch Verseifung 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-4-amino-piperidin-4-carbonsäure, FAB 362

Beispiel 19

Eine Lösung von 1 g 3-(4-(3-(4-Hydroxyamidinophenyl)-2-oxo-5R- bzw. - 5S-oxazolidinylmethyl)-1-piperazinyl)-propionsäurebenzylester (siehe Beispiel 15) in 30 ml Essigsäure unter Zusatz von 1 ml Acetanhydrid wird an 0,2 g 10%ig. Pd-C bei 20° und 1 bar bis zur Aufnahme der berechneten Menge Wasserstoff hydriert. Man filtriert, arbeitet wie üblich auf und erhält:
3-(4-(3-(4-Amidinophenyl)-2-oxo-5R-oxazolidinylmethyl)-1-piperazinyl)-propionsäure, Acetat, F. 200-220° (Zers.); $[\alpha]_D^{20}$ +9° (c = 0,5, DMSO)
bzw.
3-(4-(3-(4-Amidinophenyl)-2-oxo-5S-oxazolidinylmethyl)-1-piperazinyl)-propionsäure, Acetat, F. 200-220° (Zers.); $[\alpha]_D^{20}$ -8° (c = 0,5, DMSO).
Die nachfolgenden Beispiele betreffen pharmazeutische Zubereitungen.

**Beispiel A: Tabletten**

Ein Gemisch von 1 kg Wirkstoff der Formel I, 4 kg Lactose, 1,2 kg Maisstärke, 200 g Talk und 100 g Magnesiumstearat wird in üblicher Weise zu Tabletten verpreßt, derart, daß jede Tablette 100 mg Wirkstoff enthält.

**Beispiel B: Dragees**

Analog Beispiel A werden Tabletten gepreßt, die anschließend in üblicher Weise mit einem Überzug aus Saccharose, Maisstärke, Talk, Tragant und Farbstoff überzogen werden.

**Beispiel C: Kapseln**

500 g Wirkstoff der Formel I werden in üblicher Weise in Hartgelatinekapseln gefüllt, so daß jede Kapsel 500 mg Wirkstoff enthält.

**Beispiel D: Injektionsgläser**

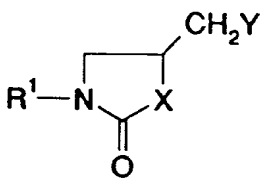
Eine Lösung von 100 g Wirkstoff der Formel I in 4 l zweifach destilliertem Wasser wird mit 2 n Salzsäure auf pH 6,5 eingestellt, steril filtriert und in Injektionsgläser abgefüllt. Man lyophilisiert unter sterilen Bedingungen und verschließt steril. Jedes Injektionsglas enthält 50 mg Wirkstoff.

**Beispiel E: Suppositorien**

Man schmilzt ein Gemisch von 50 g Wirkstoff der Formel I mit 10 g Sojalecithin und 140 g Kakaobutter, gießt in Formen und läßt erkalten. Jedes Suppositorium enthält 250 mg Wirkstoff.

## Patentansprüche

1. Verbindungen der Formel I



I

worin

| | |
|---|---|
| X | O, S, NH oder NA, |
| Y | einen unsubstituierten oder einen einfach durch $R^2$ substituierten Aziridino-, Azetidino-, Pyrrolidino-, Piperidino-, 1-Oxa-8-azaspiro[4,5]decan-8-yl, Hexahydroazepino- oder 4-$R^4$-piperazino-rest, der zusätzlich durch eine Gruppe OZ, SZ oder $N(Z)_2$ und/oder durch Carbonylsauerstoff substituiert sein kann, |
| Z | jeweils H, A, Phenyl-$C_kH_{2k}$- oder Ac, |
| $R^1$ | einen einfach durch CN, $H_2N$-$CH_2$-, $(A)_2N$-$CH_2$-, $H_2N$-C(=NH)-, $H_2N$-C(=NH)-NH-, $H_2N$-C(=NH)-NH-$CH_2$-, HO-NH-C(=NH)- oder HO-NH-C(=NH)-NH substituierten Phenylrest, |
| $R^2$ | -$C_mH_{2m}$-$COOR^3$ oder -$C_nH_{2n}$-O-$C_pH_{2p}$-$COOR^3$, |
| $R^3$ | H, A oder Benzyl, |
| $R^4$ | H, A, Benzyl oder -$C_mH_{2m}$-$COOR^3$, |
| A | jeweils Alkyl mit 1-6 C-Atomen, |
| Ac | Acyl mit 1-11 C-Atomen, |
| k und m | jeweils 0, 1, 2 oder 3, |
| n | 0, 1 oder 2, und |
| p | 1, 2 oder 3 bedeuten, |

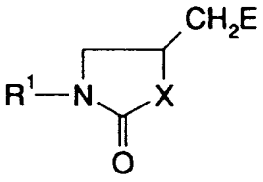
sowie deren Salze.

2. 1-(3-(4-Amidinophenyl)-2-oxo-5-oxazolidinylmethyl)-piperidin-4-carbonsäure.

3. Verfahren zur Herstellung einer Verbindung der Formel I nach Patentanspruch 1 sowie von ihren Salzen, dadurch gekennzeichnet, daß man

(a) eine Verbindung der Formel I aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt, oder daß man

(b) eine Verbindung der Formel II



II

worin

E Cl, Br, I oder eine reaktionsfähig veresterte OH-Gruppe

bedeutet, und

$R^1$ und X die oben angegebenen Bedeutungen haben

mit einer Aminoverbindung der Formel III

H-Y III

worin

Y die oben angegebene Bedeutung hat,
umsetzt, oder daß man
(c) eine Verbindung der Formel IV

$R^1$-NH-$CH_2$-CH(XH)-$CH_2$-Y IV

worin
$R^1$, X und Y die oben angegebenen Bedeutungen haben, oder eines ihrer reaktionsfähigen Derivate mit einem reaktiven Derivat der Kohlensäure umsetzt, oder daß man
(d) zur Herstellung einer Guanidinoverbindung der Formel I ($R^1$ = einfach durch $H_2N$-C(=NH)-NH-substituierter Phenylrest) eine Aminoverbindung entsprechend der Formel I, die jedoch an Stelle des Restes $R^1$ eine Aminophenylgruppe enthält, mit einem amidinierenden Mittel behandelt,
und/oder daß man in einer Verbindung der Formel I einen oder beide Reste $R^1$ und/oder Y in (einen) andere(n) Rest(e) $R^1$ und/oder Y umwandelt und/oder eine Verbindung der Formel I durch Behandeln mit einer Säure oder einer Base in eines ihrer Salze überführt.

**4.** Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Anspruch 1 und/oder eines ihrer physiologisch unbedenklichen Salze zusammen mit mindestens einem festen, flüssigen oder halbflüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform bringt.

**5.** Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt an mindestens einer Verbindung der Formel I nach Anspruch 1 und/oder einem ihrer physiologisch unbedenklichen Salze.

**6.** Verwendung von Verbindungen der Formel I nach Anspruch 1 oder von deren physiologisch unbedenklichen Salzen zur Herstellung eines Arzneimittels.

**7.** Verwendung von Verbindungen der Formel I nach Anspruch 1 oder von deren physiologisch unbedenklichen Salzen bei der Bekämpfung von Thrombosen, Herzinfarkten, Apoplexie, Osteoporose, Arteriosklerose, Entzündungen und/oderTumoren.

Europäisches Patentamt

# EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung
EP 94 10 6049

## EINSCHLÄGIGE DOKUMENTE

| Kategorie | Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile | Betrifft Anspruch | KLASSIFIKATION DER ANMELDUNG (Int.Cl.5) |
|---|---|---|---|
| X | EP-A-0 300 272 (MERCK PATENT GMBH)<br>* Ansprüche *<br>--- | 1,3-7 | C07D413/06<br>C07D263/20<br>A61K31/42 |
| X | DE-A-19 51 273 (DELALANDE S.A.)<br>* Ansprüche *<br>--- | 1,3-7 | A61K31/495<br>C07D491/10<br>//(C07D491/10,<br>307:00,221:00) |
| A | EP-A-0 443 197 (MERCK PATENT GMBH)<br>* Ansprüche *<br>----- | 1,3-7 | |

RECHERCHIERTE SACHGEBIETE (Int.Cl.5)

C07D

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

| Recherchenort | Abschlußdatum der Recherche | Prüfer |
|---|---|---|
| DEN HAAG | 22. Juli 1994 | Henry, J |

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur

T : der Erfindung zugrunde liegende Theorien oder Grundsätze
E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

EPO FORM 1503 03.82 (P04C03)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 645 376 A1**

# (12) EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: **94114519.5**

(22) Anmeldetag: **15.09.94**

(51) Int. Cl.[6]: **C07D 263/24**, C07D 413/12, A61K 31/42

(30) Priorität: **23.09.93 DE 4332384**

(43) Veröffentlichungstag der Anmeldung:
**29.03.95 Patentblatt 95/13**

(84) Benannte Vertragsstaaten:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE**

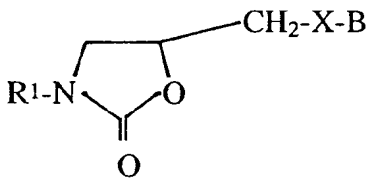
(71) Anmelder: **MERCK PATENT GmbH**
**Frankfurter Strasse 250**
**D-64293 Darmstadt (DE)**

(72) Erfinder: **Gante, Joachim, Prof. Dr.**
**Stormstrasse 4**
**D-64291 Darmstadt (DE)**

Erfinder: **Juraszyk, Horst, Dr.**
**Kleiner Ring 14**
**D-64342 Seeheim (DE)**
Erfinder: **Raddatz, Peter, Dr.**
**Akazienweg 8A**
**D-64342 Seeheim (DE)**
Erfinder: **Wurziger, Hanns, Dr.**
**Greinstrasse 7b**
**D-64291 Darmstadt (DE)**
Erfinder: **Melzer, Guido**
**Mörikestrasse 6**
**D-65719 Hofheim/Ts. (DE)**
Erfinder: **Bernotat-Danielowski, Sabine, Dr.**
**Liebigstrasse 5**
**D-61231 Bad Nauheim (DE)**

## (54) Substituierte 1-Phenyl-oxazolidin-2-on Derivate deren Herstellung und der Verwendung als Adhäsionsrezeptor-Antagonisten.

(57) Neue Oxazolidinonderivate der Formel I



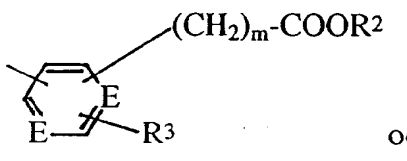
I,

worin

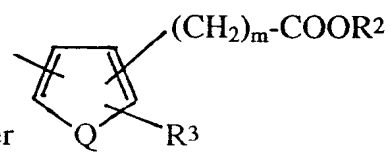
$R^1$ einen unsubstituierten oder einfach durch CN, $H_2N$-$CH_2$-, $A_2N$-$CH_2$-, $H_2N$-C(=NH)-, $H_2N$-C(=NH)-NH-, $H_2N$-C(=NH)-NH-$CH_2$-, HO-NH-C(=NH)- oder HO-NH-C(=NH)-NH- substituierten Phenylrest,

X O, S, SO, $SO_2$, -NH- oder -NA-,

B



oder



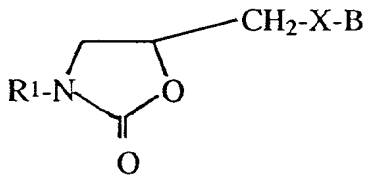
A Alkyl mit 1 bis 6 C-Atomen,

EP 0 645 376 A1

$R^2$ H, A, Li, Na, K, $NH_4$ oder Benzyl,
$R^3$ H oder $(CH_2)_n$-$COOR^2$,
E jeweils unabhängig voneinander CH oder N,
Q O, S oder NH
m 1, 2 oder 3 und
n 0, 1, 2 oder 3 bedeuten,

sowie deren physiologisch unbedenkliche Salze, hemmen die Bindung von Fibrinogen an den entsprechenden Rezeptor und können zur Behandlung von Thrombosen, Apoplexie, Herzinfarkt, Entzündungen, Arteriosklerose, Osteoporose sowie von Tumoren verwendet werden.

Die Erfindung betrifft Oxazolidinonderivate der Formel I



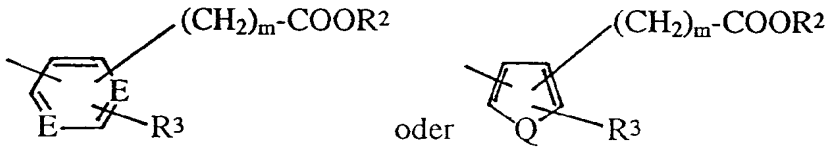
I,

worin

$R^1$ einen unsubstituierten oder einfach durch CN, $H_2N$-$CH_2$-, $A_2N$-$CH_2$-, $H_2N$-C(=NH)-, $H_2N$-C(=NH)-NH-, $H_2N$-C(=NH)-NH-$CH_2$-, HO-NH-C(=NH)- oder HO-NH-C(=NH)-NH- substituierten Phenylrest,

X O, S, SO, $SO_2$, -NH- oder -NA-,

B



A Alkyl mit 1 bis 6 C-Atomen,

$R^2$ H, A, Li, Na, K, $NH_4$ oder Benzyl,

$R^3$ H oder $(CH_2)_n$-$COOR^2$,

E jeweils unabhängig voneinander CH oder N,

Q O, S oder NH

m 1, 2 oder 3 und

n 0, 1, 2 oder 3 bedeuten,

sowie deren physiologisch unbedenkliche Salze.

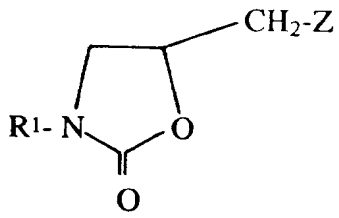
Ähnliche Verbindungen sind aus der EP-A1-0 381 033 bekannt.

Der Erfindung lag die Aufgabe zugrunde, neue Verbindungen mit wertvollen Eigenschaften aufzufinden, insbesondere solche, die zur Herstellung von Arzneimitteln verwendet werden können.

Diese Aufgabe wurde durch die Erfindung gelöst. Es wurde gefunden, daß die Verbindungen der Formel I sowie ihre Solvate und Salze bei guter Verträglichkeit wertvolle pharmakologische Eigenschaften besitzen. Insbesondere hemmen sie die Bindung von Fibrinogen, Fibronectin und des von Willebrand-Faktors an den Fibrinogenrezeptor der Blutplättchen (Glykoprotein IIb/IIIa) als auch die Bindung derselben und weiterer adhäsiver Proteine, wie Vitronectin, Kollagen und Laminin, an die entsprechenden Rezeptoren auf der Oberfläche verschiedener Zelltypen. Die Verbindungen beeinflussen somit Zell-Zell- und Zell-Matrix-Wechselwirkungen. Sie verhindern insbesondere die Entstehung von Blutplättchenthromben und können daher zur Behandlung von Thrombosen, Apoplexie, Herzinfarkt, Entzündungen, Arteriosklerose verwendet werden. Ferner haben die Verbindungen einen Effekt auf Tumorzellen, indem sie deren Metastasierung hemmen. Somit können sie auch als Anti-Tumor-Mittel eingesetzt werden.

Die Eigenschaften der Verbindungen können nach Methoden nachgewiesen werden, die in der EP-A1-0 462 960 beschrieben sind. Die Hemmung der Fibrinbindung an den Fibrinogenrezeptor kann nach der Methode nachgewiesen werden, die in der EP-A1-0 381 033 angegeben ist. Die thrombozytenaggregationshemmende Wirkung läßt sich in vitro nach der Methode von Born (Nature 4832, 927-929, 1962) nachweisen.

Gegenstand der Erfindung ist ferner ein Verfahren zur Herstellung einer Verbindung der angegebenen Formel I sowie von deren Salzen, dadurch gekennzeichnet, daß man eine Verbindung der Formel II



II,

worin

$R^1$ die in Anspruch 1 angegebene Bedeutung hat

und

Z Cl, Br, I, OH oder eine reaktionsfähig veresterte OH-Gruppe bedeutet

mit einer Verbindung der Formel III

Y-B III,

worin

B die oben angegebene Bedeutung hat

und

Y OH, SH, $NH_2$, NAH oder einen aus OH oder SH ableitbaren salzartigen Rest bedeuten,

umsetzt, oder daß man

eine Verbindung der Formel IV

$R^1$-NH-$CH_2$-CH(OH)-$CH_2$-X-B IV,

worin

$R^1$, B und X die oben angegebenen Bedeutungen haben, oder eines ihrer reaktionsfähigen Derivate mit einem reaktiven Derivat der Kohlensäure umsetzt,

oder daß man zur Herstellung einer Guanidinoverbindung der Formel I ($R^1$ = ein einfach durch $H_2N$-C(=NH)-NH- substituierter Phenylrest) eine Aminoverbindung entsprechend der Formel I, die jedoch anstelle des Restes $R^1$ eine Aminophenylgruppe enthält, mit einem amidinierenden Mittel behandelt,

oder daß man eine Verbindung der Formel I aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt,

und/oder daß man in einer Verbindung der Formel I einen oder beide Reste $R^1$ und/oder B in (einen) andere(n) Rest(e) $R^1$ und/oder B umwandelt und/oder eine Verbindung der Formel I durch Behandeln mit einer Säure oder einer Base in eines ihrer Salze überführt.

Die Verbindungen der Formel I besitzen mindestens ein chirales Zentrum und können daher in mehreren enantiomeren Formen auftreten. Alle diese Formen (z.B. D- und L-Formen) und deren Gemische (z.B. die DL-Formen) sind in der Formel I eingeschlossen.

Vor- und nachstehend haben die Reste bzw. Parameter B, X, $R^1$ bis $R^3$, A, E, Q, Y, Z, m und n die bei den Formeln I, II oder III angegebenen Bedeutungen haben, falls nicht ausdrücklich etwas anderes angegeben ist.

In den vorstehenden Formeln hat die Gruppe A 1-6, vorzugsweise 1,2,3 oder 4 C-Atome. Im einzelnen bedeutet A vorzugsweise Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, sek.-Butyl oder tert.-Butyl, ferner auch Pentyl, 1-, 2- oder 3-Methylbutyl, 1,1-, 1,2- oder 2,2-Dimethylpropyl, 1-Ethylpropyl, Hexyl, 1-, 2-, 3- oder 4-Methylpentyl.

X ist vorzugsweise O, aber auch S, NH oder NA, z.B. N-$CH_3$ oder auch SO sowie $SO_2$.

$R^1$ ist vorzugsweise ein in 4-Stellung, aber auch in 2- oder 3-Stellung wie oben angegeben substituierter Phenylrest, im einzelnen bevorzugt 2-, 3- oder insbesondere 4-Amidinophenyl; 2-, 3- oder 4-Aminomethylphenyl; 2-, 3- oder 4-Guanidinomethylphenyl; 2-, 3- oder 4-Cyanphenyl oder aber 2-, 3- oder 4-N-Alkylaminomethylphenyl, wobei in diesen Fällen Alkyl vorzugsweise für Methyl oder Ethyl steht.

B ist vorzugsweise ein- oder zweifach substituiertes Phenyl oder Pyrrolyl oder aber einfach substituiertes Thienyl, ferner auch Pyridinyl, Furanyl oder Pyrimidinyl in unsubstituierter oder substituierter Form, wobei die genannten Substituenten möglich sind. Im einzelnen steht B bevorzugt für 2-, 3- oder 4-Carboxymethyl-, 2-, 3- oder 4-Methoxycarbonyl oder -Ethoxycarbonyl-phenyl, ferner auch vorzugsweise für 2-Carboxymethyl-thien-4-yl, 2-Carboxymethylpyrrol-4-yl, 3-Carboxy-methylpyrrol-4-yl, 2,5-Dicarboxymethyl-

oder 2,3-Dicarboxymethylpyrrol-4-yl, 2-Carboxymethyl-3-carboxy- oder 2-Carboxymethyl-5-carboxy-pyrrol-4-yl,2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-Dicarboxymethylphenyl sowie Vorzugsweise auch für die Methyl- oder Ethylester der zuvor genannten bevorzugten Reste und auch für die daraus ableitbaren Li-, Na-, K- oder Ammoniumsalzreste.

$R^2$ bedeutet vorzugsweise Wasserstoff, A oder Na, während $R^3$ besonders bevorzugt für H oder Carboxymethyl steht. E bedeutet bevorzugt CH, und Q ist vorzugsweise S oder NH.

Die Parameter m und n sind bevorzugt 1, ferner aber auch 2 oder 3. Die Variable n kann darüber hinaus auch 0 sein.

Unter den Verbindungen der Formel I sind diejenigen bevorzugt, in denen mindestes einer der angegebenen Reste, Gruppen und/oder Parameter eine der angegebenen bevorzugten Bedeutungen hat. Einige Gruppen Von bevorzugten Verbindungen sind diejenigen der Formeln Ia bis Ij, die der Formel I entsprechen, worin jedoch

in Ia
- X O bedeutet;

in Ib
- X O und
- B 2-, 3- oder 4-Carboxymethylphenyl bedeutet;

in Ic
- X O und
- $R^1$ 2-, 3- oder 4-Amidinophenyl bedeutet;

in Id
- X NH oder NA und
- $R^1$ 2-, 3- oder 4-Amidinophenyl bedeutet;

in Ie
- X S und
- $R^1$ 2-, 3- oder 4-Amidinophenyl bedeutet;

in If
- X O und
- B 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Dicarboxymethylphenyl bedeutet;

in Ig
- X O und
- B 2-Carboxymethyl- oder 3-Carboxymethyl-thien-4-yl oder - pyrrol-4-yl bedeutet;

in Ih
- X O und
- B 2,3- oder 2,5-Dicarboxymethyl- oder 2-Carboxymethyl-3-carboxy- bzw. 2-Carboxymethyl-5-carboxy-pyrrol-4-yl bedeutet;

in Ii
- X O,
- B 2-, 3- oder 4-Carboxyphenyl und
- $R^1$ 2-, 3- oder 4-Amidinophenyl bedeutet;

in Ij
- X O,
- B 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Dicarboxymethylphenyl und
- $R^1$ 2-, 3- oder 4-Amidinophenyl bedeutet.

Ferner sind bevorzugt Verbindungen, die an sich den Formeln Ia bis Ij entsprechen, worin aber die Carboxygruppe des Restes B durch eine Methoxycarbonyl- oder Ethoxycarbonylgruppe ersetzt ist.

Die Verbindungen der Formel I und auch die Ausgangsstoffe zu ihrer Herstellung werden im übrigen nach an sich bekannten Methoden hergestellt wie sie in der Literatur (z.B. in den Standardwerken wie Houben-Weyl, Methoden der organischen Chemie, Georg-Thieme-Verlag, Stuttgart; ferner EP-A1-0381033, EP-A1-0462960) beschrieben sind, und zwar unter Reaktionsbedingungen, die für die genannten Umsetzungen bekannt und geeignet sind. Dabei kann man auch von an sich bekannten, hier nicht näher erwähnten Varianten Gebrauch machen.

Die Ausgangsstoffe können, falls erwünscht, auch in situ gebildet werden, so daß man sie aus dem Reaktionsgemisch nicht isoliert, sondern sofort weiter zu den Verbindungen der Formel I umsetzt.

Die Verbindungen der Formel I können erhalten werden, indem man sie aus ihren funktionellen Derivaten durch Solvolyse, insbesondere Hydrolyse, oder durch Hydrogenolyse in Freiheit setzt.

Bevorzugte Ausgangsstoffe für die Solvolyse bzw. Hydrogenolyse sind solche, die sonst der Formel I entsprechen, aber anstelle einer oder mehrerer freier Amino- und/oder Hydroxygruppen entsprechende

geschützte Amino- und/oder Hydroxygruppen enthalten, Vorzugsweise solche, die anstelle eines H-Atoms, das mit einem N-Atom verbunden ist, eine Aminoschutzgruppe tragen, insbesondere solche, die anstelle einer HN-Gruppe eine R'-N-Gruppe tragen, worin R' eine Aminoschutzgruppe bedeutet, und/oder solche, die an Stelle des H-Atoms einer Hydroxygruppe eine Hydroxyschutzgruppe tragen, z.B. solche, die der Formel I entsprechen, jedoch anstelle einer Gruppe -COOH eine Gruppe -COOR'' tragen, worin R'' eine Hydroxyschutzgruppe bedeutet.

Es können auch mehrere - gleiche oder Verschiedene - geschützte Amino- und/oder Hydroxygruppen im Molekül des Ausgangsstoffes vorhanden sein. Falls die vorhandenen Schutzgruppen Voneinander verschieden sind, können sie in vielen Fällen selektiv abgespalten werden.

Der Ausdruck "Aminoschutzgruppe" ist allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Aminogruppe vor chemischen Umsetzungen zu schützen (zu blockieren), die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an einer anderen Stelle des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind insbesondere unsubstituierte oder substituierte Acyl-, Aryl- (z.B. 2,4-Dinitrophenyl (DNP)), Aralkoxymethyl- (z.B. Benzyloxymethyl (BOM)) oder Aralkylgruppen (z.B. Benzyl, 4-Nitrobenzyl, Triphenylmethyl). Da die Aminoschutzgruppen nach der gewünschten Reaktion (oder Reaktionsfolge) entfernt werden, ist ihre Art und Größe im übrigen nicht kritisch; bevorzugt werden jedoch solche mit 1-20, insbesondere 1-8 C-Atomen. Der Ausdruck "Acylgruppe" ist im Zusammenhang mit dem vorliegenden Verfahren im weitesten Sinne aufzufassen. Er umschließt von aliphatischen, araliphatischen, aromatischen oder heterocyclischen Carbonsäuren oder Sulfonsäuren abgeleitete Acylgruppen sowie insbesondere Alkoxycarbonyl-, Aryloxycarbonyl und vor allem Aralkoxycarbonylgruppen. Beispiele für derartige Acylgruppen sind Alkanoyl wie Acetyl, Propionyl, Butyryl; Aralkanoyl wie Phenylacetyl; Aroyl wie Benzoyl oder Toloyl; Aryloxyalkanoyl wie Phenoxyacetyl; Alkoxycarbonyl wie Methoxycarbonyl, Ethoxycarbonyl, 2,2,2-Trichlorethoxycarbonyl, Isopropoxycarbonyl, tert.-Butoxycarbonyl (BOC), 2-Jodethoxycarbonyl; Aralkyloxycarbonyl wie Benzyloxycarbonyl (CBZ), 4-Methoxybenzyloxycarbonyl, 9-Fluorenylmethoxycarbonyl(FMOC). Bevorzugte Aminoschutzgruppen sind BOC, DNP und BOM, ferner CBZ, Benzyl und Acetyl.

Der Ausdruck "Hydroxyschutzgruppe" ist ebenfalls allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Hydroxygruppe vor chemischen Umsetzungen zu schützen, die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an einer anderen Stelle des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind die oben genannten unsubstituierten oder substituierten Aryl-, Aralkyl- oder Acylgruppen, ferner auch Alkylgruppen. Die Natur und Größe der Hydroxyschutzgruppen ist nicht kritisch, da sie nach der gewünschten chemischen Reaktion oder Reaktionsfolge wieder entfernt werden; bevorzugt sind Gruppen mit 1-20, insbesondere 1-10 C-Atomen. Beispiele für Hydroxyschutzgruppen sind u.a. tert.-Butyl, Benzyl, p-Nitrobenzoyl, p-Toluolsulfonyl und Acetyl, wobei Benzyl und Acetyl besonders bevorzugt sind.

Die als Ausgangsstoffe zu verwendenden funktionellen Derivate der Verbindungen der Formel I können nach üblichen Methoden hergestellt werden, wie sie z.B. in den genannten Standardwerken und Patentanmeldungen beschrieben sind, z.B. durch Umsetzung von Verbindungen, die den Formeln II und III entsprechen, wobei jedoch mindestens eine dieser Verbindungen eine Schutzgruppe anstelle eines H-Atoms enthält.

Das In-Freiheit-Setzen der Verbindungen der Formel I aus ihren funktionellen Derivaten gelingt - je nach der benutzten Schutzgruppe - z.B. mit starken Säuren, zweckmäßig mit Trifluoressigsäure oder Perchlorsäure, aber auch mit anderen starken anorganischen Säuren wie Salzsäure oder Schwefelsäure, starken organischen Carbonsäuren wie Trichloressigsäure oder Sulfonsäuren wie Benzol- oder p-Toluolsulfonsäure. Die Anwesenheit eines zusätzlichen inerten Lösungsmittels ist möglich, aber nicht immer erforderlich.

Als inerte Lösungsmittel eignen sich Vorzugsweise organische, beispielsweise Carbonsäuren wie Essigsäure, Ether wie Tetrahydrofuran Oder Dioxan, Amide wie Dimethylformamid (DMF), halogenierte Kohlenwasserstoffe wie Dichlormethan, ferner auch Alkohole wie Methanol, Ethanol oder Isopropanol sowie Wasser. Ferner kommen Gemische der Vorgenannten Lösungsmittel in Frage. Trifluoressigsäure wird vorzugsweise im Überschuß ohne Zusatz eines weiteren Lösungsmittels verwendet, Perchlorsäure in Form eines Gemisches aus Essigsäure und 70%iger Perchlorsäure im Verhältnis 9:1. Die Reaktionstemperaturen für die Spaltung liegen zweckmäßig zwischen etwa 0 und etwa 50°; Vorzugsweise arbeitet man zwischen 15 und 30° (Raumtemperatur).

Die BOC-Gruppe kann z.B. bevorzugt mit 40%iger Trifluoressigsäure in Dichlormethan oder mit etwa 3 bis 5 n HCl in Dioxan bei 15-60° abgespalten weden, die FMOC-Gruppe mit einer etwa 5-20%igen Lösung von Dimethylamin, Diethylamin oder Piperidin in DMF bei 15-50°. Eine Abspaltung der DNP-Gruppe gelingt z.B. auch mit einer etwa 3-10%igen Lösung von 2-Mercaptoethanol in DMF/Wasser bei 15-30°.

Hydrogenolytisch entfernbare Schutzgruppen (z.B. BOM, CBZ oder Benzyl) können z.B. durch Behandeln mit Wasserstoff in Gegenwart eines Katalysators (z.B. eines Edelmetallkatalysators wie Pälladium, zweckmäßig auf einem Träger wie Kohle) abgespalten werden. Als Lösungsmittel eignen sich dabei die oben angegebenen, insbesondere z.B. Alkohole wie Methanol oder Ethanol oder Amide wie DMF. Die Hydrogenolyse wird in der Regel bei Temperaturen zwischen etwa 0 und 100 ° und Drucken zwischen etwa 1 und 200 bar, bevorzugt bei 20-30 ° und 1-10 bar durchgeführt. Eine Hydrogenolyse der CBZ-Gruppe gelingt z.B. gut an 5-10%igem Pd-C in Methanol bei 20-30 °.

Verbindungen der Formel I können bevorzugt auch durch Reaktion eines Oxazolidinons der Formel II mit einer Verbindung der Formel III erhalten werden. Dabei bedient man sich zweckmäßig der an sich bekannten Methoden der Veretherung oder der N-Alkylierung von Aminen.

Die Abgangsgruppe Z der Formel II bedeutet Vorzugsweise Cl, Br, I, $C_1$- bis $C_6$-Alkylsulfonyloxy wie Methan- oder Ethansulfonyloxy oder $C_6$-$C_{10}$-Arylsulfonyloxy wie Benzol-, p-Toluol- oder 1 - oder 2-Naphthalinsulfonyloxy.

Die Reaktion gelingt vorzugsweise in Gegenwart einer zusätzlichen Base, z.B. eines Alkali- oder Erdalkalimetall-hydroxids oder carbonats wie Natrium-, Kalium- oder Calciumhydroxid, Natrium-, Kalium- oder Calciumcarbonat, in einem inerten Lösungsmittel z.B. einem halogenierten Kohlenwasserstoff wie Dichlormethan, einem Ether wie THF oder Dioxan, einem Amid wie DMF oder Dimethylacetamid, einem Nitril wie Acetonitril, bei Temperaturen zwischen etwa -10 und 200, vorzugsweise zwischen 0 und 120 °. Falls die Fluchtgruppe Z von I verschieden ist, empfiehlt sich ein Zusatz eines Iodids wie Kaliumiodid.

Die Ausgangsstoffe der Formel II sind in der Regel neu. Sie können z.B. hergestellt werden durch Reaktion eines substituierten Anilins der Formel $R^1$-$NH_2$, worin $R^1$ die angegebene Bedeutung hat, mit einer Verbindung der Formel $R^5CH_2$-$CHR^6$-$CH_2OH$ (worin $R^5$ Z, $R^6$ $OR^7$, $R^7$ eine Schutzgruppe, $R^5$ und $R^6$ zusammen auch O bedeuten) zu einer Verbindung der Formel $R^1$-NH-$CH_2$-$CHR^8$-$CH_2OH$ (worin $R^8$ $OR^7$ oder OH bedeutet), gegebenenfalls Abspaltung der Schutzgruppe $R^7$ zu Verbindungen der Formel $R^1$-NH-$CH_2$-CH(OH)-$CH_2OH$, Reaktion mit einem Derivat der Kohlensäure wie Diethylcarbonat zu 3-$R^1$-5-hydroxymethyl-2-oxazolidinonen und Umwandlung der Hydroxymethylgruppe in eine $CH_2Z$-Gruppe, z.B. mit $SOCl_2$, $SOBr_2$, Methansulfonylchlorid oder p-Toluolsulfonylchlorid. Die Verbindungen der Formel Y-B (III) sind in der Regel bekannt oder in Analogie zu bekannten Verbindungen herstellbar.

Verbindungen der Formel I können ferner erhalten werden durch Reaktion einer Verbindung der Formel IV (oder eines reaktionsfähigen Derivats davon) mit einem reaktiven Derivat der Kohlensäure.

Als Kohlensäurederivate eignen sich insbesondere Dialkylcarbonate wie Diethylcarbonat, ferner auch Chlorameisensäurealkylester wie Ethylchlorformiat. Bevorzugt dient das Kohlensäurederivat, das zweckmäßig im Überschuß eingesetzt wird, auch als Lösungs- bzw. Suspensionsmittel. Es kann aber auch eines der angegebenen Lösungsmittel anwesend sein, sofern es bei dieser Umsetzung inert ist. Weiterhin empfiehlt sich der Zusatz einer Base, insbesondere eines Alkalimetallalkoholats wie Kalium-tert.-butylat. Man arbeitet zweckmäßig bei Reaktionstemperaturen zwischen 0 und 150 °, vorzugsweise zwischen 70 und 120 °.

Die Ausgangsstoffe der Formel IV sind in der Regel neu. Sie sind z.B. erhältlich durch Funktionalisierung der oben genannten Verbindungen der Formel $R^1$-NH-$CH_2$-CH(OH)-$CH_2OH$ zu Verbindungen der Formel $R^1$-NH-$CH_2$-CH(OH)-$CH_2$-Zund Reaktion mit Verbindungen der Formel B-Y (III).

Zur Herstellung von Verbindungen der Formel I, worin $R^1$ eine Guanidinophenylgruppe bedeutet kann man eine entsprechende Aminophenylverbindung mit einem amidinierenden Mittel behandeln. Als amidinierendes Mittel ist 1-Amidino-3,5-dimethylpyrazol bevorzugt, das insbesondere in Form seines Nitrats eingesetzt wird. Man arbeitet zweckmäßig unter Zusatz einer Base wie Triethylamin oder Ethyl-diisopropylamin in einem inerten Lösungsmittel oder Lösungsmittelgemisch, z.B. Wasser/Dioxan bei Temperaturen zwischen 0 und 120 °, vorzugsweise 60 und 120 °.

Weiterhin ist es möglich, in einer Verbindung der Formel I einen oder beide der Reste $R^1$ und/oder B in (einen) andere(n) Rest(e) $R^1$ und/oder B umzuwandeln.

Insbesondere kann man Cyangruppen zu Aminomethylgruppen reduzieren oder in Amidinogruppen umwandeln, Carboxylgruppen verestern, Estergruppen spalten, Benzylgruppen hydrogenolytisch entfernen, Aminomethylgruppen in Guanidinomethylgruppen überführen.

Eine Reduktion von Cyangruppen zu Aminomethylgruppen gelingt zweckmäßigerweise durch katalytische Hydrierung, z. B. an Raney-Nickel bei Temperaturen zwischen 0 und 100 °, vorzugsweise 10 und 30 °, und Drucken zwischen 1 und 200 bar, vorzugsweise bei Normaldruck, in einem inerten Lösungsmittel, z.B. einem niederen Alkohol wie Methanol oder Ethanol, zweckmäßig in Gegenwart von Ammoniak. Arbeitet man z.B. bei etwa 20 ° und 1 bar, so bleiben im Ausgangsmaterial vorhandene Benzylester- oder N-Benzylgruppen erhalten. Will man diese hydrogenolytisch spalten, so verwendet man zweckmäßig einen Edelmetallkatalysator, vorzugsweise Pd-Kohle, wobei man der Lösung eine Säure wie Essigsäure sowie auch Wasser zusetzen kann.

Zur Herstellung eines Amidins der Formel I ($R^1$ = Amidinophenyl) kann man an ein Nitril der Formel I ($R^1$ = Cyanphenyl) Ammoniak anlagern. Die Anlagerung erfolgt bevorzugt mehrstufig, indem man in an sich bekannter Weise a) das Nitril mit $H_2S$ in ein Thioamid umwandelt, das mit einem Alkylierungsminel, z.B. $CH_3I$, in den entsprechenden S-Alkyl-imidothioester übergeführt wird, welcher seinerseits mit $NH_3$ zum Amidin reagiert, b) das Nitril mit einem Alkohol, z.B. Ethanol in Gegenwart von HCl in den entsprechenden Imidoester umwandelt und diesen mit Ammoniak behandelt, oder c) das Nitril mit Lithium- bis-(trimethylsilyl)amid umsetzt und das Produkt anschließend hydrolysiert.

Analog sind die entsprechenden N-Hydroxy-amidine der Formel I ($R^1$ = durch HO-NH-C(=NH)-substituiertes Phenyl) aus den Nitrilen erhältlich, wenn man nach a) oder b), aber mit Hydroxylamin anstelle von Ammoniak arbeitet.

Zur Veresterung kann man eine Säure der Formel I ($R^2$ = H) mit einem Überschuß eines Alkohols der Formel $R^2$-OH ($R^2$ = A oder Benzyl) behandeln, zweckmäßig in Gegenwart einer starken Säure wie Salzsäure oder Schwefelsäure bei Temperaturen zwischen 0 und 100, vorzugsweise 20 und 50°.

Umgekehrt kann ein Ester der Formel I ($R^2$ = A oder Benzyl), in die entsprechende Säure der Formel I ($R^2$ = H) umgewandelt werden, zweckmäßig durch Solvolyse nach einer der oben angegebenen Methoden, z.B. mit NaOH oder KOH in Wasser-Dioxan bei Temperaturen zwischen 0 und 40°, vorzugsweise 10 und 30°.

Eine Base der Formel I kann mit einer Säure in das zugehörige Säureadditionssalz übergeführt werden. Für diese Umsetzung kommen insbesondere Säuren in Frage, die physiologisch unbedenkliche Salze liefern. So können anorganische Säuren verwendet werden, z.B. Schwefelsäure, Salpetersäure, Halogenwasserstoffsäuren wie Chlorwasserstoffsäure oder Bromwasserstoffsäure, Phosphorsäuren wie Orthophosphorsäure, Sulfaminsäure, ferner organische Säuren, insbesondere aliphatische, alicyclische, araliphatische, aromatische oder heterocyclische ein- oder mehrbasige Carbon-, Sulfon- oder Schwefelsäuren, z.B. Ameisensäure, Essigsäure, Trifluoressigsäure, Propionsäure, Pivalinsäure, Diethylessigsäure, Malonsäure, Bernsteinsäure, Pimelinsäure, Fumarsäure, Maleinsäure, Milchsäure, Weinsaure, Äpfelsäure, Citronensäure, Gluconsäure, Ascorbinsäure, Nicotinsäure, Isonicotinsäure, Methan- oder Ethansulfonsäure, Ethandisulfonsäure, 2-Hydroxyethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Naphthalin-mono- und -disulfonsäuren, Laurylschwefelsäure. Salze mit physiologisch nicht unbedenklichen Säuren, z.B. Pikrate, können zur Isolierung und/oder Aufreinigung der Verbindungen der Formel I verwendet werden.

Die freien Basen der Formel I können falls gewünscht, aus ihren Salzen durch Behandlung mit Starken Basen wie Natrium- oder Kaliumhydroxid, Natrium- oder Kaliumcarbonat in Freiheit gesetzt werden.

Es ist auch möglich, Carbonsäuren der Formel I ($R^2$ = H) durch Umsetzung mit entsprechenden Basen in ihre Metall- oder Ammoniumsalze umzuwandeln, z.B. ihre Natrium-, Kalium- oder Calciumsalze.

Die Verbindungen der Formel I enthalten ein oder mehrere chirale Zentren und können daher in racemischer oder in optisch-aktiver Form vorliegen. Erhaltene Racemate können nach an sich bekannten Methoden mechanisch oder chemisch in die Enantiomeren getrennt werden. Vorzugsweise werden aus dem racemischen Gemisch durch Umsetzung mit einem optisch-aktiven Trennmittel Diastereomere gebildet. Als Trennmittel eignen sich z.B. optisch aktive Säuren, wie die D- und L-Formen von Weinsäure, Diacetylweinsäure, Dibenzoylweinsäure, Mandelsäure, Äpfelsäure, Milchsäure oder die verschiedenen optisch-aktiven Camphersulfonsäuren wie $\beta$-Camphersulfonsäure.

Vorteilhaft ist auch eine Enantiomerentrennung mit Hilfe einer mit einem optisch aktiven Trennmittel (z.B. Dinitrobenzoyl-phenyl-glycin) gefüllten Säule; als Laufmittel eignet sich z.B. ein Gemisch Hexan/Isopropanol/Acetonitril.

Natürlich ist es auch möglich, optisch-aktive Verbindungen der Formel I nach den oben beschriebenen Methoden zu erhalten, indem man Ausgangsstoffe (z.B. solche der Formel II) verwendet, die bereits optisch-aktiv sind.

Die neuen Verbindungen der Formel I und ihre physiologisch unbedenklichen Salze können zur Herstellung pharmazeutischer Präparate verwendet werden, indem man sie zusammen mit mindestens einem Träger- oder Hilfsstoff und, falls erwünscht, zusammen mit einem oder mehreren weiteren Wirkstoff(en) in eine geeignete Dosierungsform bringt. Die so erhaltenen Zubereitungen können als Arzneimittel in der Human- oder Veterinärmedizin eingesetzt werden. Als Trägersubstanzen kommen organische oder anorganische Stoffe in Frage, die sich für die enterale (z.B. orale oder rektale) oder parenterale Applikation oder für eine Applikation in Form eines Inhalations-Sprays eignen und mit den neuen Verbindungen nicht reagieren, beispielsweise Wasser, pflanzliche Öle, Benzylalkohole, Polyethylenglykole, Glycerintriacetat und andere Fettsäureglyceride, Gelatine, Sojalecithin, Kohlehydrate wie Lactose oder Starke, Magnesiumstearat, Talk, Cellulose. Zur oralen Anwendung dienen insbesondere Tabletten, Dragees, Kapseln, Sirupe, Säfte oder Tropfen; von Interesse sind speziell Lacktabletten und Kapseln mit magensaftresistenten Überzügen bzw. Kapselhüllen. Zur rektalen Anwendung dienen Suppositorien, zur parenteralen Applikation Lösungen,

vorzugsweise ölige oder wässerige Lösungen, ferner Suspensionen, Emulsionen oder Implantate.

Für die Applikation als Inhalations-Spray können Sprays verwendet werden, die den Wirkstoff entweder gelöst oder suspendiert in einem Treibgasgemisch enthalten. Zweckmäßig verwendet man den Wirkstoff dabei in mikronisierter Form, wobei ein oder mehrere zusätzliche physiologisch verträgliche Lösungsmittel zugegen sein können, z.B. Ethanol. Inhalationslösungen können mit Hilfe üblicher Inhalatoren verabfolgt werden. Die neuen Verbindungen können auch lyophilisiert und die erhaltenen Lyophilisate z.B. zur Herstellung von Injektionspräparaten verwendet werden. Die angegebenen Zubereitungen können sterilisiert sein und/oder Hilfsstoffe wie Konservierungs-, Stabilisierungs- und/oder Netzmittel, Emulgatoren, Salze zur Beeinflussung des osmotischen Druckes, Puffersubstanzen, Farbund/oder Aromastoffe enthalten. Sie können, falls erwünscht auch einen oder mehrere weitere Wirkstoffe enthalten, z.B. ein oder mehrere Vitamine.

Die erfindungsgemäßen Substanzen werden in der Regel in Analogie zu anderen bekannten, im Handel befindlichen Pharmaka, insbesondere aber in Analogie zu den in der EP-A-459256 beschriebenen Verbindungen verabreicht, vorzugsweise in Dosierungen zwischen etwa 5 mg und 1 g, insbesondere zwischen 50 und 500 mg pro Dosierungseinheit. Die tägliche Dosierung liegt vorzugsweise zwischen etwa 0,1 und 20 mg/kg, insbesondere 1 und 10 mg/kg Körpergewicht. Die spezielle Dosis für jeden bestimmten Patienten hängt jedoch von den verschiedensten Faktoren ab, beispielsweise von der Wirksamkeit der eingesetzten speziellen Verbindung, vom Alter, Körpergewicht, allgemeinen Gesundheitszustand, Geschlecht, von der Kost, vom Verabfolgungszeitpunkt und -weg, von der Ausscheidungsgeschwindigkeit, Arzneistoffkombination und Schwere der jeweiligen Erkrankung, welcher die Therapie gilt. Die orale Applikation ist bevorzugt.

Vor- und nachstehend sind alle Temperaturen in °C angegeben. In den nachfolgenden Beispielen bedeutet "übliche Aufarbeitung": Man gibt, falls erforderlich, Wasser hinzu, stellt je nach Konstitution des Endprodukts auf pH-Werte zwischen 2 und 8 ein, extrahiert mit Ethylacetat oder Dichlormethan, trennt ab, trocknet die organische Phase über Natriumsulfat, dampft ein und reinigt durch Chromatographie an Kieselgel und/oder Kristallisation.

**Beispiel 1**

Zu einer Lösung von 1,7 g Na-p-methoxycarbonylmethyl-phenolat [erhältlich durch Überführung von p-Hydroxybenzylcyanid in die entsprechende Carbonsäure, Veresterung mit Methanol zu p-Methoxycarbonylmethylphenol und anschließende Umwandlung in das Phenolat] in 20 ml Dimethylformamid (DMF) gibt man 1 Äquivalent NaH und rührt 30 Min. bei Raumtemperatur. Danach fügt man 3,0g 3-p-Cyanphenyl-5-methansulfonyloxy-methyl-oxazolidin-2-on ("A") [erhältlich durch Reaktion von p-Aminobenzonitril mit 2,3-Epoxypropan-1-ol zu p-(N-2,3-Dihydroxypropylamino)-benzonitril,Umsetzung mit Diethylcarbonat in Gegenwart von K-tert.-butylat zu 3-p-Cyanphenyl-5-hydroxymethyl-oxazolidin-2-on und anschließende Veresterung mit Methansulfonylchlorid], gelöst in 10 ml DMF, hinzu und rührt erneut 15 Min. bei Raumtemperatur. Nach Entfernung des Lösungsmittels und üblicher Aufarbeitung erhält man das 3-p-Cyanphenyl-5-(p-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on, F. 114-115°.

Analog erhält man durch Umsetzung von "A"

mit Na-o-methoxycarbonylmethyl-phenolat das 3-p-Cyan-phenyl-5-(o-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on, $M^+ + 1 = 366$;

mit Na-m-methoxycarbonylmethyl-phenolat das 3-p-Cyan-phenyl-5-(m-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on, F. 129-130°;

mit Na-2,4-bis-(methoxycarbonylmethyl)-phenolat das 3-p-Cyan-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;

mit Na-2,5-bis-(methoxycarbonylmethyl)-phenolat das 3-p-Cyan-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;

mit Na-2,6-bis-(methoxycarbonylmethyl)-phenolat das 3-p-Cyan-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;

mit Na-3,4-bis-(methoxycarbonylmethyl)-phenolat das 3-p-Cyan-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;

mit Na-3,5-bis-(methoxycarbonylmethyl)-phenolat das 3-p-Cyan-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolldin-2-on;

mit 2-Methoxycarbonylmethyl-4-hydroxy-thiophen-Na-Salz das 3-p-Cyan-phenyl-5-(2-(methoxycarbonyl-methyl)-thien-4-yl-oxy-methyl)-oxazolidin-2-on;

mit 3-Methoxycarbonylmethyl-4-hydroxy-thiophen-Na-Salz das 3-p-Cyan-phenyl-5-(3-(methoxycarbonyl-methyl)-thien-4-yl-oxy-methyl)-oxazolidin-2-on;

mit 2-Methoxycarbonylmethyl-3-hydroxy-thiophen-Na-Salz das 3-p-Cyan-phenyl-5-(2-(methoxycarbonyl-methyl)-thien-3-yl-oxy-methyl)-oxazolidin-2-on;

mit 2-Methoxycarbonylmethyl-4-hydroxy-thiophen-Na-Salz das 3-p-Cyan-phenyl-5-(2-(methoxycarbonyl-methyl)-thien-4-yl-oxy-methyl)-oxazolidin-2-on;

mit 3-Methoxycarbonylmethyl-4-hydroxy-thiophen-Na-Salz das 3-p-Cyan-phenyl-5-(3-(methoxycarbonyl-methyl)-thien-4-yl-oxy-methyl)-oxazolidin-2-on;

mit 2-Methoxycarbonylmethyl-3-carboxy-4-hydroxy-pyrrol-Na-Salz das 3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxizolidon-2-on;

mit 2-Carboxy-3-hydroxy-5-methoxycarbonylmethyl-pyrrol-Na-Salz das 3-p-Cyan-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 2**

Eine Lösung von 0,9 g 3-p-Cyanphenyl-5-(p-methoxycarbonyl-methylphenoxymethyl)-oxazolidin-2-on (F. 114-115°) in 40 ml 10%iger methanolischer $NH_3$-Lösung wird an 0,6 g Raney-Ni bei Raumtemperatur und 1 bar bis zum Ende der $H_2$-Aufnahme hydriert. Nach Filtrieren und Eindampfen erhält man durch übliche Aufarbeitung 3-p-Aminomethylphenyl-5-(p-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on.

Analog erhält man durch Hydrierung der entsprechenden Nitrile:
3-p-Aminomethyl-phenyl-5-(o-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(m-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 3**

Man löst 2,4 g 3-p-Aminomethyl-phenyl-5-(p-methoxycarbonyl-methylphenoxymethyl)-oxazolidin-2-on in 20 ml Dichlormethan, gibt 12 ml Trifluoressigsäure hinzu und rührt 20 Min. bei Raumtemperatur. Nach Eindampfen und üblicher Aufarbeitung erhält man 3-p-Aminomethylphenyl-5-(p-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on

Analog erhält man durch Verseifung der entsprechenden Ester die folgenden Carbonsäuren:
3-p-Cyanphenyl-5-(p-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(o-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(m-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-[2,4-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Cyan-phenyl-5-[2,5-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Cyan-phenyl-5-[2,6-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Cyan-phenyl-5-[3,4-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Cyan-phenyl-5-[3,5-bis-(carboxy-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(2-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(3-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(2-carboxy-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(2-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(3-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(2-carboxy-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Cyan-phenyl-5-(2-carboxy-5-carboxy-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(p-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(o-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(m-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[2,4-bis-(carboxy-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[2,5-bis-(carboxy-methyl)-phenoxymethyl]-oxazolidin-2-on;

3-p-Aminomethyl-phenyl-5-[2,6-bis-(carboxy-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[3,4-bis-(carboxy-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-[3,5-bis-(carboxy-methyl)-phenoxymethyl]-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(3-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-carboxy-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(3-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-carboxy-methyl-3-carboxy-pyrrol-4-yl-oxymethyl)-oxazolidin-2-on;
3-p-Aminomethyl-phenyl-5-(2-carboxy-5-carboxy-methyl-pyrrol-3-yl-oxymethyl)-oxazolidin-2-on.

**Beispiel 4**

Zu einer Lösung von 0,6 g 3-p-Aminomethyl-phenyl-5-(p-carboxy-methylphenoxymethyl)-oxazolidin-2-on in 20 ml THF fügt man 20 ml 20%ige NaOH-Lösung hinzu und rührt 24 Std. bei Raumtemperatur. Man erhält 3-p-Aminomethyl-phenyl-5-(p-carboxy-methyl-phenoxymethyl)-oxazolidin-2-on-Na-Salz, F. 286-287 °.

**Beispiel 5**

Eine Lösung von 0,2 g 1-Amidino-3,5-dimethylpyrazol-nitrat in 17 ml Dioxan und 5 ml Wasser wird mit 0,17 ml Ethyldiisopropylamin versetzt und 15 Min. gerührt. Anschließend gibt man 0,4 g 3-p-Aminomethylphenyl-5-(p-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidon-2-on hinzu, kocht das Gemisch 30 Std., dampft ein und arbeitet wie üblich auf. Man erhält 3-p-Guanidinomethyl-phenyl-5-(p-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on.

Analog erhält man

mit 3-p-Aminomethyl-phenyl-5-(o-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-(o-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(m-methoxycarbonyl-methylphenoxy-methyl)-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-(m-methoxycarbonyl-methyl-phenoxymethyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenoxymethyl]-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy -methyl)-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidon-2-on-das
3-p-Guanidinomethyl-phenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-(2-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on das
3-p-Guanidinomethyl-phenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidon-2-on-das
3-p-Guanidinomethyl-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxypyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-p-Aminomethyl-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidon-2-on-das
3-p-Guanidinomethyl-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazoidin-2-on.

**Beispiel 6**

Man leitet in eine Lösung von 1,2 g 3-p-Cyanphenyl-5-(p-methoxycarbonyl-methyl-phenoxy-methyl)-oxazolidon-2-on [erhältlich gemäß Beispiel 1] in 50 ml Pyridin und 7 ml Triethylamin bei -10 ° $H_2S$-Gas ein. Anschließend rührt man 14 Std. bei Raumtemperatur, dampft ein, löst den Rückstand in 50 ml Aceton und versetzt mit 9 ml Methyliodid. Nachdem man erneut 6 Std. gerührt hat, filtriert man ab, wäscht den Rückstand mit 5 ml Aceton, löst denselben in 30 mi Methanol, gibt 4,6 g Ammoniumacetat hinzu und rührt 24 Std. bei Raumtemperatur. Nach üblicher Aufarbeitung erhält man 3-p-Amidino-phenyl-5-(p-methoxycarbonyl-methyl-phenoxymethyl-)oxazolidin-2-on, (Semi-Hydroiodid), F. 151-152 °.

Analog erhält man

aus 3-p-Cyan-phenyl-5-(o-methoxycarbonyl-methyl-phenoxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(o-methoxycarbonyl-methyl-phenoxy-methyl)-oxazolidin-2-on (Hydroiodid), $M^+ + 1 = 384$;

aus 3-p-Cyan-phenyl-5-(m-methoxycarbonyl-methyl-phenoxy-methyl)-oxazolid in-2-on:
3-p-Amidino-phenyl-5-(m-methoxycarbonyl-methyl-phenoxy-methyl)-oxazolidin-2-on (Hydroiodid), $M^+ + 1 = 384$;

aus 3-p-Cyan-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on:
3-p-Amidino-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on:
3-p-Amidino-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on:
3-p-Amidino-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Amidino-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on:
3-p-Amidino-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenoxy-methyl]-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(2-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;

aus 3-p-Cyan-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on:
3-p-Amidino-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 7**

Analog Beispiel 3 erhält man durch Verseifung der entsprechenden Ester aus Beispiel 6 die folgenden Carbonsäuren:

3-p-Amidino-phenyl-5-(p-carboxy-methyl-phenoxy-methyl)-oxazolidin-2-on, F.281 °.
3-p-Amidino-phenyl-5-(o-carboxy-methyl-phenoxy-methyl)-oxazolidin-2-on, F. 274 °;
3-p-Amidino-phenyl-5-(m-carboxy-methyl-phenoxy-methyl)-oxazolidin-2-on (Hydrochlorid), F. 271 °;
3-p-Amidino-phenyl-5-[2,4-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Amidino-phenyl-5-[2,5-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Amidino-phenyl-5-[2,6-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Amidino-phenyl-5-[3,4-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Amidino-phenyl-5-[3,5-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(2-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(3-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(2-carboxy-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(2-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(3-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;

3-p-Amidino-phenyl-5-(2-carboxy-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidino-phenyl-5-(2-carboxy-5-carboxy-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 8**

Analog Beispiel 3 erhält man durch Verseifung der entsprechenden Ester aus Beispiel 5 die folgenden Carbonsäuren:
3-p-Guanidinomethyl-phenyl-5-(p-carboxy-methyl-phenoxy-methyl)-oxazolidin-2-on, F. >300 °;
3-p-Guanidinomethyl-phenyl-5-(o-carboxy-methyl-phenoxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(m-carboxy-methyl-phenoxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-[2,4-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-[2,5-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-[2,6-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-[3,4-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-[3,5-bis-(carboxy-methyl)-phenoxy-methyl]-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(2-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(3-carboxy-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(2-carboxy-methyl-thiophen-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(2-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(3-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(2-carboxy-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Guanidinomethyl-phenyl-5-(2-carboxy-5-carboxy-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 9**

Analog Beispiel 1 erhält man ausgehend von Na-p-methoxycarbonylmethyl-thiophenolat [erhältlich durch Überführung von p-Mercaptobenzylcyanid in die entsprechende Carbonsäure, Veresterung mit Methanol zu p-Methoxycarbonylmethyl-thiophenol und anschließende Umwandlung in das Thiophenolat] durch Umsetzung mit 3-p-Cyanphenyl-5-methansulfonyloxy-methyl-oxazolidin-2-on ("A") [erhältlich gemäß Bsp. 1] das 3-p-Cyanphenyl-5-(p-methoxycarbonyl-methyl-phenylthio-methyl)-oxazolidin-2-on.

Analog erhält man durch Umsetzung von "A"
mit Na-o-methoxycarbonylmethyl-thiophenolat das
3-p-Cyan-phenyl-5-(o-methoxycarbonyl-methyl-phenylthio-methyl)-oxazolidin-2-on;
mit Na-m-methoxycarbonylmethyl-thiophenolat das
3-p-Cyan-phenyl-5-(m-methoxycarbonyl-methyl-phenylthio-methyl)-oxazolidin-2-on;
mit Na-2,4-bis-(methoxycarbonylmethyl)-thiophenolat das
3-p-Cyan-phenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
mit Na-2,5-bis-(methoxycarbonylmethyl)-thiophenolat das
3-p-Cyan-phenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
mit Na-2,6-bis-(methoxycarbonylmethyl)-thiophenolat das
3-p-Cyan-phenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
mit Na-3,4-bis-(methoxycarbonylmethyl)-thiophenolat das
3-p-Cyan-phenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
mit Na-3,5-bis-(methoxycarbonylmethyl)-thiophenolat das
3-p-Cyan-phenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
mit 2-Methoxycarbonylmethyl-4-hydroxy-thiophen-Na-Salz das
3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-Methoxycarbonylmethyl-4-hydroxy-thiophen-Na-Salz das
3-p-Cyan-phenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 2-Methoxycarbonylmethyl-3-hydroxy-thiophen-Na-Salz das
3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
mit 2-Methoxycarbonylmethyl-4-hydroxy-pyrrol-Na-Salz das
3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 3-Methoxycarbonylmethyl-4-hydroxy-pyrrol-Na-Salz das
3-p-Cyan-phenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 2-Methoxycarbonylmethyl-3-carboxy-4-hydroxy-pyrrol-Na-Salz das
3-p-Cyan-phenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
mit 2-Carboxy-3-hydroxy-5-methoxycarbonylmethyl-pyrrol-Na-Salz das

3-p-Cyan-phenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 10**

Analog Beispiel 6 erhält man ausgehend von den Nitrilen aus Beispiel 9 die folgenden Amidinophenyl-oxazolidin-2-on-Derivate:
3-p-Amidinophenyl-5-(p-methoxycarbonyl-methyl-phenylthio-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(o-methoxycarbonyl-methyl-phenylthio-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(m-methoxycarbonyl-methyl-phenylthio-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,6-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on,
3-p-Amidinophenyl-5-[3,5-bis-(methoxycarbonyl-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(3-methoxycarbonyl-methyl-thien-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-methoxycarbonyl-methyl-thien-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(3-methoxycarbonyl-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-methoxycarbonyl-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-carboxy-5-methoxycarbonyl-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 11**

Analog Beispiel 3 erhält man durch Verseifung der entsprechenden Ester aus Beispiel 10 die folgenden Carbonsäuren:
3-p-Amidinophenyl-5-(p-carboxy-methyl-phenylthio-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(o-carboxy-methyl-phenylthio-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(m-carboxy-methyl-phenylthio-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,4-bis-(carboxy-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,5-bis-(carboxy-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,6-bis-(carboxy-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[3,4-bis-(carboxy-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[3,5-bis-(carboxy-methyl)-phenylthio-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-carboxy-methyl-thiophen-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(3-carboxy-methyl-thiophen-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-carboxy-methyl-thiophen-3-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(3-carboxy-methyl-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-carboxy-methyl-3-carboxy-pyrrol-4-yl-oxy-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(2-carboxy-5-carboxy-methyl-pyrrol-3-yl-oxy-methyl)-oxazolidin-2-on.

**Beispiel 12**

Analog Beispiel 1 erhält man ausgehend von p-Methoxycarbonyl-methyl-anilin [erhältlich durch Überführung von p-Amino-benzylcyanid in p-Amino-phenylessigsäure und Veresterung mit Methanol] durch Umsetzung mit 3-p-Cyanphenyl-5-methansulfonyloxy-methyl-oxazolidin-2-on ("A") [erhältlich gemäß Bsp. 1] das 3-p-Cyanphenyl-5-(p-methoxycarbonyl-methylphenylamino-methyl)-oxazolidin-2-on.

Analog erhält man durch Umsetzung von "A"
mit o-Methoxycarbonylmethyl-anilin das
3-p-Cyanphenyl-5-(o-methoxycarbonyl-methyl-phenylamino-methyl)-oxazolidin-2-on;
mit m-Methoxycarbonylmethyl-anilin das
3-p-Cyanphenyl-5-(m-methoxycarbonyl-methyl-phenylamino-methyl)-oxazolidin-2-on;
mit 2,4-Bis-(methoxycarbonylmethyl)-anilin das
3-p-Cyanphenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenylamino-methyl]-oxazolidin-2-on;
mit 2,5-Bis-(methoxycarbonylmethyl)-anilin das
3-p-Cyanphenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenylamino-methyl]-oxazolidin-2-on;
mit 3,4-Bis-(methoxycarbonylmethyl)-anilin das

3-p-Cyanphenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenylamino-methyl]-oxazolidin-2-on.

**Beispiel 13**

Analog Beispiel 6 erhält man ausgehend von den Nitrilen aus Beispiel 9 die folgenden Amidinophenyl-oxazolidin-2-on-Derivate:
3-p-Amidinophenyl-5-(p-methoxycarbonyl-methyl-phenylamino-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(o-methoxycarbonyl-methyl-phenylamino-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(m-methoxycarbonyl-methyl-phenylamino-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,4-bis-(methoxycarbonyl-methyl)-phenylamino-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,5-bis-(methoxycarbonyl-methyl)-phenylamino-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[3,4-bis-(methoxycarbonyl-methyl)-phenylamino-methyl]-oxazolidin-2-on.

**Beispiel 14**

Analog Beispiel 3 erhält man durch Verseifung der entsprechenden Ester aus Beispiel 13 die folgenden Carbonsäuren:
3-p-Amidinophenyl-5-(p-carboxy-methyl-phenylamino-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(o-carboxy-methyl-phenylamino-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-(m-carboxy-methyl-phenylamino-methyl)-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,4-bis-(carboxy-methyl)-phenylamino-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[2,5-bis-(carboxy-methyl)-phenylamino-methyl]-oxazolidin-2-on;
3-p-Amidinophenyl-5-[3,4-bis-(carboxy-methyl)-phenylamino-methyl]-oxazolidin-2-on.

**Beispiel 15**

Analog Beispiel 1 erhält man ausgehend von p-Methoxycarbonylmethyl-N-methyl-anilin [erhältlich durch Überführung von p-N-Methyl-aminobenzylcyanid in p-Methylaminophenylessigsäure und Veresterung mit Methanol] durch Umsetzung mit 3-p-Cyanphenyl-5-methansulfonyloxy-methyl-oxazolidin-2-on ("A") [erhältlich gemäß Bsp. 1] das 3-p-Cyanphenyl-5-(p-methoxycarbonylmethyl-phenyl-N-methylamino-methyl)-oxazolidin-2-on.

**Beispiel 16**

Analog Beispiel 6 erhält man ausgehend von dem Nitril aus Beispiel 15 3-p-Amidinophenyl-5-(p-methoxycarbonyl-methyl-phenyl-N-methylamino-methyl)-oxazolidin-2-on.

**Beispiel 17**

Analog Beispiel 3 erhält man durch Verseifung des Esters aus Beispiel 16 3-p-Amidinophenyl-5-(p-carboxy-methyl-phenyl-N-methylamino-methyl)-oxazolidin-2-on.

Die folgenden Beispiele betreffen pharmazeutische Zubereitungen:

**Beispiel A: Injektionsgläser**

Eine Lösung von 100 g eines Wirkstoffes der Formel I und 5 g Dinatriumhydrogenphosphat in 3 l zweifach destilliertem Wasser wird mit 2 n Salz-Säure auf pH 6,5 eingestellt, steril filtriert, in Injektionsgläser abgefüllt, lyophilisiert und steril verschlossen. Jedes Injektionsglas enthält 5 mg Wirkstoff.

**Beispiel B: Suppositorien**

Man schmilzt ein Gemisch von 20 mg eines Wirkstoffes der Formel I mit 100g Sojalecithin und 1400 g Kakaobutter, gießt in Formen und läßt erkalten. Jedes Suppositorium enthält 20 mg Wirkstoff.

**Beispiel C: Lösung**

Man bereitet eine Lösung aus 1 g eines Wirkstoffes der Formel I, 9,38 g $NaH_2PO_4 \times 2\ H_2O$, 28,48 g $Na_2HPO_4 \times 12\ H_2O$ und 0,1 g Benzalkoniumchlorid in 940 ml zweifach destilliertem Wasser. Man stellt auf

pH 6,8 ein, füllt auf 1 l auf und sterilisiert durch Bestrahlung. Diese Lösung kann in Form von Augentropfen verwendet werden.

**Beispiel D: Salbe**

Man mischt 500 mg eines Wirkstoffes der Formel I mit 99,5 g Vaseline unter aseptischen Bedinungen.

**Beispiel E: Tabletten**

Ein Gemisch von 1 kg Wirkstoff der Formel I, 4 kg Lactose, 1,2 kg Kartoffelstärke, 0,2 kg Talk und 0,1 kg Magnesiumstearat wird in üblicher Weise zu Tabletten verpreßt, derart, daß jede Tablette 10 mg Wirkstoff enthält.

**Beispiel F: Dragees**

Analog Beispiel E werden Tabletten gepreßt, die anschließend in üblicher Weise mit einem Überzug aus Saccharose, Kartoffelstarke, Talk, Tragant und Farbstoff überzogen werden.

**Beispiel G: Kapseln**

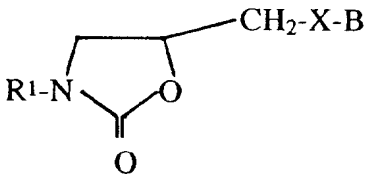
2 kg Wirkstoff der Formel I werden in üblicher Weise in Hartgelatinekapseln gefüllt, so daß jede Kapsel 20 mg des Wirkstoffs enthält.

**Beispiel H: Ampullen**

Eine Lösung von 1 kg Wirkstoff der Formel I in 60 l zweifach destilliertem Wasser wird in Ampullen abgefüllt, unter aseptischen Bedingungen lyophilisiert und steril verschlossen. Jede Ampulle enthält 10 mg Wirkstoff.

**Patentansprüche**

**1.** Oxazolidinonderivate der Formel I



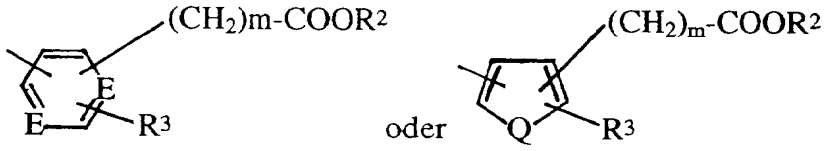
I,

**worin**

$R^1$ einen unsubstituierten oder einfach durch CN, $H_2N$-$CH_2$-, $A_2N$-$CH_2$-, $H_2N$-C(=NH)-, $H_2N$-C(=NH)-NH-, $H_2N$-C(=NH)-**NH-$CH_2$-, HO-NH-C(=NH)- oder HO-NH-C(=NH)-NH-**substituierten Phenylrest,

X O, S, SO, $SO_2$, -NH- oder -NA-,

B



A Alkyl mit 1 bis 6 C-Atomen,

$R^2$ H, A, Li, Na, K, $NH_4$ oder Benzyl,

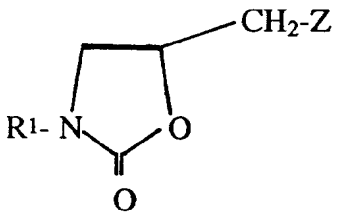
$R^3$ H oder $(CH_2)_n$-$COOR^2$,
E jeweils unabhängig voneinander CH oder N,
Q O, S oder NH
m 1, 2 oder 3 und
n 0, 1, 2 oder 3 bedeuten,
sowie deren physiologisch unbedenkliche Salze.

**2.**

(a) 3-p-Amidino-phenyl-5-(p-carboxymethyl-phenoxy-methyl)-oxazolidin-2-on;
(b) 3-p-Amidino-phenyl-5-(p-methoxycarbonylmethyl-phenoxy-methyl)-oxazolidin-2-on;
(c) 3-p-Aminomethyl-phenyl-5-(p-carboxymethyl-phenoxy-methyl)-oxazolidin-2-on-Natriumsalz;
(d) 3-p-Guanidinomethy-phenyl-5-(p-carboxymethyl-phenoxy-methyl)-oxazolidin-2-on.

**3.** Eine enantiomere Verbindung der Formel I gemäß Anspruch 1 oder eines seiner Salze.

**4.** Verfahren zur Herstellung von Verbindungen der Formel I gemaß Anspruch 1 sowie deren Salzen, dadurch gekennzeichnet, daß man eine Verbindung der Formel II




II,

worin
$R^1$ die in Anspruch 1 angegebene Bedeutung hat
und
Z Cl, Br, I, OH oder eine reaktionsfähig veresterte OH-Gruppe bedeutet,
mit einer Verbindung der Formel III

Y-B III,

worin
B die oben angegebene Bedeutung hat
und
Y OH, SH, $NH_2$, NAH oder einen aus OH oder SH ableitbaren salzartigen Rest bedeuten,
umsetzt, oder daß man
eine Verbindung der Formel IV

$R^1$-NH-$CH_2$-CH(OH)-$CH_2$-X-B IV,

worin
$R^1$, B und X die oben angegebenen Bedeutungen haben, oder eines ihrer reaktionsfähigen Derivate mit einem reaktiven Derivat der Kohlensäure umsetzt,
oder daß man zur Herstellung einer Guanidinoverbindung der Formel I ($R^1$ = ein einfach durch $H_2N$-C-(=NH)-NH- substituierter Phenylrest) eine Aminoverbindung entsprechend der Formel I, die jedoch anstelle des Restes $R^1$ eine Aminophenylgruppe enthält, mit einem amidinierenden Mittel behandelt,
oder daß man eine Verbindung der Formel I aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt,
und/oder daß man in einer Verbindung der Formel I einen oder beide Reste $R^1$ und/oder B in (einen) andere(n) Rest(e) $R^1$ und/oder B umwandelt und/oder eine Verbindung der Formel I durch Behandeln mit einer Säure oder einer Base in eines ihrer Salze überführt.

**5.** Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Anspruch 1 und/oder eines ihrer physiologisch unbedenklichen Salze

zusammen mit mindestens einem festen, flüssigen oder halbflüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform bringt.

6. Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt an mindestens einer Verbindung der Formel I nach Anspruch 1 und/oder einem ihrer physiologisch unbedenklichen Salze.

7. Verwendung von Verbindungen der Formel I nach Anspruch 1 oder von deren physiologisch unbedenklichen Salzen zur Herstellung eines Arzneimittels.

8. Verwendung von Verbindungen der Formel I nach Anspruch 1 oder von deren physiologisch unbedenklichen Salzen bei der Bekämpfung von Thrombosen, Herzinfarkten, Apolexie, Osteoporose, Arteriosklerose, Entzündungen und/oder Tumoren.

Europäisches Patentamt

# EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung
EP 94 11 4519

## EINSCHLÄGIGE DOKUMENTE

| Kategorie | Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile | Betrifft Anspruch | KLASSIFIKATION DER ANMELDUNG (Int.Cl.6) |
|---|---|---|---|
| P,X | EP-A-0 605 729 (TAIHO PHARMACEUTICAL CO., LTD.) 13. Juli 1994<br>* Verbindung 189 und 192 *<br>* Ansprüche 1,2,4-6,8,13 *<br>--- | 1,3-7 | C07D263/24<br>C07D413/12<br>A61K31/42 |
| Y | EP-A-0 300 272 (MERCK PATENT GMBH) 25. Januar 1989<br>* das ganze Dokument *<br>--- | 1-8 | |
| D,Y | EP-A-0 381 033 (F. HOFFMANN - LA ROCHE AG) 8. August 1990<br>* das ganze Dokument *<br>--- | 1-8 | |
| Y | EP-A-0 443 197 (MERCK PATENT GMBH) 28. August 1991<br>* das ganze Dokument *<br>--- | 1-8 | |
| Y | JOURNAL OF MEDICINAL CHEMISTRY, Bd.35, Nr.23, 13. November 1992 Seiten 4393 - 4407<br>ALIG L. ET AL. 'Low molecular weight, non-peptide fibrinogen receptor antagonists'<br>* das ganze Dokument *<br>--- | 1-8 | RECHERCHIERTE SACHGEBIETE (Int.Cl.6)<br>C07D<br>A61K |
| Y | JOURNAL OF MEDICINAL CHEMISTRY, Bd.36, Nr.13, 25. Juni 1993 Seiten 1811 - 1819<br>ZABLOCKI J.A. ET AL. 'Potent in vitro and in vivo inhibitors of platelet aggregation based upon the Arg-Gly-Asp-Phe sequence of fibrinogen. A proposal on the nature of the binding interaction between the Arg-guanidine of RGDX mimetics and the platelet GP IIb-IIIa receptor'<br>* das ganze Dokument *<br>---<br>-/-- | 1-8 | |

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

| Recherchenort | Abschlußdatum der Recherche | Prüfer |
|---|---|---|
| MÜNCHEN | 13. Dezember 1994 | Hartrampf, G |

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur

T : der Erfindung zugrunde liegende Theorien oder Grundsätze
E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

EPO FORM 1503 03.82 (P04C03)

Europäisches Patentamt

# EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung
EP 94 11 4519

## EINSCHLÄGIGE DOKUMENTE

| Kategorie | Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile | Betrifft Anspruch | KLASSIFIKATION DER ANMELDUNG (Int.Cl.6) |
|---|---|---|---|
| E | EP-A-0 623 615 (MERCK PATENT GMBH) 9. November 1994<br>* das ganze Dokument *<br>----- | 1-8 | |
| | | | RECHERCHIERTE SACHGEBIETE (Int.Cl.6) |

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

| Recherchenort | Abschlußdatum der Recherche | Prüfer |
|---|---|---|
| MÜNCHEN | 13. Dezember 1994 | Hartrampf, G |

**KATEGORIE DER GENANNTEN DOKUMENTE**

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur

T : der Erfindung zugrunde liegende Theorien oder Grundsätze
E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
L : aus andern Gründen angeführtes Dokument

& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

EPO FORM 1503 03.82 (P04C03)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 738 726 A1

# (12) EUROPÄISCHE PATENTANMELDUNG

(43) Veröffentlichungstag:
**23.10.1996 Patentblatt 1996/43**

(21) Anmeldenummer: **96105539.9**

(22) Anmeldetag: **09.04.1996**

(51) Int. Cl.[6]: **C07D 417/04**, A61K 31/425, C07D 413/04, C07D 263/58, C07D 419/04, C07F 9/6584, C07F 9/6558, C07D 417/14, C07D 413/06

(84) Benannte Vertragsstaaten:
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**

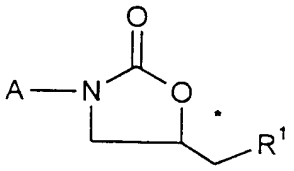
(30) Priorität: **21.04.1995 DE 19514769**
**27.11.1995 DE 19544106**

(71) Anmelder: **BAYER AG**
**51368 Leverkusen (DE)**

(72) Erfinder:
- **Stolle, Andreas, Dr.**
  **42115 Wuppertal (DE)**
- **Häbich, Dieter, Dr.**
  **42115 Wuppertal (DE)**
- **Bartel, Stephan, Dr.**
  **51465 Bergisch Gladbach (DE)**
- **Riedl, Bernd, Dr.**
  **42115 Wuppertal (DE)**
- **Ruppelt, Martin, Dr.**
  **42115 Wuppertal (DE)**
- **Wild, Hanno, Dr.**
  **Orange, Connecticut 06477 (US)**
- **Endermann, Rainer, Dr.**
  **42113 Wuppertal (DE)**
- **Bremm, Klaus-Dieter, Dr.**
  **45661 Recklinghausen (DE)**
- **Kroll, Hein-Peter, Dr.**
  **42115 Wuppertal (DE)**
- **Labischinski, Harald, Prof. Dr.**
  **42109 Wuppertal (DE)**
- **Schaller, Klaus, Dr.**
  **42109 Wuppertal (DE)**
- **Werling, Hans-Otto, Dr.**
  **42115 Wuppertal (DE)**

## (54) Heteroatomhaltige Benzocyclopentanoxazolidinone mit antibakteriellen Wirkung

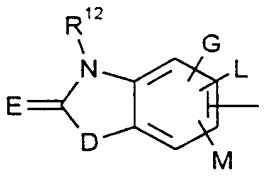
(57) Die Erfindung betrifft heteroatomhaltige Benzocyclopentanoxazolidinone der Formel I, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.



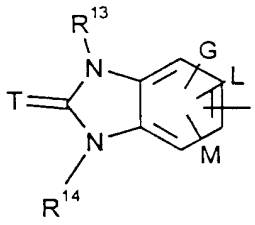

(I)

EP 0 738 726 A1

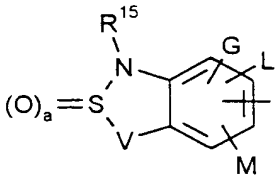
A steht für einen Rest der Formel



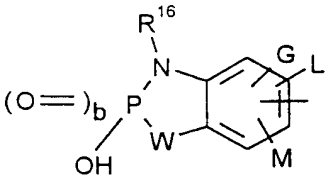

,




,




oder



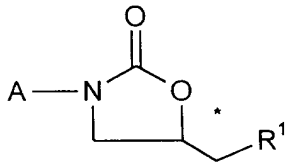
## Beschreibung

Die vorliegende Erfindung betrifft heteroatomhaltige Benzocyclopentanoxazolidinone, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

Aus den Publikationen US 5 254 577, US 4 705 799, EP 311 090, US 4 801 600, US 4 921 869, US 4 965 268, EP 312 000 und C.H. Park et al., J. Med. Chem. 35, 1156 (1992) sind N-Aryloxazolidinone mit antibakterieller Wirkung bekannt. Außerdem sind 3-(Stickstoff-substituierte)phenyl-5-beta-amidomethyloxazolidin-2-one aus der EP 609 905 A1 bekannt.

Ferner werden in der PCT 93 08 179 A Oxazolidinonderivate mit einer Monoaminoxidase inhibitorischer Wirkung beschrieben.

Die vorliegende Erfindung betrifft heteroatomhaltige Benzocyclopentanoxazolidinone der allgemeinen Formel (I)



(I)

in welcher

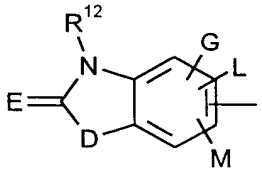
| | |
|---|---|
| $R^1$ | für Azido, Hydroxy oder für eine Gruppe der Formel - $OR^2$, $O\text{-}SO_2R^3$ oder $-NR^4R^5$ steht, worin |
| $R^2$ | geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet, |
| $R^3$ | geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet, das gegebenenfalls durch geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen substituiert ist, |
| $R^4$ und $R^5$ | gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 8 Kohlenstoffatomen oder eine Aminoschutzgruppe bedeuten, oder |
| $R^4$ oder $R^5$ | eine Gruppe der Formel $-CO\text{-}R^6$, $P(O)(OR^7)(OR^8)$ oder - $SO_2\text{-}R^9$ bedeutet, worin |
| $R^6$ | Cycloalkyl oder Halogen-substituiertes Cycloalkyl mit jeweils 3 bis 6 Kohlenstoffatomen, Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeutet, oder |
| $R^6$ | geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 8 Kohlenstoffatomen bedeutet, die gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert sind, oder geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeutet, oder eine Gruppe der Formel $-NR^{10}R^{11}$ bedeutet, worin |
| $R^{10}$ und $R^{11}$ | gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder |

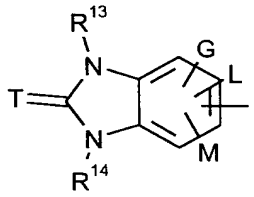
$R^6$ einen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeutet, der gegebenenfalls durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert ist

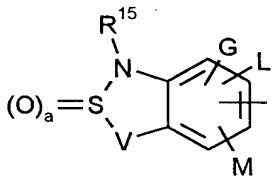
$R^7$ und $R^8$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,

$R^9$ geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet

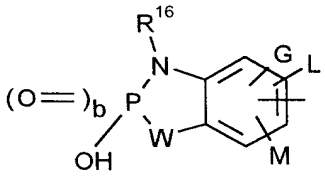
A für einen Rest der Formel



,


,



oder

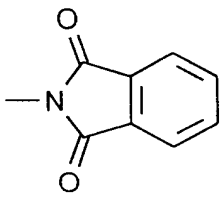



steht,
worin

G, L und M gleich oder verschieden sind und
für Wasserstoff, Carboxy, Halogen, Cyano, Formyl, Trifluormethyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder für eine Gruppe der Formel - $CO\text{-}NR^{17}R^{18}$ stehen,
worin

$R^{17}$ und $R^{18}$ gleich oder verschieden sind und
Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeuten,

$R^{12}$ Wasserstoff, Cycloalkylcarbonyl oder Cycloalkyl mit jeweils 3 bis 6 Kohlenstoffatomen, oder geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen bedeutet, oder geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 10 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Azido, Trifluormethyl, Pyridyl, Halogen, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen, Benzyloxycarbonyl, Aryl mit 6 bis 10 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen und/oder durch eine Gruppe der Formel $-(CO)_c\text{-}NR^{19}R^{20}$, $R^{21}\text{-}N\text{-}SO_2\text{-}R^{22}$, $R^{23}R^{24}\text{-}N\text{-}SO_2\text{-}$, $R^{25}\text{-}S(O)_d\text{-}$ oder



substituiert ist,
worin

c — eine Zahl 0 oder 1 bedeutet,

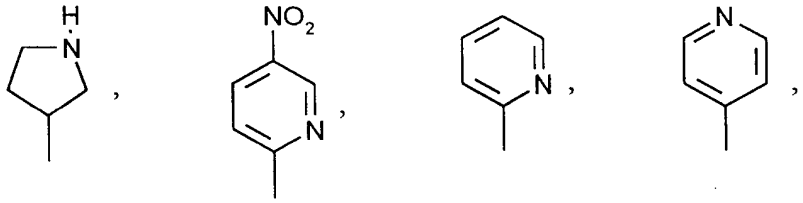
$R^{19}$, $R^{20}$ und $R^{21}$ — die oben angegebene Bedeutung von $R^{17}$ und $R^{18}$ haben und mit dieser gleich oder verschieden sind, oder gemeinsam mit dem Stickstoffatom einen 5-bis 6-gliedrigen, gesättigten Heterocyclus mit gegebenenfalls einem weiteren Heteroatom aus der Serie N, S und/oder O bilden, der seinerseits gegebenenfalls, auch an einem weiteren Stickstoffatom, durch geradkettiges oder verzweigtes Alkyl oder Acyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,

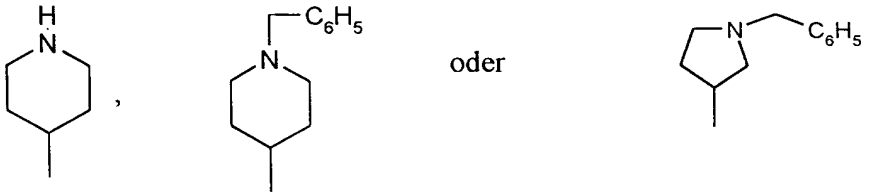
$R^{23}$ und $R^{24}$ — die oben angegebene Bedeutung von $R^{17}$ und $R^{18}$ haben und mit dieser gleich oder verschieden sind,

d — eine Zahl 0, 1 oder 2 bedeutet,

$R^{22}$ und $R^{25}$ — gleich oder verschieden sind und geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder

$R^{12}$ — einen Rest der Formeln





bedeutet oder
eine Gruppe der Formel $-COCCl_3$ oder geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls Trifluormethyl, Trichlormethyl oder durch eine Gruppe der Formel $-OR^{26}$ substituiert ist,
worin

| | |
|---|---|
| $R^{26}$ | Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Aryl mit bis zu 10 Kohlenstoffatomen substituiert ist,<br>oder |
| $R^{12}$ | eine Gruppe der Formel $-(CO)_e-NR^{27}R^{28}$, $-NR^{29}-SO_2R^{30}$, $R^{31}R^{32}-N-SO_2-$ oder $R^{33}-S(O)_f$ bedeutet,<br>worin |
| e | die oben angegebene Bedeutung von c hat und mit dieser gleich oder verschieden ist, |
| $R^{27}$ und $R^{28}$ und $R^{29}$ | jeweils die oben angegebene Bedeutung von $R^{19}$, $R^{20}$ und $R^{21}$ haben und mit dieser gleich oder verschieden sind, |
| $R^{31}$ und $R^{32}$ | die oben angegebene Bedeutung von $R^{17}$ und $R^{18}$ haben und mit dieser gleich oder verschieden sind, |
| f | die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist, |
| $R^{30}$ und $R^{33}$ | die jeweils oben angegebene Bedeutungen von $R^{22}$ und $R^{25}$ haben und mit dieser gleich oder verschieden sind, |
| D | ein Sauerstoff oder Schwefelatom bedeutet, |
| E | ein Sauerstoff- oder Schwefelatom oder eine Gruppe der Formel NH bedeutet, |
| T | ein Sauerstoffatom oder die NH-Gruppe bedeutet, |
| $R^{13}$ und $R^{14}$ | die oben angegebene Bedeutung von $R^{12}$ haben und mit dieser gleich oder verschieden sind,<br>oder |
| T | ein Schwefelatom bedeutet,<br>mit der Maßgabe, daß $R^{13}$ und $R^{14}$ die oben angegebene Bedeutung von $R^{12}$ haben, aber nicht für Wasserstoff stehen,<br>oder im Fall, daß $R^{12}$, $R^{13}$ und $R^{14}$ nicht für Wasserstoff stehen, E und/oder T eine Gruppe der Formel $NR^{34}$ bedeuten, worin $R^{34}$ mit Ausnahme von Wasserstoff die oben angegebene Bedeutung von $R^{12}$ hat und mit dieser gleich oder verschieden ist,<br>oder |
| $R^{34}$ | Cyano oder eine Gruppe der Formel $-CO_2R^{35}$ bedeutet,<br>worin |
| $R^{35}$ | Benzyl oder Phenyl bedeutet, die gegebenenfalls durch Nitro oder Halogen substituiert sind, |
| V und W | die oben angegebene Bedeutung von D haben oder die oben aufgeführte Gruppe $N-R^{14}$ bedeuten und mit dieser gleich oder verschieden sind, |
| a | eine Zahl 1 oder 2 bedeutet, |
| b | eine Zahl 0 oder 1 bedeutet, |
| $R^{15}$ und $R^{16}$ | die oben angegebene Bedeutung von $R^{12}$ haben und mit dieser gleich oder verschieden sind, |

und deren tautomere Formen, Isomere und Salze.

Tautomerie der erfindungsgemäßen Verbindungen bezieht sich in Abhängigkeit der oben aufgeführten Substituentendefinitionen von E, T, $R^{12}$, $R^{13}$ und $R^{14}$ auf die Möglichkeit der Verlagerung der exocyclischen Doppelbindungen in den 5-gliedrigen Heterocyclus.

Physiologisch unbedenkliche Salze der heteroatomhaltigen Benzocyclopentanoxazolidinone können Salze der erfindungsgemäßen Stoffe mit Mineralsäuren, Carbonsäuren oder Sulfonsäuren sein. Besonders bevorzugt sind z.B. Salze mit Chlorwasserstoffsäure, Bromwasserstoffsäure, Schwefelsäure, Phosphorsäure, Methansulfonsäure, Ethansulfonsäure, Toluolsulfonsäure, Benzolsulfonsäure, Naphthalindisulfonsäure, Essigsäure, Propionsäure, Milchsäure, Weinsäure, Zitronensäure, Fumarsäure, Maleinsäure oder Benzoesäure.

Als Salze können Salze mit üblichen Basen genannt werden, wie beispielsweise Alkalimetallsalze (z.B. Natrium- oder Kaliumsalze), Erdalkalisalze (z.B. Calcium-oder Magnesiumsalze) oder Ammoniumsalze, abgeleitet von Ammoniak oder organischen Aminen wie beispielsweise Diethylamin, Triethylamin, Ethyldiisopropylamin, Prokain, Dibenzylamin, N-Methylmorpholin, Dihydroabiethylamin, 1-Ephenamin oder Methyl-piperidin.

Als Salze können außerdem Reaktionsprodukte mit $C_1$-$C_4$-Alkylhalogenide, insbesondere $C_1$-$C_4$-Alkyljodide fungieren.

Heteroyclus steht im allgemeinen für einen 5- bis 6-gliedrigen, gesättigten oder ungesättigten Ring, der als Heteroatome bis zu 3 Sauerstoff-, Schwefel- und/oder Stickstoffatome enthalten kann. Bevorzugt werden genannt: Thienyl, Furyl, Pyrrolyl, Pyrazolyl, Pyridyl, Pyrimidyl, Pyrazinyl, Pyridazinyl, Thiazolyl, Oxazolyl, Imidazolyl, Pyrrolidinyl, Piperidinyl oder Piperazinyl.

Dazu gehören auch über N-gebundene, 5- bis 6-gliedrige gesättigte Heterocyclen, die außerdem als Heteroatome bis zu 2 Sauerstoff-, Schwefel- und/oder Stickstoffatome enthalten können, wie beispielsweise Piperidyl, Morpholinyl oder Piperazin oder Pyrrolidinyl. Besonders bevorzugt sind Piperidyl, Morphlinyl und Pyrrolidinyl.

Hydroxyschutzgruppe im Rahmen der oben angegebenen Definition steht im allgemeinen für eine Schutzgruppe aus der Reihe: Trimethylsilyl, Triisopropylsilyl, tert. Butyl-dimethylsilyl, Benzyl, Benzyloxycarbonyl, 2-Nitrobenzyl, 4-Nitrobenzyl, tert. Butyloxycarbonyl, Allyloxycarbonyl, 4-Methoxybenzyl, 4-Methoxybenzyloxycarbonyl, Tetrahydropyranyl, Formyl, Acetyl, Trichloracetyl, 2,2,2-Trichlorethoxycarbonyl, Methoxyethoxymethyl, [2-(Trimethylsilyl)ethoxy]methyl, Benzoyl, 4-Methylbenzoyl, 4-Nitrobenzoyl, 4-Fluorbenzoyl, 4-Chlorbenzoyl oder 4-Methoxybenzoyl. Bevorzugt sind Acetyl, tert. Butyldimethylsilyl oder Tetrahydropyranyl.

Aminoschutzgruppe im Rahmen der Erfindung sind die üblichen in der Peptid-Chemie verwendeten Aminoschutzgruppen.

Hierzu gehören bevorzugt: Benzyloxycarbonyl, 2,4-Dimethoxybenzyloxycarbonyl, 4-Methoxybenzyloxycarbonyl, Methoxycarbonyl, Ethoxycarbonyl, tert.Butoxycarbonyl, Allyloxycarbonyl, Phthaloyl, 2,2,2-Trichlorethoxycarbonyl, Fluorenyl-9-methoxycarbonyl, Formyl, Acetyl, 2-Chloracetyl, 2,2,2-Trifluoracetyl, 2,2,2-Trichloracetyl, Benzoyl, 4-Chlorbenzoyl, 4-Brombenzoyl, 4-Nitrobenzoyl, Phthalimido, Isovaleroyl oder Benzyloxymethylen, 4-Nitrobenzyl, 2,4-Dinitrobenzyl, 4-Nitrophenyl, 4-Methoxyphenyl oder Triphenylmethyl.

Die erfindungsgemäßen Verbindungen können in stereoisomeren Formen, die sich entweder wie Bild und Spiegelbild (Enantiomere), oder die sich nicht wie Bild und Spiegelbild (Diastereomere) verhalten, existieren. Die Erfindung betrifft sowohl die Enantiomeren oder Diastereomeren oder deren jeweiligen Mischungen. Die Racemformen lassen sich ebenso wie die Diastereomeren in bekannter Weise in die stereoisomer einheitlichen Bestandteile trennen

Bevorzugt sind Verbindungen der allgemeinen Formel (I),
in welcher

| | |
|---|---|
| $R^1$ | für Azido, Hydroxy oder für eine Gruppe der Formel - $OR^2$, $O\text{-}SO_2R^3$ oder $-NR^4R^5$ steht, |
| | worin |
| $R^2$ | geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet, |
| $R^3$ | geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Phenyl oder Tolyl bedeutet |
| $R^4$ und $R^5$ | gleich oder verschieden sind und<br>Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten,<br>oder |

$R^4$ oder $R^5$ eine Gruppe der Formel -CO-$R^6$, P(O)($OR^7$)($OR^8$) oder -$SO_2$-$R^9$ bedeutet,
worin

$R^6$ Cyclopropyl, Fluor-substituiertes Cyclpropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeutet, oder

$R^6$ geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen bedeutet, die gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert sind, oder
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeutet, oder
eine Gruppe der Formel -$NR^{10}R^{11}$ bedeutet,
worin

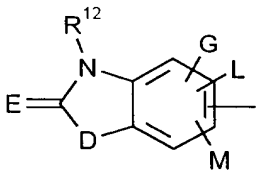
$R^{10}$ und $R^{11}$ gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, oder

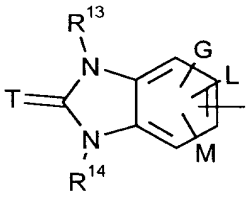
$R^6$ Isoxazolyl, Furyl, Thienyl, Pyrryl, Oxazolyl oder Imidazolyl bedeutet, die gegebenenfalls durch Methyl substituiert sind

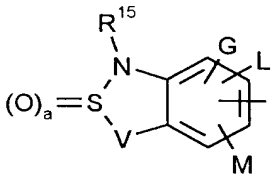
$R^7$ und $R^8$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

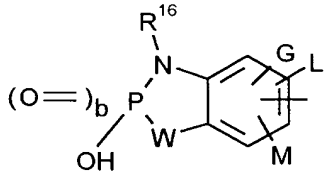
$R^9$ geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet,

A für einen Rest der Formel



,


,


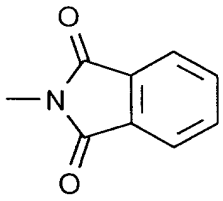

oder



steht,
worin

G, L und M gleich oder verschieden sind und
für Wasserstoff, Carboxy, Fluor, Chlor, Brom, Jod, Cyano, Trifluormethyl, Formyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder für eine Gruppe der Formel -CO-$NR^{17}R^{18}$ stehen,
worin

$R^{17}$ und $R^{18}$ gleich oder verschieden sind und
Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeuten,

$R^{12}$ Wasserstoff, Cyclopropylcarbonyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, oder
geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 4 Kohlenstoffatomen, oder geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 9 Kohlenstoffatomen bedeutet, die gegebenenfalls durch Cyano, Azido, Trifluormethyl, Pyridyl, Fluor, Chlor, Brom, Hydroxy, Phenyl, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 5 Kohlenstoffatomen, Benzyloxycarbony, Naphthyl, Cyclopropyl, Cyclopentyl, Cyclohexyl und/oder durch eine Gruppe der Formel $-(CO)_c-NR^{19}R^{20}$, $R^{21}-N-SO_2-R^{22}$, $R^{23}R^{24}-N-SO_2-$, $R^{25}-S(O)_d-$ oder



substituiert ist,
worin

c eine Zahl 0 oder 1 bedeutet,

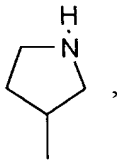
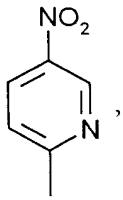
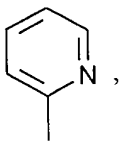
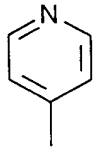
$R^{19}$, $R^{20}$ und $R^{21}$ die oben angegebene Bedeutung von $R^{17}$ und $R^{18}$ haben und mit dieser gleich oder verschieden sind, oder gemeinsam mit dem Stickstoffatom einen Morpholinyl-, Pyrrolidinyl-, Piperazinyl- oder Piperidylring bilden, die gegebenenfalls, auch über die freie N-Funktion, durch Methyl, Ethyl oder Acetyl substituiert sind,

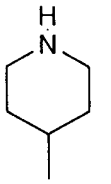
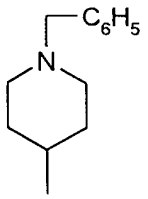
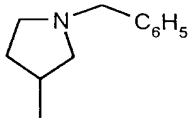
$R^{23}$ und $R^{24}$ die oben angegebene Bedeutung von $R^{17}$ und $R^{18}$ haben und mit dieser gleich oder verschieden sind,

d eine Zahl 0, 1 oder 2 bedeutet,

$R^{22}$ und $R^{25}$ gleich oder verschieden sind und
geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder

$R^{12}$ einen Rest der Formeln


,

,

,

,



oder


bedeutet oder
eine Gruppe der Formel $-COCCl_3$ oder geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Trifluormethyl, Trichlormethyl oder eine Gruppe der Formel $-OR^{26}$ substituiert ist,
worin

| | |
|---|---|
| $R^{26}$ | Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Phenyl oder Naphthyl substituiert ist, oder |
| $R^{12}$ | eine Gruppe der Formel $-(CO)_e-NR^{27}R^{28}$, $-NR^{29}-SO_2R^{30}$, $R^{31}R^{32}-N-SO_2-$ oder $R^{33}-S(O)_f$ bedeutet, worin |
| e | die oben angegebene Bedeutung von c hat und mit dieser gleich oder verschieden ist, |
| $R^{27}$, $R^{28}$ und $R^{29}$ | die jeweils oben angegebene Bedeutung von $R^{19}$, $R^{20}$ und $R^{21}$ haben und mit dieser gleich oder verschieden sind, |
| $R^{31}$ und $R^{32}$ | die oben angegebene Bedeutung von $R^{17}$ und $R^{18}$ haben und mit dieser gleich oder verschieden sind, |
| f | die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist, |
| $R^{30}$ und $R^{33}$ | die jeweils oben angegebene Bedeutungen von $R^{22}$ und $R^{25}$ haben und mit dieser gleich oder verschieden sind, |
| D | ein Sauerstoff oder Schwefelatom bedeutet, |
| E | ein Sauerstoff- oder Schwefelatom oder eine Gruppe der Formel NH bedeutet, |
| T | ein Sauerstoffatom oder die NH-Gruppe bedeutet, |
| $R^{13}$ und $R^{14}$ | die oben angegebene Bedeutung von $R^{12}$ haben und mit dieser gleich oder verschieden sind, oder |
| T | ein Schwefelatom bedeutet, mit der Maßgabe, daß $R^{13}$ und $R^{14}$ die oben angegebene Bedeutung von $R^{12}$ haben, aber nicht für Wasserstoff stehen, oder im Fall, daß $R^{12}$, $R^{13}$ und $R^{14}$ nicht für Wasserstoff stehen, E und/oder T eine Gruppe der Formel $NR^{34}$ bedeuten, worin $R^{34}$ mit Ausnahme von Wasserstoff die oben angegebene Bedeutung von $R^{12}$ hat und mit dieser gleich oder verschieden ist, oder |
| $R^{34}$ | Cyano oder eine Gruppe der Formel $-CO_2R^{35}$ bedeutet, worin |

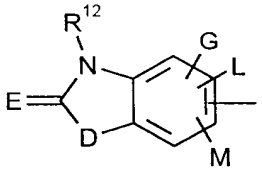
| | |
|---|---|
| $R^{35}$ | Benzyl oder Phenyl bedeutet, die gegebenenfalls durch Nitro, Fluor, Chlor oder Brom substituiert sind, |
| V und W | die oben angegebene Bedeutung von D haben oder die oben aufgeführte Gruppe N-$R^{14}$ bedeuten und mit dieser gleich oder verschieden sind, |
| a | eine Zahl 1 oder 2 bedeutet, |
| b | eine Zahl 0 oder 1 bedeutet, |
| $R^{15}$ und $R^{16}$ | die oben angegebene Bedeutung von $R^{12}$ haben und mit dieser gleich oder verschieden sind, |

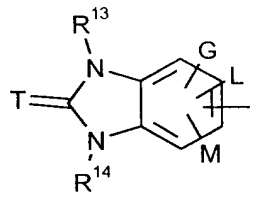
und deren tautomeren Formen und Salze.

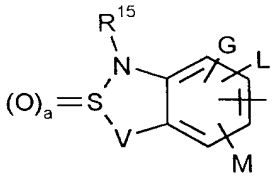
Besonders bevorzugt sind Verbindungen der allgemeinen Formel (I),
in welcher

| | |
|---|---|
| $R^1$ | für Azido, Hydroxy oder für eine Gruppe der Formel - $OR^2$, O-$SO_2R^3$ oder - $NR^4R^5$ steht, |
| | worin |
| $R^2$ | geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet, |
| $R^3$ | Methyl, Ethyl, Phenyl oder Toluolyl bedeutet, |
| $R^4$ und $R^5$ | gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 5 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten, |
| | oder |
| $R^4$ oder $R^5$ | eine Gruppe der Formel -CO-$R^6$, P(O)($OR^7$)($OR^8$) oder -$SO_2R^9$ bedeutet, |
| | worin |
| $R^6$ | Cyclopropyl, Fluor-substituiertes Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeutet, |
| $R^6$ | geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 5 Kohlenstoffatomen bedeutet, die gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert sind, oder |
| | geradkettiges oder verzweigtes Thioalkyl-oder Acyl ist jeweils bis zu 4 Kohlenstoffatomen bedeutet, oder |
| | eine Gruppe der Formel -$NR^{10}R^{11}$ bedeutet, worin |
| $R^{10}$ und $R^{11}$ | gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten, oder |
| $R^6$ | Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeutet, die gegebenenfalls durch Methyl substituiert sind |
| $R^7$ und $R^8$ | gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten, |
| $R^9$ | Methyl oder Phenyl bedeutet, |

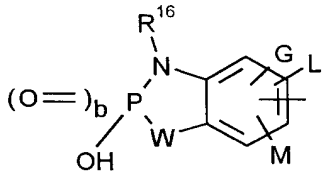
A für einen Rest der Formel



,


,


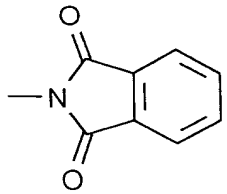

oder




steht,
worin

G, L und M gleich oder verschieden sind und für Wasserstoff, Carboxy, Fluor, Chlor, Brom, Jod, Cyano, Formyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder für eine Gruppe -CO-$NH_2$ stehen,

$R^{12}$ Wasserstoff, Cyclopropylcarbonyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, oder
geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 3 Kohlenstoffatomen, oder
geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 8 Kohlenstoffatomen bedeutet, die gegebenenfalls durch Cyano, Azido, Trifluormethyl, Pyridyl, Fluor, Chlor, Brom, Phenyl, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 4 Kohlenstoffatomen, Benzyloxycarbonyl, Cyclopropyl, Cyclopentyl, Cyclohexyl und/oder durch eine Gruppe der Formel -$(CO)_c$-$NR^{19}R^{20}$, $R^{21}$-N-$SO_2$-$R^{22}$, $R^{23}R^{24}$-N-$SO_2$-, $R^{25}$-S$(O)_d$- oder




substituiert sind,
worin

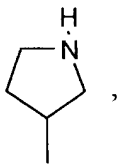
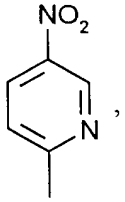
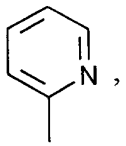
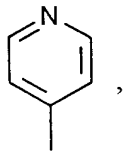
c eine Zahl 0 oder 1 bedeutet,

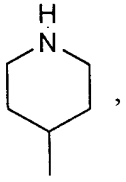
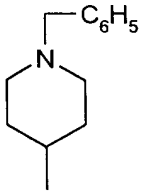
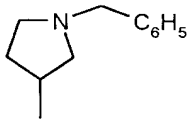
$R^{19}$, $R^{20}$, $R^{21}$, $R^{23}$ und $R^{24}$ gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

d eine Zahl 0, 1 oder 2 bedeutet,

$R^{22}$ und $R^{25}$ gleich oder verschieden sind und
geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder

$R^{12}$ einen Rest der Formeln


,

,

,

,


,

oder


bedeutet oder
eine Gruppe der Formel $-COCCl_3$ oder geradkettiges oder verzweigtes Acyl mit bis zu 4 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Trifluormethyl, Trichlormethyl, eine Gruppe der Formel $-OR^{26}$ substituiert ist,
worin

$R^{26}$ Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Phenyl substituiert ist,
oder

$R^{12}$ eine Gruppe der Formel $-(CO)_e-NR^{27}R^{28}$ oder $R^{33}-S(O)_f$ bedeutet,
worin

e die Zahl 1 bedeutet,

$R^{27}$ und $R^{28}$ gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

f die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist,

$R^{33}$ Methyl, Phenyl, Tolyl oder Benzyl bedeutet,

D ein Sauerstoff oder Schwefelatom bedeutet,

E ein Sauerstoff- oder Schwefelatom oder eine Gruppe der Formel NH bedeutet,

T ein Sauerstoffatom oder die NH-Gruppe bedeutet,

$R^{13}$ und $R^{14}$ die oben angegebene Bedeutung von $R^{12}$ haben und mit dieser gleich oder verschieden sind,
oder

T ein Schwefelatom bedeutet, mit der Maßgabe, daß $R^{13}$ und $R^{14}$ die oben angegebene Bedeutung von $R^{12}$ haben, aber nicht für Wasserstoff stehen,
oder im Fall, daß $R^{12}$, $R^{13}$ und $R^{14}$ nicht für Wasserstoff stehen, E und/oder T

eine Gruppe der Formel $NR^{34}$ bedeuten, worin $R^{34}$ mit Ausnahme von Wasserstoff die oben angegebene Bedeutung von $R^{12}$ hat und mit dieser gleich oder verschieden ist, oder

$R^{34}$ Cyano oder eine Gruppe der Formel $-CO_2R^{35}$ bedeutet,
worin

$R^{35}$ Benzyl oder Phenyl bedeutet, die gegebenenfalls durch Nitro substituiert sind,

V und W die oben angegebene Bedeutung von D haben oder die oben aufgeführte Gruppe $N-R^{14}$ bedeuten und mit dieser gleich oder verschieden sind,

a eine Zahl 1 oder 2 bedeutet,

b eine Zahl 0 oder 1 bedeutet,

$R^{15}$ und $R^{16}$ die oben angegebene Bedeutung von $R^{12}$ haben und mit dieser gleich oder verschieden sind,

und deren tautomeren Formen und Salze.

Ganz besonders bevorzugt sind Verbindungen der allgemeinen Formel (I),
in welcher
G, L und M für Wasserstoff stehen und der Oxazolidinonrest in den Positionen 5 oder 6 an den Phenylring angebunden ist.

Außerdem wurden Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) gefunden, dadurch gekennzeichnet, daß man

[A] Verbindungen der allgemeinen Formeln (II) oder (III)

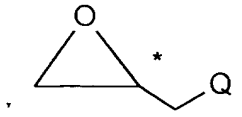
$$A\text{-}N{=}C{=}O \qquad (II)$$

oder

$$A\text{-}CO\text{-}N_3 \qquad (III)$$

in welchen

A die oben angegebene Bedeutungen hat,
mit Lithiumbromid/$(C_4H_9)_3$ P(O) und Epoxiden der allgemeinen Formel (IV)




(IV)

in welcher

Q für $C_1$-$C_6$-Acyloxy steht,

in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base
umsetzt,
und im Fall $R^1$ = OH durch eine typische Esterverseifung oder durch eine typische Umesterung die Hydroxyfunktion freisetzt,
oder

[B] Verbindungen der allgemeinen Formel (V)

$$A\text{-}NH\text{-}CO_2\text{-}X \qquad (V)$$

in welcher

A die oben angegebene Bedeutung hat
und

X für eine typische Schutzgruppe, vorzugsweise Benzyl steht,

in inerten Lösemitteln und in Anwesenheit einer Base, beispielsweise Lithiumalkylen oder Lithium-N-alkyl- oder Lithium-N-silylalkylamiden, vorzugsweise N-Butyllithium, mit Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

[C] im Fall $R^1$ = OH, zunächst Verbindungen der allgemeinen Formel (III) durch Abspaltung von Stickstoff in Alkoholen in die Verbindungen der allgemeinen Formel (Va)

$$A\text{-}NH\text{-}CO_2\text{-}Y \qquad (Va)$$

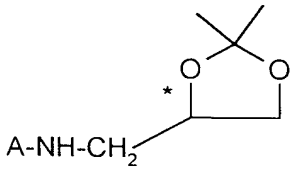
in welcher

A die oben angegebene Bedeutung hat
und

Y für geradkettiges oder verzweigtes $C_2$-$C_6$-Alkyl, vorzugsweise n-Butyl steht,

überführt,
und in einem zweiten Schritt wie unter [A] beschrieben in inerten Lösemitteln und in Anwesenheit einer Base, vorzugsweise Lithium-N-alkyl-oder N-Silylalkylamiden oder n-Butyllithium und Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

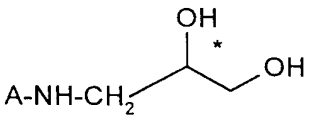
[D] Verbindungen der allgemeinen Formel (VI)




(VI)

in welcher

A die oben angegebene Bedeutung hat,
entweder direkt mit Säuren und Kohlensäurediethylester
umsetzt,
oder zunächst durch Umsetzung der Verbindungen der allgemeinen Formel (VI) mit Säuren die Verbindungen der allgemeinen Formel (VII)




(VII)

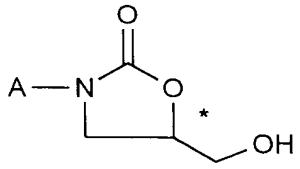
in welcher

A die oben angegebene Bedeutung hat,

herstellt,

und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert,
oder

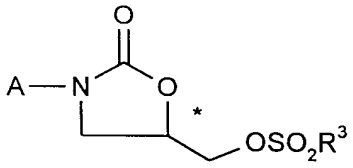
[E] zunächst Verbindungen der allgemeinen Formel (Ia)



(Ia)

in welcher

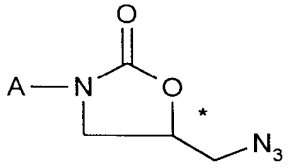
A die oben angegebene Bedeutung hat, durch Umsetzung mit ($C_1$-$C_4$)-Alkyl- oder Phenylsulfonsäurechloriden in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)



(Ib)

in welcher

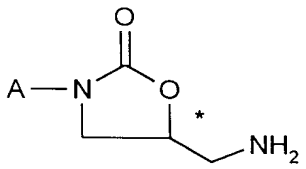
A und $R^3$ die oben angegebene Bedeutung haben,
überführt,
anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (Ic)



(Ic)

in welcher

A die oben angegebene Bedeutung hat,
herstellt,
in einem weiteren Schritt durch Umsetzung mit ($C_1$-$C_4$-O)$_3$-P oder $PPh_3$, vorzugsweise $(CH_3O)_3P$
in inerten Lösemitteln und mit Säuren in die Amine der allgemeinen Formel (Id)



(Id)

in welcher

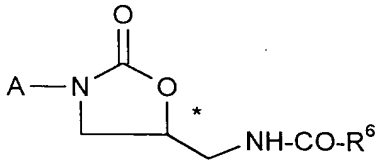
A die oben angegebene Bedeutung hat,
überführt,
und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (VIII)

$$R^{36}\text{-}CO\text{-}R^{6} \qquad \text{(VIII)}$$

in welcher

$R^6$ die oben angegebene Bedeutung hat
und

$R^{36}$ für Halogen, vorzugsweise für Chlor oder für den Rest $-OCOR^6$ steht, in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



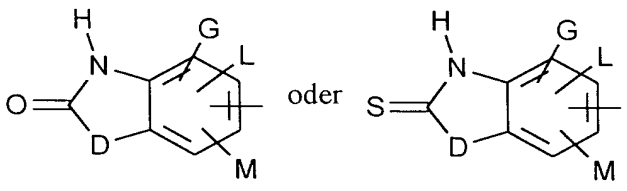
(Ie)

in welcher

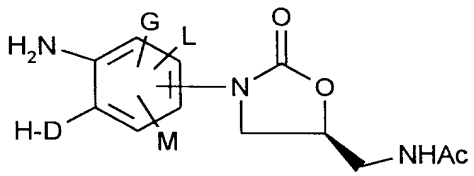
A und $R^6$ die oben angegebene Bedeutung haben,

herstellt,
oder

[F] im Fall A =

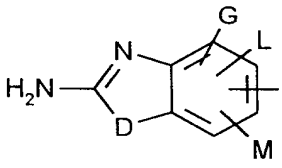


Verbindungen der allgemeinen Formel (IX)



(IX)

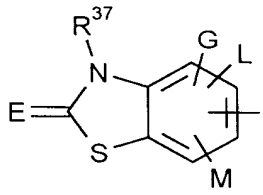
in welcher
G, L, M und D die oben angegebene Bedeutung haben,
entweder mit Carbonyldiimidazol bzw. Thiocarbonyldiimidazol in Dimethylformamid oder durch Umsetzung mit KS-$CO_2$-$C_2H_5$ / $CH_3OH$ und anschließender Zugabe von Wasser cyclisiert,
im Fall A =



die Verbindungen der allgemeinen Formel (IX) mit BrCN / $H_2O$ / $CH_3OH$ umsetzt,
oder

[G] im Fall $R^{12} \neq H$, ausgehend von den Verbindungen mit $R^1$ = NH-$COCH_3$ eine Acylierung oder eine Alkylierung unter Doppelbindungsverschiebung durchführt, oder

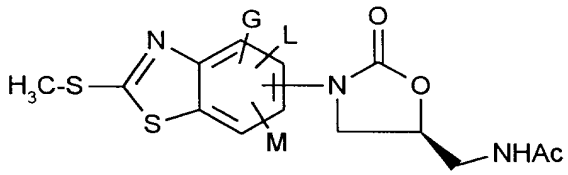
Verbindungen der allgemeinen Formel (I) mit dem Rest



worin

$R^{37}$ $C_1$ -$C_{10}$-Alkyl, vorzugsweise $C_1$-$C_3$-Alkyl bedeutet
und E = O,

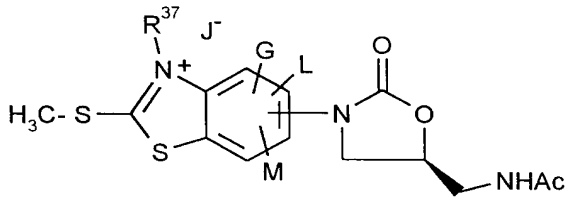
Verbindungen der allgemeinen Formel (X)



(X)

in welcher
G, L und M die oben angegebene Bedeutung haben,

zunächst durch Umsetzung mit $C_1$-$C_{10}$-Alkylhalogeniden, bevorzugt $C_1$-$C_3$-Alkyljodiden, in inerten Lösemitteln in die Salze der Verbindungen der allgemeinen Formel (XI)



(XI)

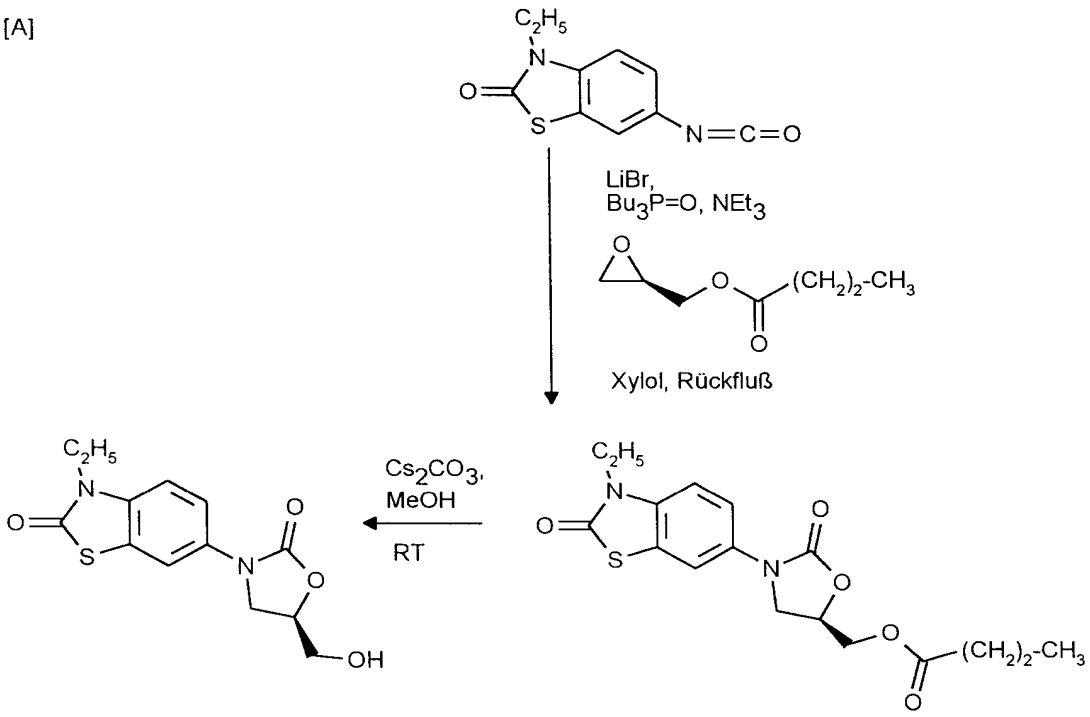
in welcher

$R^{37}$ für $C_1$-$C_{10}$-Alkyl, vorzugsweise für $C_1$-$C_3$-Alkyl steht,

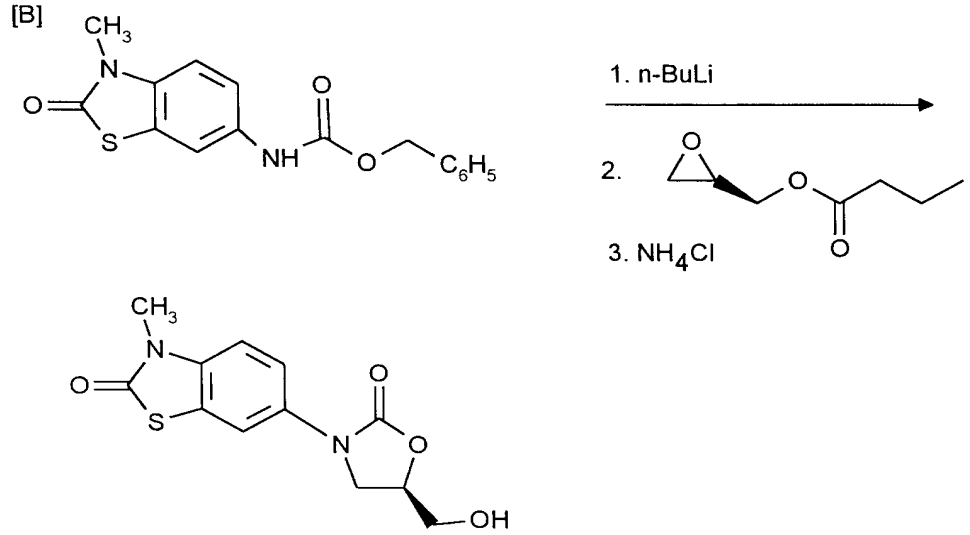
und
G, L und M die oben angegebene Bedeutung haben,
überführt,
und in einem letzten Schritt mit Methanol zur Reaktion bringt,
und im Fall E = S Verbindungen der allgemeinen Formel (XI) einer Thermolyse unterzieht,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
und gegebenenfalls weitere Substituenten oder bereits vorhandene funktionelle Gruppen nach üblichen Methoden, wie beispielsweise Alkylierung, Redoxreaktionen, Substitutionsreaktionen und/oder Verseifungen oder Ein- und Abbau von Schutzgruppen, einführt bzw. derivatisiert.

Die erfindungsgemäßen Verfahren können durch folgende Formelschemata beispielhaft erläutert werden:

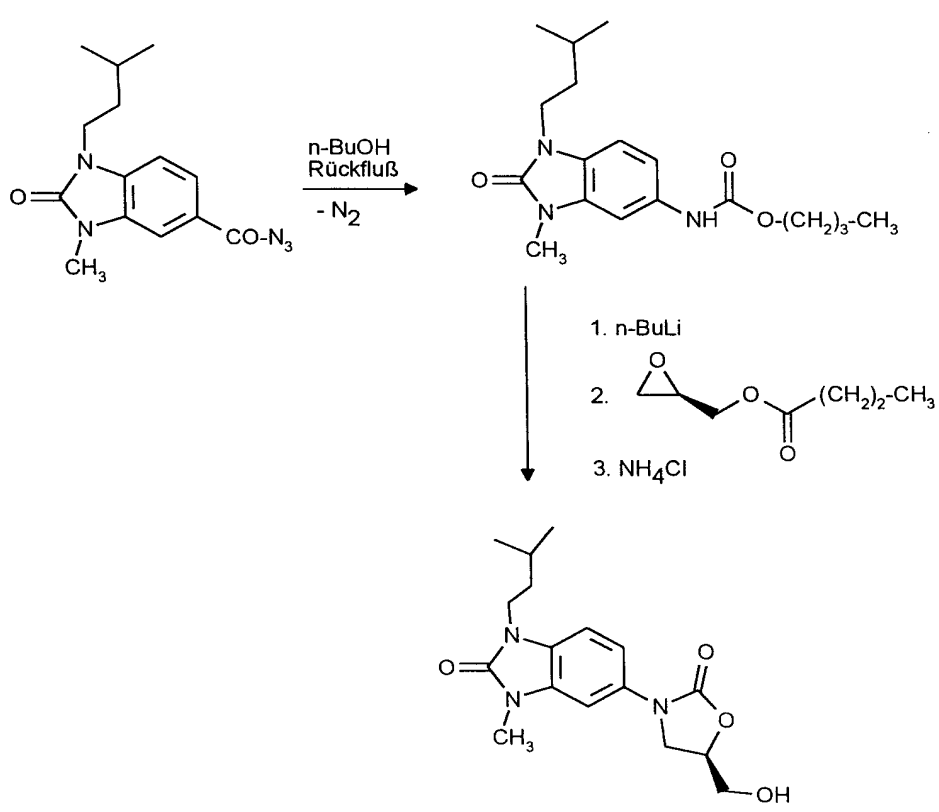
[A]



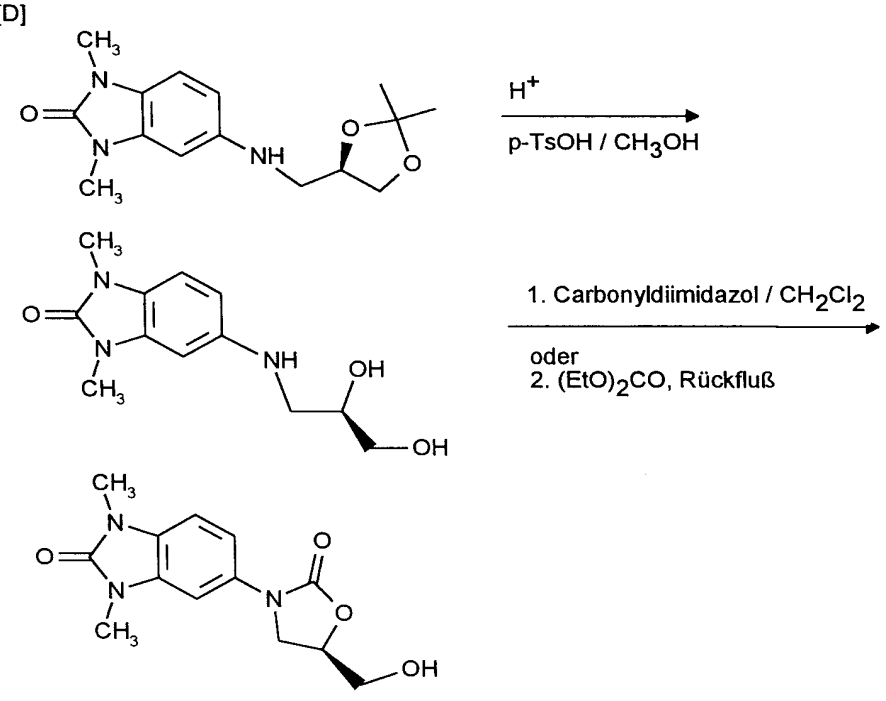

[B]



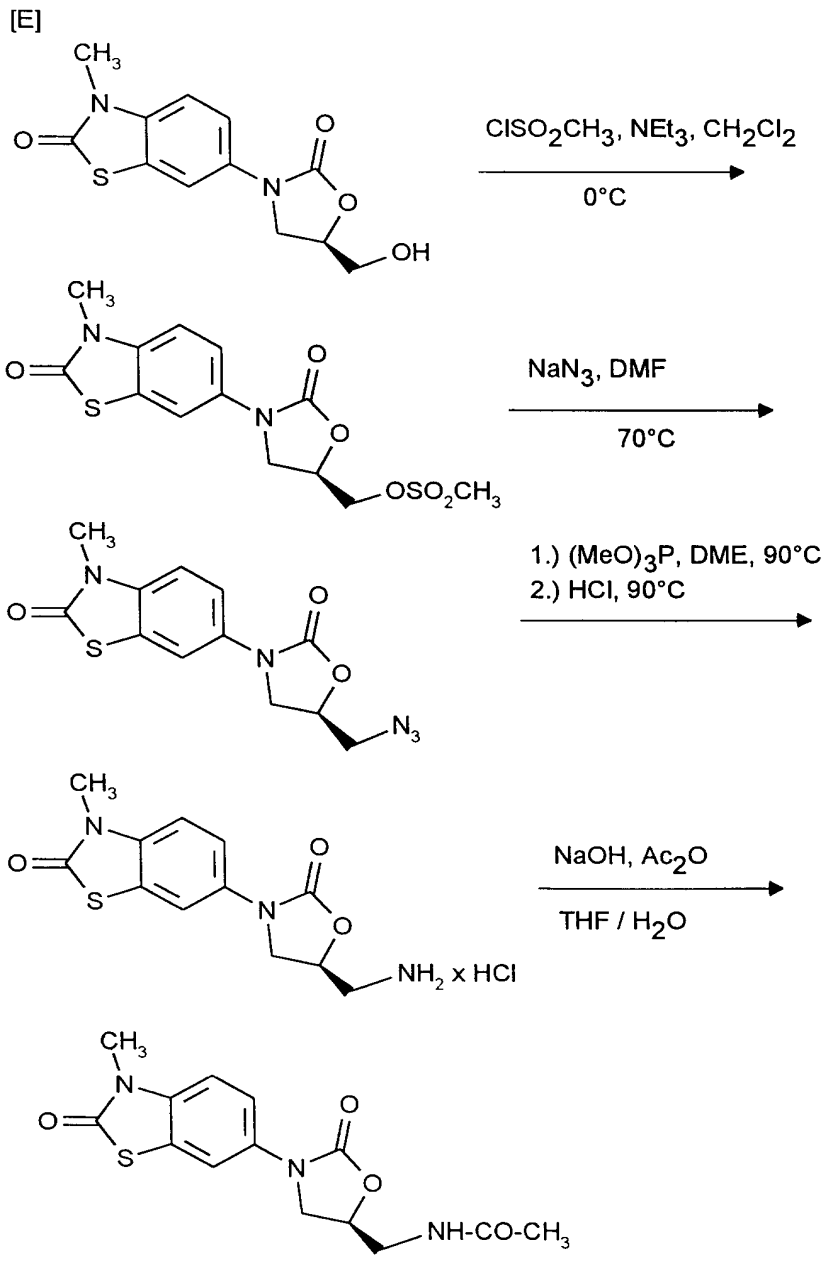
[C]


n-BuOH
Rückfluß
- $N_2$
1. n-BuLi
2.
3. $NH_4Cl$

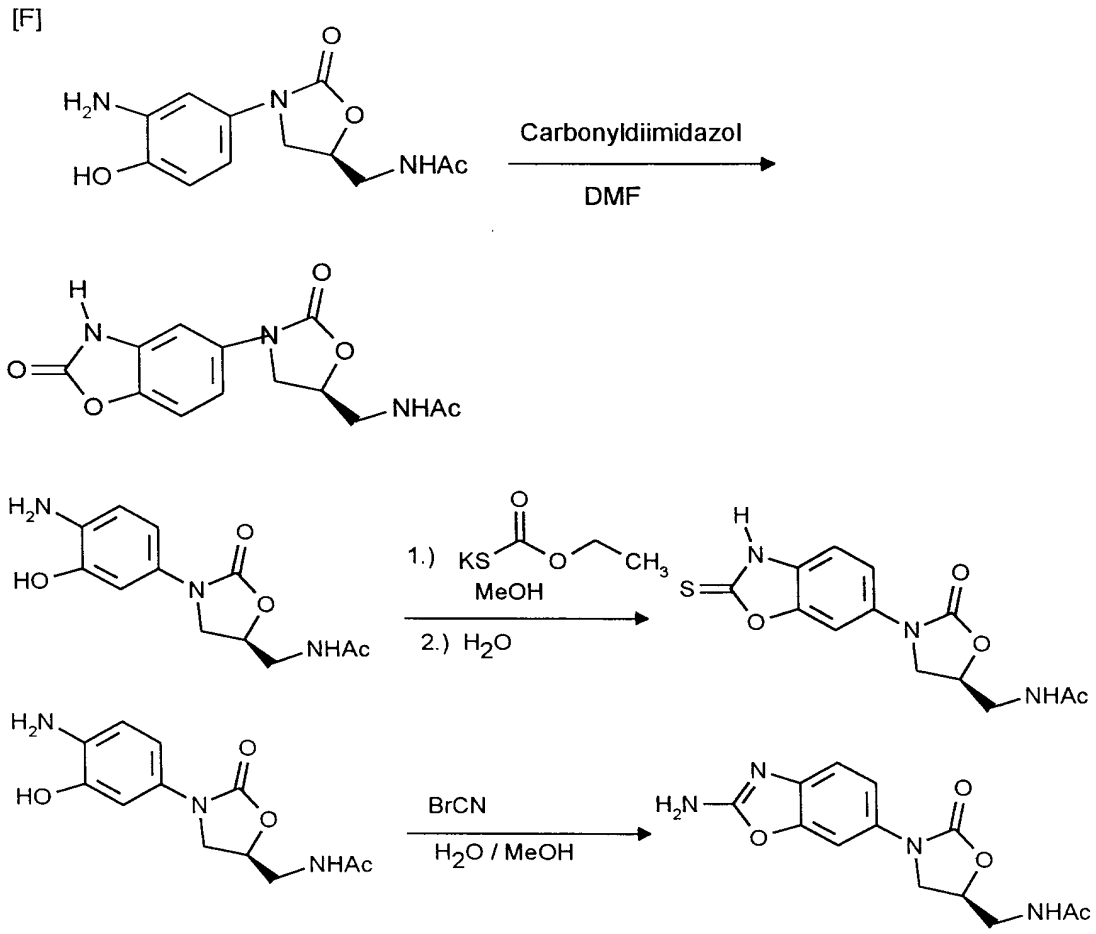
[D]


$H^+$
p-TsOH / $CH_3OH$
1. Carbonyldiimidazol / $CH_2Cl_2$
oder
2. $(EtO)_2CO$, Rückfluß

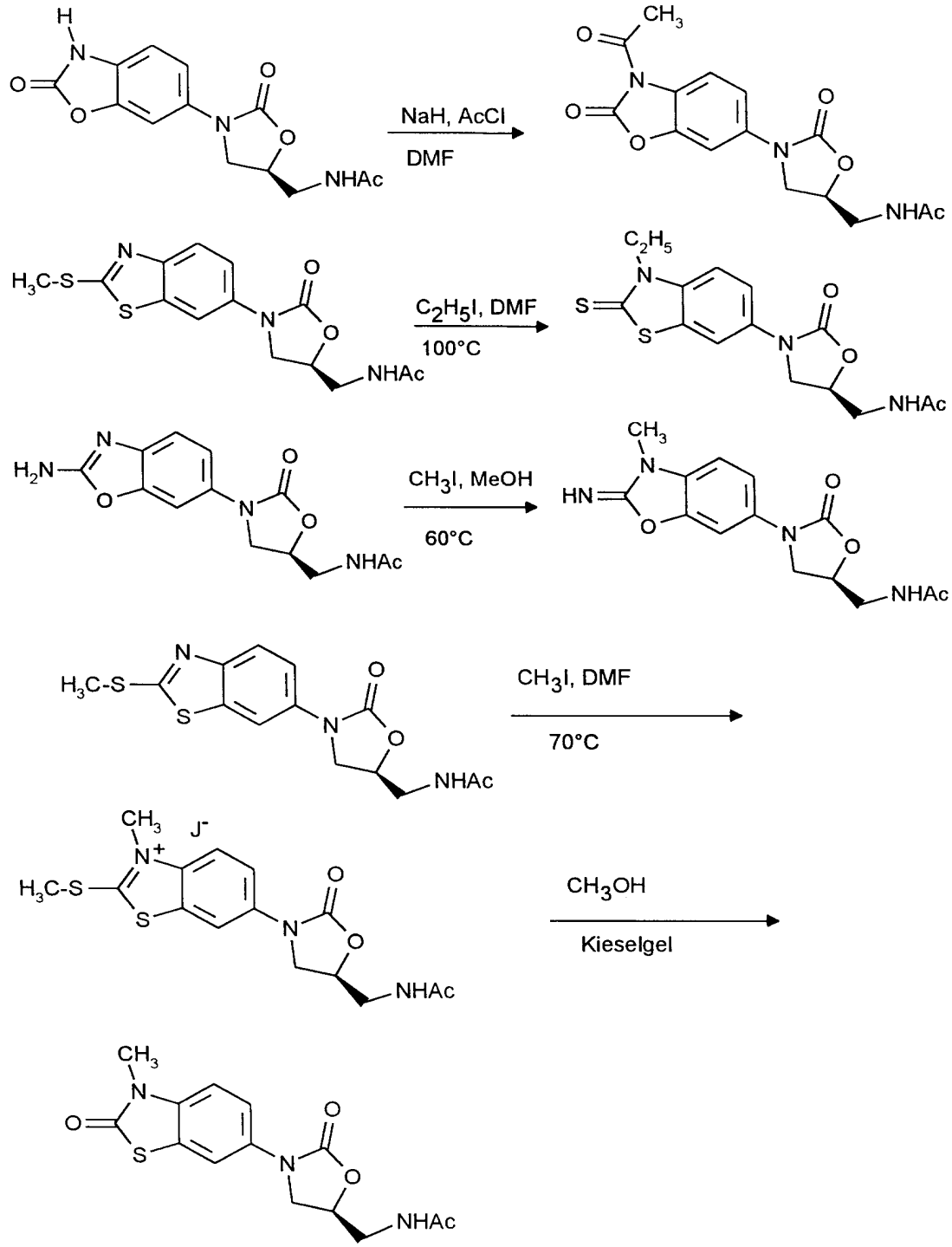
[E]


CH3
N
O
S
O
N
O
OH
ClSO2CH3, NEt3, CH2Cl2
0°C
OSO2CH3
NaN3, DMF
70°C
N3
1.) (MeO)3P, DME, 90°C
2.) HCl, 90°C
NH2 x HCl
NaOH, Ac2O
THF / H2O
NH-CO-CH3

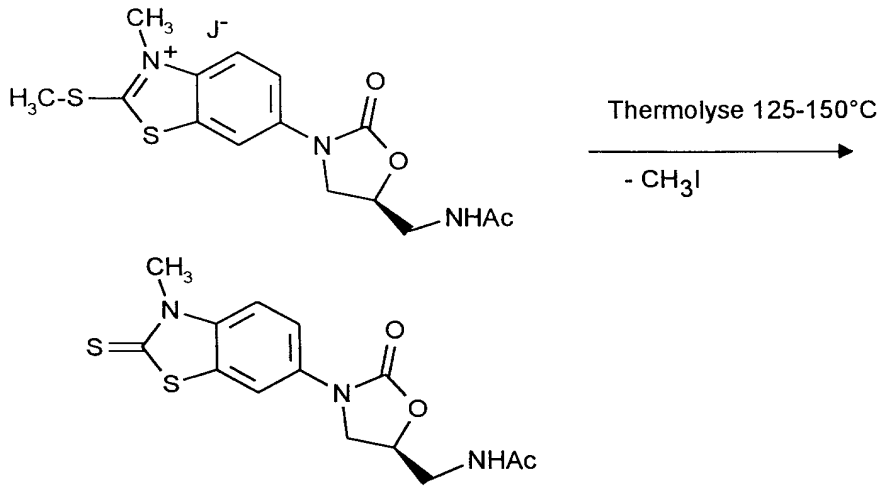
[F]



[G]


NaH, AcCl
DMF
$C_2H_5I$, DMF
100°C
$CH_3I$, MeOH
60°C
$CH_3I$, DMF
70°C
$CH_3OH$
Kieselgel
NHAc
$J^-$

[G]




Als Lösemittel eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether oder tert.Butylmethylether, oder Ketone wie Aceton oder Butanon, oder Amide wie Dimethylformamid oder Hexamethyl-phosphorsäuretriamid, oder Kohlenwasserstoffe wie Hexan, Benzol, Dichlorbenzol, Xylol oder Toluol, oder Dimethylsulfoxid, Acetonitril, Essigester, oder Halogenkohlenwasserstoffe wie Methylenchlorid, Chloroform oder Tetrachlorkohlenstoff, oder Pyridin, Picolin oder N-Methylpiperidin. Ebenso können Gemische der genannten Lösemittel verwendet werden.

Als Basen eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen anorganischen oder organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natrium- oder Kaliummethanolat, oder Natrium- oder Kaliumethanolat, oder organische Amine wie Ethyldiisopropylamin, Triethylamin, Picolin, Pyridine oder N-Methylpiperidin, oder Amide wie Natriumamid oder Lithiumdiisopropylamid, oder Lithium-N-silylalkylamide, wie beispielsweise Lithium-N-(bis)triphenylsilylamid oder Lithiumalkyle wie n-Butyllithium.

Die Base wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 3 mol bezogen auf 1mol der Verbindungen der allgemeinen Formeln (II), (III), (IV) und (Va) eingesetzt.

Alle Umsetzungen werden im allgemeinen bei normalem, erhöhtem oder bei erniedrigtem Druck durchgeführt (z.B. 0,5 bis 5 bar). Im allgemeinen arbeitet man bei Normaldruck.

Das Verfahren [A] erfolgt bevorzugt in Xylol oder Dichlorbenzol, gegebenenfalls in Gegenwart von Triethylamin, unter Rückfluß.

Die basenkatalysierte Umesterung wird mit einem der oben aufgeführten Alkohole, vorzugsweise Methanol, in einem Temperaturbereich von -10°C bis +40°C, vorzugsweise bei Raumtemperatur durchgeführt.

Als Basen eignen sich im allgemeinen Natriumhydrogencarbonat, Natriummethanolat, Hydrazinhydrat, Kaliumcarbonat oder Caesiumcarbonat. Bevorzugt ist Caesiumcarbonat.

Das Verfahren [B] erfolgt in einem der oben aufgeführten Ether mit Lithiumalkylverbindungen oder Lithium-N-silylamiden, wie beispielsweise n-Butyllithium, Lithiumdiisopropylamid oder Lithium-bistrimethylsilylamid, vorzugsweise in Tetrahydrofuran und Lithium-bis-trimethylsilylamid oder n-Butyllithium, in einem Temperaturbereich von -100°C bis +20°C, vorzugsweise von -75°C bis -40°C.

Für das Verfahren [C] eignen sich für den 1. Schritt vorzugsweise die oben aufgeführten Alkohole, im Falle der anschließenden Cyclisierung Tetrahydrofuran.

Als Basen für die Cyclisierung eignen sich vorzugsweise die oben aufgeführten Lithium-N-silylalkylverbindungen oder n-Butyllithium. Besonders bevorzugt ist n-Butyllithium.

Der erste Reaktionsschritt wird bei der Siedetemperatur des entsprechenden Alkohols, die Cyclisierung in einem Temperaturbereich von -70°C bis Raumtemperatur durchgeführt.

Die Cyclisierung [D] wird in Anwesenheit eines Hilfsmittels und/oder Anwesenheit einer Säure durchgeführt.

Als Säuren eignen sich im allgemeinen anorganische Säuren wie beispielsweise Salzsäure oder Schwefelsäure, oder organische Carbonsäuren mit 1-6 C-Atomen, gegebenenfalls substituiert durch Fluor, Chlor und/oder Brom, wie

beispielsweise Essigsäure, Trifluoressigsäure, Trichloressigsäure oder Propionsäure, oder Sulfonsäuren mit $C_1$-$C_4$-Alkylresten oder Arylresten wie beispielsweise Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure oder Toluolsulfonsäure. Besonders bevorzugt ist Salzsäure.

Die Säure wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 2 mol, bezogen auf 1 mol der Verbindungen der allgemeinen Formel (VI) eingesetzt.

Als Hilfsmittel eignen sich die üblichen Reagenzien wie Phosgen, Carbonyldiimidazol oder Kohlensäurediethylester oder Chlorameisensäuretrichlormethylester. Bevorzugt sind Carbonyldiimidazol, Kohlensäurediethylester oder Chlorameisensäuretrichlormethylester.

Als Lösemittel eignen sich die oben aufgeführten Halogenkohlenwasserstoffe. Bevorzugt ist Methylenchlorid.

Die Cyclisierungen erfolgen im allgemeinen in einem Temperaturbereich von -20°C bis 100°C, vorzugsweise bei -20°C bis Raumtemperatur.

Die Acylierung [E] erfolgt im allgemeinen in einem der oben aufgeführten Ether oder Halogenkohlenwasserstoffen, vorzugsweise Tetrahydrofuran oder Methylenchlorid, in einem Temperaturbereich von -30°C bis 50°C, bevorzugt von -10°C bis Raumtemperatur.

Die Reduktionen erfolgen im allgemeinen mit Hydriden in inerten Lösemitteln oder mit Boranen, Diboranen oder ihren Komplexverbindungen.

Die Reduktionen können im allgemeinen durch Wasserstoff in Wasser oder in inerten organischen Lösemitteln wie Alkoholen, Ethern oder Halogenkohlenwasserstoffen, oder deren Gemischen, mit Katalysatoren wie Raney-Nickel, Palladium, Palladium auf Tierkohle oder Platin, oder mit Hydriden oder Boranen in inerten Lösemitteln, gegebenenfalls in Anwesenheit eines Katalysators durchgeführt werden.

Bevorzugt werden die Reduktionen mit Hydriden, wie komplexen Borhydriden oder Aluminiumhydriden sowie Boranen durchgeführt. Besonders bevorzugt werden hierbei Natriumborhydrid, Lithiumborhydrid, Natriumcyanoborhydrid, Lithiumaluminiumhydrid, Natrium-bis-(2-methoxyethoxy)aluminiumhydrid oder Boran-Tetrahydrofuran eingesetzt.

Die Reduktion der Azide [E] erfolgt mit $(CH_3O)_3P$ und Salzsäure.

Die Reduktion erfolgt im allgemeinen in einem Temperaturbereich von - 50°C bis zum jeweiligen Siedepunkt des Lösemittels, bevorzugt von -20°C bis +90°C.

Als Lösemittel eignen sich hierbei alle inerten organischen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, Tetrahydrofuran, Glykoldimethylether, oder Diethylenglykoldimethylether oder Amide wie Hexamethylphosphorsäuretriamid oder Dimethylformamid, oder Essigsäure. Ebenso ist es möglich, Gemische der genannten Lösemittel zu verwenden.

Die Abspaltung der Hydroxyschutzgruppen erfolgt im allgemeinen nach üblicher Methode, beispielsweise durch hydrogenolytische Spaltung der Benzylether in den oben aufgeführten inerten Lösemitteln in Anwesenheit eines Katalysators mit Wasserstoff-Gas.

Die Abspaltung der Aminoschutzgruppe erfolgt im allgemeinen, ebenfalls nach üblichen Methoden, abspaltet und zwar vorzugsweise Boc mit Salzsäure in Dioxan, Fmoc mit Piperidin und Z mit HBr/HOAc oder durch Hydrogenolyse.

Die oben aufgeführten anderen Derivatisierungsreaktionen erfolgen im allgemeinen nach denen in Compendium of Organic Synthetic Methods, T.T Harrison und S. Harrison, Wiley Interscience, publizierten Methoden.

Bevorzugt werden Redoxreaktionen, reduktive Aminierung, Umesterung und die Halogenisierung von Methylgruppen mit N-Bromsuccinimid (NBS) oder N-Chlorsuccinimid (NCS) aufgeführt, die im folgenden beispielhaft erläutert werden.

Als Lösemittel für die Alkylierung eignen sich übliche organische Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Ether wie Diethylether, Dioxan, Tetrahydrofuran, Glykoldimehylether, oder Kohlenwasserstoffe wie Benzol, Toluol, Xylol, Hexan, Cyclohexan oder Erdölfraktionen, oder Halogenkohlenwasserstoffe wie Dichlormethan, Trichlormethan, Tetrachlormethan, Dichlorethylen, Trichlorethylen oder Chlorbenzol, oder Essigester, oder Triethylamin, Pyriden, Dimethylsulfoxid, Dimethylformamid, Acetonitril, Aceton oder Nitromethan. Ebenso ist es möglich, Gemische der genannten Lösemittel zu verwenden. Bevorzugt sind Dichlormethan, Dimethylsulfoxid und Dimethylformamid.

Die Alkylierung wird in den oben aufgeführten Lösemitteln bei Temperaturen von 0°C bis +150°C, vorzugsweise bei Raumtemperaturen bis +100°C, bei Normaldruck durchgeführt.

Die Amidierung und die Sulfoamidierung erfolgen im allgemeinen in inerten Lösemitteln in Anwesenheit einer Base und eines Dehydratisierungsmittels.

Als Lösemittel eignen sich hierbei inerte organische Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören Halogenkohlenwasserstoffe wie Dichlormethan, Trichlormethan, Tetrachlormethan, 1,2-Dichlorethan, Trichlorethan, Tetrachlorethan, 1,2-Dichlorethan oder Trichlorethylen, Kohlenwassserstoffe wie Benzol, Xylol, Toluol, Hexan, Cyclohexan, oder Erdölfraktionen, Nitromethan, Dimethylformamid, Acetonitril oder Tetrahydrofuran. Ebenso ist es möglich, Gemische der Lösemittel einzusetzen. Besonders bevorzugt sind Dichlormethan und Tetrahydrofuran.

Als Basen für die Amidierung und die Sulfoamidierung eignen sich die üblichen basischen Verbindungen. Hierzu gehören vorzugsweise Alkali- und Erdalkalihydroxide wie Lithiumhydroxid, Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, Alkalihydride wie Natriumhydrid, Alkali- oder Erdalkalicarbonate wie Natriumcarbonat, Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natriummethanolat oder -ethanolat, Kaliummethanolat oder -ethanolat oder Kalium-tert.-buylat, oder organische Amine wie Benzyltrimethylammoniumhydroxid, Tetrabutylammoniumhydroxid, Pyridin, Triethylamin oder N-Methylpiperidin.

Die Amidierung und die Sulfoamidierung werden im allgemeinen in einem Temperaturbereich von 0°C bis 150°C, bevorzugt bei 25°C bis 40°C, durchgeführt.

Die Amidierung und die Sulfoamidierung werden im allgemeinen bei Normaldruck durchgeführt. Es ist aber auch möglich, das Verfahren bei Unterdruck oder bei Überdruck durchzuführen (z.B. in einem Bereich von 0,5 bis 5 bar).

Bei der Durchführung der Amidierung und der Sulfoamidierung wird die Base im allgemeinen in einer Menge von 1 bis 3 Mol, bevorzugt von 1 bis 1,5 Mol, bezogen auf 1 Mol der jeweiligen Carbonsäure, eingesetzt.

Als Dehydratisierungsreagenzien eignen sich Carbodiimide wie beispielsweise Diisopropylcarbodiimid, Dicyclohexylcarbodiimid oder N-(3-Dimethylaminopropyl)--N'-ethylcarbodiimid-Hydrochlorid oder Carbonylverbindungen wie Carbonyldiimidazol oder 1,2-Oxazoliumverbindungen wie 2-Ethyl-5-phenyl-1,2-oxazolium-3-sulfonat oder Propanphosphorsäureanhydrid oder Isobutylchloroformat oder Benzotriazolyloxy-tris-(dimethylamino)phosphonium-hexyfluorophosphat oder Phosphonsäurediphenylesteramid oder Methansulfonsäurechlorid, gegebenenfalls in Anwesenheit von Basen wie Triethylamin oder N-Ethylmorpholin oder N-Methylpiperidin oder 4-Dimethylaminopyridin.

Als Basen eignen sich für die Verseifung die üblichen anorganischen Basen. Hierzu gehören bevorzugt Alkalihydroxide oder Erdalkalihydroxide wie beispielsweise Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat oder Natriumhydrogencarbonat. Besonders bevorzugt werden Natriumhydroxid oder Kaliumhydroxid eingesetzt.

Als Lösemittel eignen sich für die Verseifung Wasser oder die für eine Verseifung üblichen organischen Lösemittel. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol, Isopropanol oder Butanol, oder Ether wie Tetrahydrofuran oder Dioxan, oder Dimethylformamid oder Dimethylsulfoxid. Besonders bevorzugt werden Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol verwendet. Ebenso ist es möglich, Gemische der genannten Lösemittel einzusetzen.

Die Verseifung wird im allgemeinen in einem Temperaturbereich von 0°C bis +100°C, bevorzugt von +20°C bis +80°C durchgeführt.

Im allgemeinen wird die Verseifung bei Normaldruck durchgeführt. Es ist aber auch möglich, bei Unterdruck oder bei Überdruck zu arbeiten (z.B. von 0,5 bis 5 bar).

Bei der Durchführung der Verseifung wird die Base im allgemeinen in einer Menge von 1 bis 3 Mol, bevorzugt von 1 bis 1,5 Mol bezogen auf 1 Mol des Esters eingesetzt. Besonders bevorzugt verwendet man molare Mengen der Reaktanden.

Die Veresterung erfolgt im allgemeinen mit den entsprechenden Alkoholen in Anwesenheit von Säuren, vorzugsweise Schwefelsäure, in einem Temperaturbereich von 0°C bis 150°C, vorzugsweise von 50°C bis 100°C und Normaldruck.

Die Verbindungen der allgemeinen Formeln (IV) und (VIII) sind bekannt oder können nach üblichen Methoden hergestellt werden.

Die Verbindungen der allgemeinen Formel (VII) sind größtenteils neu und können beispielsweise wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (II) sind teilweise bekannt oder neu und können dann beispielsweise hergestellt werden, indem man die entsprechenden Amine mit Chlorameisensäuretrichlorethylester in einem der oben aufgeführten Lösemittel, vorzugsweise Xylol bei Rückflußtemperatur umsetzt.

Die Verbindungen der allgemeinen Formel (III) sind teilweise bekannt oder neu und können dann beispielsweise hergestellt werden, indem man ausgehend von den entsprechenen Carbonsäuren entweder mit Chlorameisensäureisobutylester / Aceton, Natriumazid/Wasser oder mit Diphenylphosphorylazid / Tetrahydrofuran oder mit Xylol oder Methylenchlorid in Gegenwart einer der oben angegebenen Basen, vorzugsweise Triethylamin, bei -10°C bis Raumtemperatur umsetzt.

Die Verbindungen der allgemeinen Formeln (V) und (Va) sind teilweise bekannt oder neu und können entweder durch Abspaltung von Stickstoff aus den entsprechenden Carbonsäureaziden und Umsetzung mit den entsprechenden Alkoholen oder durch Umsetzung der entsprechenden Amine mit Chlorameisensäureestern, vorzugsweise Chlorameisensäurebenzylester in einem der oben aufgeführten Lösemittel, vorzugsweise Tetrahydrofuran oder Dioxan, in einem Temperaturbereich von -10°C bis 200°C, vorzugsweise von 0°C bis 150°C, hergestellt werden.

Die Verbindungen der allgemeinen Formel (Ia) sind neu und können beispielsweise wie unter [A], [B], [D] oder [E] beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (Ib), (Ic), (Id) und (Ie) sind neu und können wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (VI) sind größtenteils bekannt oder neu und können beispielsweise hergestellt werden, indem man ausgehend von den freien Aminen (Ia) entweder mit dem Acetonid von Glycerinaldehyd in Methanol und in Anwesenheit von Natriumacetat / Natriumcyanborhydrid oder von Natriumboranat und Methanol in einem Temperaturbereich von -20°C bis +40°C, bevorzugt von -10°C bis 20°C und Normaldruck umsetzt.

Die Umsetzung der Verbindungen der allgemeinen Formel (IX) [F] erfolgt in einem Temperaturbereich von -10°C bis 150°C, vorzugsweise von 10°C bis 60°C und Normaldruck.

Die Verbindungen der allgemeinen Formel (IX) sind vom Bedeutungsumfang der EP 609 905 umfaßt, als konkrete Verbindungen aber neu und können in Analogie zu dem oben aufgeführten Verfahren [E] durch Einsatz von Acetylchlorid hergestellt werden.

Die Acylierungen [G] erfolgen im allgemeinen in einem der oben aufgeführten Lösemitteln, vorzugsweise Dimethylformamid, in Anwesenheit einer Base, vorzugsweise Natriumhydrid, in einem Temperaturbereich von 0°C bis 150°C, vorzugsweise von 20°C bis 80°C und Normaldruck.

Die Alkylierungen unter Doppelbindungsverlagerung erfolgen in Abhängigkeit des Restes A in einem der oben aufgeführten Lösemitteln` vorzugsweise Dimethylformamid oder Methanol, in einem Temperaturbereich von 30°C bis 150°C, vorzugsweise von 50°C bis 110°C und Normaldruck.

Die Umsetzung zu den Verbindungen der allgemeinen Formel (XI) [G] erfolgt in einem der oben aufgeführten Lösemitteln, vorzugsweise Dimethylformamid in einem Temperaturbereich von -10°C bis 150°C, vorzugsweise von 20°C bis 70°C und Normaldruck.

Die Thermolyse [G] erfolgt in einem Temperaturbereich von 80°C bis 200°C, bevorzugt von 125°C bis 150°C.

Die Oxidation zum S-oxid erfolgt im allgemeinen in einem der oben aufgeführten Lösemittel, vorzugsweise in Methylenchlorid mit Oxidationsmitteln wie beispielsweise Metachlorperbenzoesäure, Wasserstoffperoxid, Peressigsäure oder Oxon, vorzugsweise mit Metachlorperbenzoesäure in einem Temperaturbereich von 0°C bis 80°C, bevorzugt von 20°C bis 60°C.

Die Verbindungen der Formel (X) sind als konkrete Verbindungen neu und können in Analogie zu dem oben aufgeführten Verfahren [E] hergestellt werden.

Die Verbindungen der allgemeinen Formel (XI) sind neu und können wie oben beschrieben hergestellt werden.

Die MHK-Werte wurden mit Hilfe der Mikrodilutionsmethode in BH-Medium bestimmt. Jede Prüfsubstanz wurde im Nährmedium gelöst. In der Mikrotiterplatte wurde durch serielle Verdünnung eine Konzentrationsreihe der Prüfsubstanzen angelegt. Zur Inokulation wurden Übernachtkulturen der Erreger verwandt, die zuvor im Nährmedium 1:250 verdünnt wurden. Zu 100 µl der verdünnten, wirkstoffhaltigen Nährlösungen wurden je 100 µl Inokulationslösung gegeben.

Die Mikrotiterplatten wurden bei 37°C bebrütet und nach ca. 20 Stunden (stapho) oder nach 3 bis 5 Tagen (Mycobacterium) abgelesen. Der MHK-Wert (µg/ml) gibt die niedrigste Wirkstoffkonzentration an, bei der kein Wachstum zu erkennen war.

MHK-Werte (µg/ml):

| Bsp.-Nr. | Staph. 133 | Staph. 48N | Staph 25701 | Staph. 9TV | E. coli Neumann | Klebs. 57 USA | Psdm. Bonn |
|---|---|---|---|---|---|---|---|
| 17 | 8 | 8 | 8 | 8 | >64 | >64 | >64 |
| 18 | 0,25 | 0,25 | 0,25 | 0,06 | >64 | >64 | >64 |
| 22 | 1 | 1 | 1 | 0,5 | >64 | >64 | >64 |
| 24 | 8 | 16 | 16 | 16 | >64 | >64 | >64 |
| 37 | 1 | 1 | 1 | 0,5 | 16 | 64 | 64 |
| 38 | 4 | 4 | 4 | 1 | >64 | >64 | >64 |
| 39 | 4 | 4 | 4 | 4 | >64 | >64 | >64 |
| 43 | 0,25 | 0,125 | 0,25 | 0,125 | >32 | >64 | >64 |
| 44 | 0,5 | 0,5 | 0,5 | 0,5 | >64 | >64 | >64 |
| 38 | 4 | 4 | 4 | 1 | >64 | >64 | >64 |
| 47 | 0,5 | 0,5 | 0,5 | 0,25 | 32 | 64 | >64 |
| 56 | 0,5 | 0,5 | 0,5 | 0,25 | 64 | >64 | >64 |
| 70 | 0,5 | 0,5 | 0,5 | 0,5 | >64 | >64 | >64 |

| Bsp.-Nr. | Staph. 133 | Staph. 48N | Staph 25701 | Staph. 9TV | E. coli Neumann | Klebs. 57 USA | Psdm. Bonn |
|---|---|---|---|---|---|---|---|
| 62 | 1 | 1 | 1 | 0,5 | >64 | >64 | >64 |
| 84 | 1 | 1 | 1 | 0,5 | 64 | >64 | >64 |
| 94 | 0,5 | 0,5 | 0,5 | 0,25 | 64 | >64 | >64 |

MHK-Werte (µg/ml)
Keim: Mycobacterium smegmacis

| Bsp.-Nr. | DSM 43061 | DSM 43078 | DSM 43277 | DSM 43299 | DSM 43464 | DSM 43465 |
|---|---|---|---|---|---|---|
| 18 | 0,25 | 0,25 | 0,25 | 1 | 1 | 0,5 |
| 56 | 1 | 1 | 0,25 | 1 | 4 | 0,5 |
| 54 | 4 | 1 | 2 | 4 | 16 | 4 |
| 70 | 0,25 | 0,125 | 0,5 | 2 | 8 | 1 |

Die erfindungsgemäßen Verbindungen der allgemeinen Formeln (I), (Ia), (Ib), (Ic), (Id), (Id) und (Ie) weisen bei geringer Toxizität ein breites antibakterielles Spektrum, speziell gegen gram-positive Bakterien sowie Mycobacterien, Corynebacterien, Haemophilus Influenzae und Anaerobae Keime auf. Diese Eigenschaften ermöglichen ihre Verwendung als chemotherapeutische Wirkstoffe in der Human- und Tiermedizin.

Die erfindungsgemäßen Verbindungen sind gegen ein breites Spektrum von Mikroorganismen wirksam. Mit ihrer Hilfe können gram-positive Bakterien und bakterienähnliche Mikroorganismen, wie Mycoplasmen, bekämpft sowie die durch diese Erreger hervorgerufenen Erkrankungen verhindert, gebessert und/oder geheilt werden.

Besonders wirksam sind die erfindungsgemäßen Verbindungen gegen Bakterien und bakterienähnliche Mikroorganismen. Sie sind daher besonders gut zur Prophylaxe und Chemotherapie von lokalen und systemischen Infektionen in der Human- und Tiermedizin geeignet, die durch solche Erreger hervorgerufen werden.

Zur vorliegenden Erfindung gehören pharmazeutische Zubereitungen, die neben nicht-toxischen, inerten pharmazeutisch geeigneten Trägerstoffen eine oder mehrere erfindungsgemäße Verbindungen enthalten oder die aus einem oder mehreren erfindungsgemäßen Wirkstoffen bestehen, sowie Verfahren zur Herstellung dieser Zubereitungen.

Der oder die Wirkstoffe können gegebenenfalls in einem oder mehreren der oben angegebenen Trägerstoffe auch in mikroverkapselter Form vorliegen.

Die therapeutisch wirksamen Verbindungen sollen in den oben aufgeführten pharmazeutischen Zubereitungen vorzugsweise in einer Konzentration von etwa 0,1 bis 99,5, vorzugsweise von etwa 0,5 bis 95 Gew.-%, der Gesamtmischung vorhanden sein.

Die oben aufgeführten pharmazeutischen Zubereitungen können außer den erfindungsgemäßen Verbindungen auch weitere pharmazeutische Wirkstoffe enthalten.

Im allgemeinen hat es sich sowohl in der Human- als auch in der Veterinärmedizin als vorteilhaft erwiesen, den oder die erfindungsgemäßen Wirkstoffe in Gesamtmengen von etwa 0,5 bis etwa 500, vorzugsweise 5 bis 100 mg/kg Körpergewicht je 24 Stunden, gegebenenfalls in Form mehrerer Einzelgaben, zur Erzielung der gewünschten Ergebnisse zu verabreichen. Eine Einzelgabe enthält den oder die erfindungsgemäßen Wirkstoffe vorzugsweise in Mengen von etwa 1 bis etwa 80, insbesondere 3 bis 30mg/kg Körpergewicht.

Die erfindungsgemäßen Verbindungen können zum Zweck der Erweiterung des Wirkungsspektrums und um eine Wirkungssteigerung zu erreichen auch mit anderen Antibiotika kombiniert werden.

Anhang zum experimentellen Teil

Liste der verwendeten Laufmittelgemische zur Chromatographie:

| | |
|---|---|
| I | Dichlormethan : Methanol |
| II | Toluol : Ethylacetat |
| III | Acetonitril : Wasser |
| IV | Ethylacetat |
| V | Petrolether : Ethylacetat |
| VI | Dichlormethan : Ethanol |
| VII | Toluol : Ethanol |
| VIII | Toluol : Ethanol : Triethylamin |

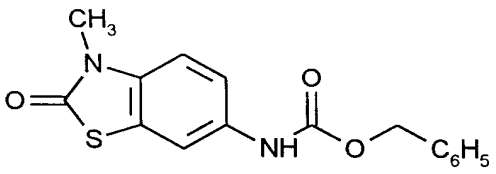
Abkürzungen:

| | |
|---|---|
| Z | Benzyloxycarbonyl |
| Boc | tert.Butoxycarbonyl |
| DMF | Dimethylformamid |
| Ph | Phenyl |
| Me | Methyl |
| THF | Tetrahydrofuran |
| CDI | Carbonyldiimidazol |
| DCE | Dichlorethan |

**Ausgangsverbindungen**

**Beispiel I**

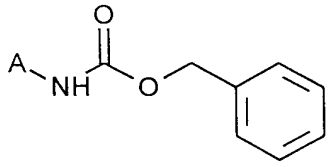
6-(Benzyloxycarbonylamino)-3-methyl-2-benzothiazolinon

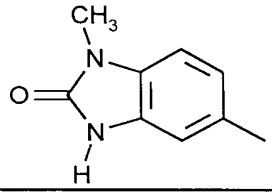
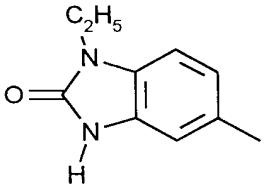
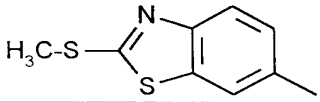


1,76 g (8,12 mmol) 6-Amino-3-methyl-2(3H)-benzothiazolon-hydrochlorid (J. Heterocyclic Chem. 1992, 29, 1069) in 17 ml Wasser, 14 ml THF und 17 ml ges. $NaHCO_3$-Lösung werden bei 0°C tropfenweise mit 1,3 ml (9,10 mmol) Chlorameisensäurebenzylester versetzt. Nach 1 h werden 120 ml Wasser hinzugegeben, das THF im Vakuum abgezogen, der Niederschlag abgesaugt, dreimal mit Wasser, zweimal mit Petrolether gewaschen und bei 60°C getrocknet.
Ausbeute: 2,44 g (96%)
Smp.: 183°C
$R_f$ (II, 7:3) = 0,39
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 7,77 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,23 - 7,45 (m, 6H, Ph), 7,22 (d, J = 6 Hz, 1H, Benzothiazolinon 4-H); 5,15 (s, 2H); 3,38 (s, 3H-$CH_3$).

Wie für Beispiel I beschrieben erhält man aus den entsprechenden Aminen mit Chlorameisensäurebenzylester die in Tabelle I aufgeführten Verbindungen:

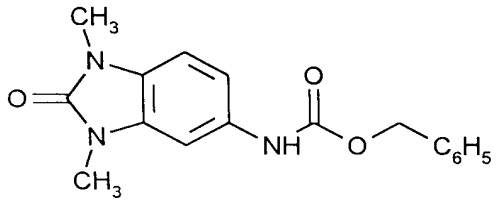
**Tabelle I:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (DCI, $NH_3$) m/z $(M+H)^+$ |
|---|---|---|---|---|---|
| II |  | 96 | 241 | 0,24 (I, 95:5) | 298 |
| III |  | 99 | 211 | 0,43 (I, 9:1) | 312 |
| IV |  | 96 | 111 | 0,71 (II, 1:4) | 331 |

**Beispiel V**

5-(Benzyloxycarbonylamino)-1,3-dimethyl-2-benzoimidazolinon



Eine gerührte Suspension von 2,49 g (8,37 mmol) der Verbindung aus Beispiel II, 3,47 g (25,11 mmol) Kaliumcarbonat und 1,90 ml (30,97 mmol) Iodmethan in 50 ml Ethanol wird 1,5 h zum Rückfluß erhitzt. Das Gemisch darf abkühlen, die Feststoffe werden bei einer Temperatur von 30°C durch Filtration abgetrennt und das Filtrat wird im Vakuum eingedampft. Der Rückstand wird in 50 ml Dichlormethan gelöst, mit $MgSO_4$ gut durchgerührt und nach Abdampfen des Lösemittels im Hochvakuum über Sicapent getrocknet. Man erhält 2,28 g (87%) der Titelverbindung als farblose Kristalle.

Schmp.: 176°C

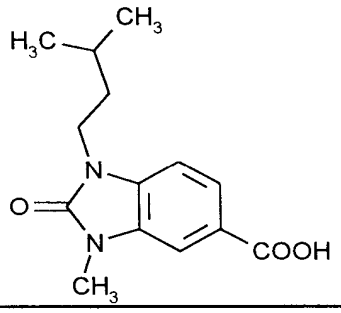
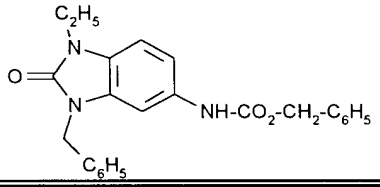
$R_f$ = 0,48 (Dichlormethan : Methanol 95:5)

MS (EI, 70 eV) m/z = 311 $(M)^+$

$^1$H-NMR (200 MHz, [$D_6$]DMSO): $\delta$ = 9,70 (bs, 1H, NHCO); 7,40 (m, 6H, H arom.); 7,01 (s, 2H, H arom.); 5,12 (s, 2H, $CH_2$); 3,30, 3,31 (2s, 6H, $NCH_3$).

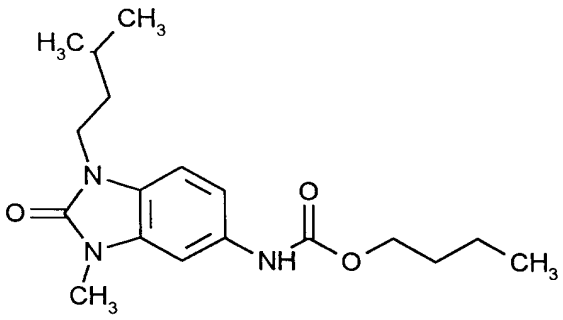
Wie für Beispiel V beschrieben erhält man durch Alkylierung der Verbindungen aus Tabelle I die in Tabelle II aufgeführten Verbindungen:

## Tabelle II:

| Bsp.-Nr. | Verbindung | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (CI) m/z $(M+H)^+$ |
|---|---|---|---|---|---|
| VI |  | 77 | / | 0,31 (I, 9:1) | 265 |
| VII |  | 75 | 147 | 0,44 (I, 97:3) | 402 |

**Beispiel VIII**

5-Butyloxycarbonylamino-1-(3'-methylbutyl)-2-benzoimidazolinon



Zu einer auf 0°C gekühlten Lösung von 1,58 g (6,0 mmol) der Verbindung aus Beispiel VI und 1,0 ml (7,21 mmol) Triethylamin in 12 ml Aceton tropft man langsam 1,1 ml (7,8 mmol) Chlorameisensäureisobutylester in 5 ml Aceton. Man rührt 45 min bei 0°C und tropft dann langsam 586 mg (9,02 mmol) Natriumazid in 3 ml Wasser zu. Man rührt 1 Stunde bei 0°C und gibt den Ansatz auf 50 ml Eiswasser. Es wird mit Xylol (3 x 2 ml) extrahiert und die vereinigten organischen Phasen über $MgSO_4$ getrocknet. Diese Lösung wird dann zu 20 ml siedendem n-Butanol langsam zugetropft

(heftige Gasentwicklung). Nach beendeter Zugabe wird noch 10 min. unter Rückfluß gekocht, dann auf RT abgekühlt, und das n-Butanol am Rotationsverdampfer abgezogen. Der Rückstand wird an 85 g Kieselgel chromatographiert. Man erhält 448 mg (22%) eines farblosen Öls.

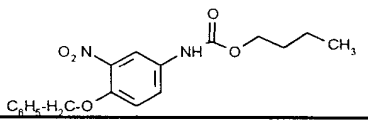
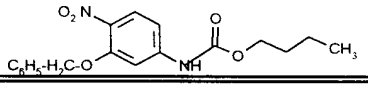
$R_f$ (II, 7:3) = 0,25

MS (CI): m/z = 334 ($M^+$ + H)

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 9,50 (bs, 1H, NH); 7,32 (bs, 1H, Ph); 7,00 (bs, 2H, Ph); 4,10 (t, J = 7 Hz, 2H, $CH_2$); 3,80 (t, J = 6 Hz, 2H, $CH_2$); 3,32 (s, 3H, $NCH_3$); 1,30 - 1,72 (m, 8H); 0,80 - 1,10 (m, 11H).

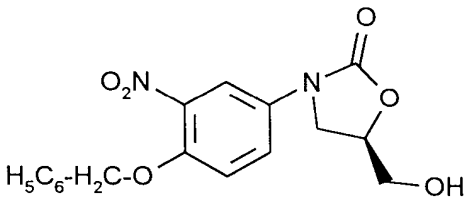
Wie für Beispiel VIII beschrieben erhält man durch Umsetzung der entsprechenden Säuren die in der Tabelle III aufgeführten Verbindungen:

**Tabelle III:**

| Bsp.-Nr. | Verbindung | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (DCI, $NH_3$] m/z $(M+H)^+$ |
|---|---|---|---|---|---|
| IX |  | 78 | 121-122 | 0,67 (VII, 95:5) | 345 |
| X |  | 63 | 133 | 0,51 (VII, 95:5) | 345 |

**Beispiel XI**

(5R)-3-(4-Benzyloxy-3-nitrophenyl)-5-(hydroxymethyl)-oxazolidin-2-on



23,0 g (66,7 mmol) der Verbindung aus Beispiel IX werden in 200 ml THF gelöst und auf 0°C gekühlt. Nun werden langsam ca. 68 ml 1,0 M LiHMDS-Lösung in THF zugetropft. Anschließend werden 9,5 ml (68 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf RT kommen, versetzt mit gesättigter Ammoniumchloridlösung und zieht im Vakuum das THF ab. Der entstandene Niederschlag wird abgesaugt, mit Wasser und Ether gewaschen und im Hochvakuum getrocknet.

Ausbeute: 20,85 g (91%)

Smp.: 128-130°C

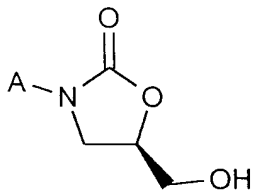
$R_f$ (II, 1:1) = 0,21

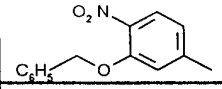
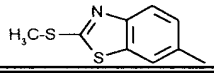
MS (FAB): m/z = 345 (M+)

$^1$H-NMR ([$D_6$] DMSO): $\delta$ = 8,0 (d, 1H, Ph), 7,62 (d, 1H, Ph), 7.30 - 7,50 (m, 6H, Ph), 5,30 (s, 2H, $CH_2$); 5,25 (t, 1H, OH); 4,68 - 4,80 (m, 1H,5-H); 4,15 (t, 1H, 4-H); 3,90 (dd, 1H, 4-H); 3,55 - 3,75 (m, 2H, $CH_2O$).

In Analogie zur Vorschrift des Beispiels XI werden die in der Tabelle IV aufgeführten Verbindungen hergestellt:

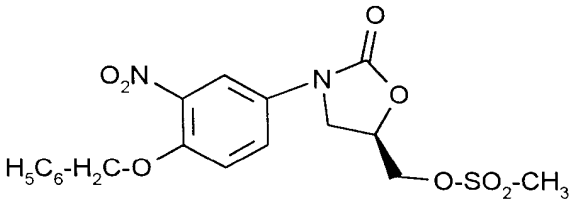
**Tabelle IV**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | Rf (Laufmittel, Verhältnis) | $[\alpha]20_D$ (DMSO) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|---|
| XII |  | 73 | 137-139 | 0,28 (II, 1:1) | -38,1 (c=0,985) | 345 |
| XIII |  | 67 | 156 | 0,24 (II, 1:4) | | 297 |

**Beispiel XIV**

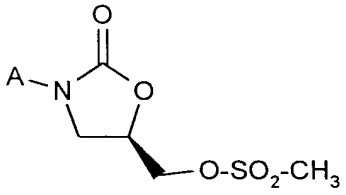
(5R)-3-(4-Benzyloxy-3-nitrophenyl)-5-(methylsulfonyloxymethyl)oxazolidin-2-on

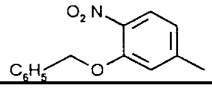
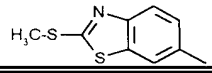


Eine auf 0°C gekühlte Lösung von 71,5 g (208 mmol) der Verbindung aus Beispiel XI und 35 ml (250 mmol) Triethylamin in 650 ml wasserfreiem THF wird langsam mit 23,6 ml (230 mmol) Methansulfonsäurechlorid versetzt. Man rührt 3 h bei 0°C und gibt auf Eiswasser. Der entstandene Niederschlag wird abgesaugt, mit Wasser und Toluol gewaschen und im Hochvakuum getrocknet. Ausbeute: 65,8 g (75%)
Smp.: 149-150°C
$R_f$ (VII, 5:1) = 0,36
MS (FAB): m/z = 423 ($M^+$)
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,12 (d, J = 1 Hz, 1H, Ph); 7,75 (dd, J = 6 Hz, J = 1 Hz, 1H, Ph); 7,35 - 7,55 (m, 6H, Ph); 5,30 (s, 2H, $CH_2$); 4,40 - 4,60 (m, 2H, $CH_2O$); 4,22 (t, J = 9 Hz, 1H, 4-H); 3,85 (dd, J = 9 Hz, J = 5 Hz, 1H, 4-H); 3,25 (s, 3H, $SO_2CH_3$).

In Analogie zur Vorschrift des Beispiels XIV werden die in der Tabelle V aufgeführten Verbindungen hergestellt:

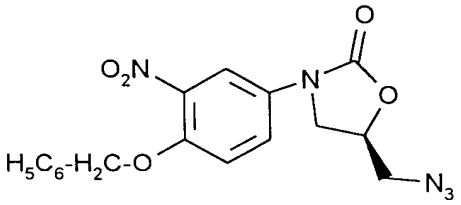
**Tabelle V:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]^{20}_D$ (DMSO) | MS (FAB) m/z ($M^+$ +H) |
|---|---|---|---|---|---|---|
| XV |  | 92 | 140-142 | 0,34 (VII, 5:1) | -48,8 (c=1,01) | 423 |
| XVI |  | 82 | 106 | 0,41 (I, 95.5) | / | 375 |

**Beispiel XVII**

(5R)-3-(4-Benzyloxy-3-nitrophenyl)-5-(azidomethyl)oxazolidin-2-on



Eine Lösung von 25,7 g (60,8 mmol) der Verbindung aus Beispiel XI in 200 ml wasserfreiem DMF wird mit 4,4 g (66,9 mmol) Natriumazid versetzt und 12 h bei 70°C gerührt. Man läßt auf Raumtemperatur abkühlen und rührt 200 ml Eiswasser ein. Der entstandene Niederschlag wird abfiltriert, mit Wasser und Petrolether gewaschen und im Vakuum getrocknet.

Ausbeute: 21,4 g (95%)

Smp.: 158-160°C

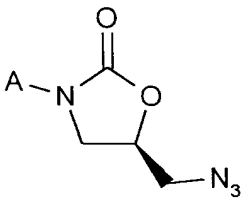
$R_f$ (VII, 5:1) = 0,48

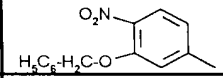
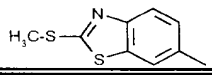
MS (EI) : m/z = 370 ($M^+$)

$^1$H-NMR -([$D_6$]DMSO): $\delta$ = 8,05 (d, 1H, J = 8 Hz, Ph); 7,25 - 7,50 (m, 7H, Ph); 5,30 (s, 2H, $CH_2$); 4,85 - 5,05 (m, 1H, 5-H); 4,23 (t, J= 9 Hz, 1H, 4-H); 3,55 - 3,90 (m, 3H, 4-H, $CH_2N_3$).

In Analogie zur Vorschrift des Beispiels XVII werden die in Tabelle VII aufgeführten Verbindungen hergestellt:

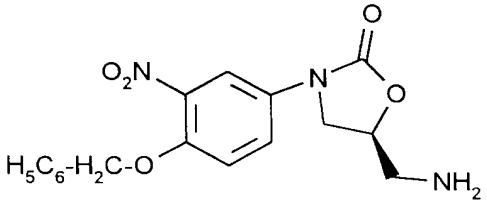
**Tabelle VII:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]^{20}_d$ (DMSO) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|---|
| XVIII |  | 92 | 138-140 | 0,26 (VII, 5:1) | -119,4° (c=1,1) | 370 |
| XIX |  | 95 | 136 | 0,59 (I, 95:5) | / | 322 |

**Beispiel XX**

(5S)-3-(4-Benzyloxy-3-nitrophenyl)-5-(aminomethyl)oxazolidin-2-on



Eine Lösung von 53,1 g (144 mmol) der Verbindung aus Beispiel XVII in 160 ml 1,2-Dimethoxyethan wird auf 50°C erwärmt. Man tropft langsam 20,4 ml (173 mmol) Trimethylphosphit zu (Gasentwicklung) und rührt nach beendeter Zugabe 2 h bei 90°C. Nun tropft man 36 ml 6 N HCl zu und rührt nochmals 22 h bei 90°C. Man läßt auf Raumtemperatur abkühlen, gibt 810 ml 0,1 N HCl hinzu, wäscht die wäßrige Phase mit Ether (3x 320 ml) und stellt anschließend auf pH = 9. Die wäßrige Phase wird mit Essigester (3 x 650 ml) extrahiert (2 x 300 ml), die vereinigten organischen Phasen mit ges. NaCl-Lösung gewaschen (1 x 100 ml) und getrocknet ($Na_2SO_4$). Die Lösemittel werden im Vakuum abgezogen und im Hochvakuum getrocknet.

Ausbeute: 47,2 g (96%)

Smp.: 135-136°C

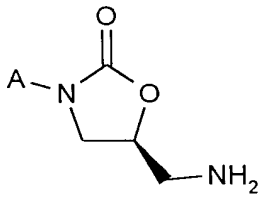
$R_f$ (VIII, 85:10:5) = 0,05

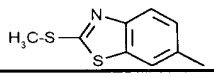
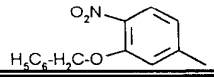
MS (EI): m/z = 344 ($M^+$)

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,3 - 9,1 (bs, 3H, $NH_3$); 8,15 (d, 1H, Ph); 7,3 - 7,8 (m, 7H, Ph); 5,30 (v, 2H, $CH_2$); 4,9 - 5,1 (m, 1H, 4-H); 4,20 (m, 1H, 5-H); 4,00 (m, 1H, 5-H); 3,10 - 3,40 (m, 2H, $CH_2N$).

In Analogie zur Vorschrift des Beispiels XX werden die in der Tabelle VIII aufgeführten Verbindungen hergestellt:

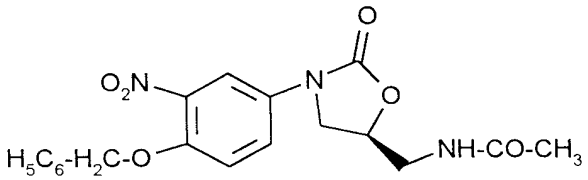
**Tabelle VIII:**



| Bsp.-Nr. | D | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (FAB) m/z ($M^+$) |
|---|---|---|---|---|---|
| XXI |  | 83 | 110 | 0,09 (III, 9:1) | |
| XXII |  | 89 | 132-134 | 0,08 (VIII, 85:10:5) | 344 |

**Beispiel XXIII**

(5S)-3-(4-Benzyloxy-3-nitrophenyl)-5-(acetylaminomethyl)oxazolidin-2-on



Zu einer auf 0°C gekühlten Lösung von 47,2 g (137 mmol) der Verbindung aus Beispiel XX und 29,04 ml (212 mmol) Triethylamin in 500 ml wasserfreiem THF tropft man langsam 14,6 ml (205 mmol) Acetylchlorid. Man rührt 2 h bei 0°C nach und gibt auf Eiswasser. Der Niederschlag wird abgesaugt, mit Wasser und Ether gewaschen, und im Hochvakuum über $P_2O_5$ getrocknet.

Ausbeute: 48,9 g (93%)

Smp.: 177-178°C

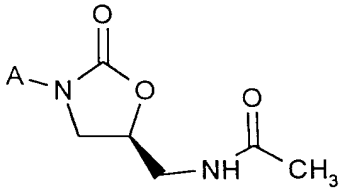
$R_f$ (VII, 1:1) = 0,51

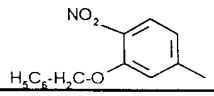
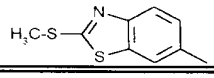
MS (FAB) m/z = 386 $(M+H)^+$

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,24 (t, J = 4 Hz, 1H, NH); 8,10 (d, J = 1 Hz, 1H, Ph); 7,75 (dd, J = 6 Hz, J = 1 Hz, 1H, Ph); 7,20 - 7,50 (m, 6H, Ph); 5,30 (s, 2H, $CH_2$); 4,70 - 4,80 (m, 1H, 5-H); 4,15 (t, J = 9 Hz, 1H, 4-H); 3,70 (dd, J = 9 Hz, J = 5 Hz, 1H, H-4); 3,35 - 3,50 (m, 5H, $CH_2N$, $NCH_3$); 1,83 (s, 3H, $COCH_3$).

In Analogie zur Vorschrift des Beispiels XXIII werden die in Tabelle IX aufgeführten Verbindungen hergestellt:

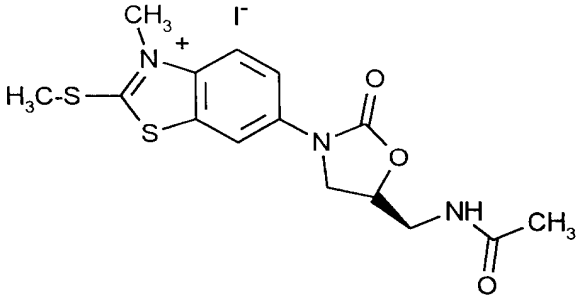
**Tabelle IX:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]^{20}_D$ (DMSO) | MS (FAB) m/z (M+H) |
|---|---|---|---|---|---|---|
| XXIV |  | 86 | 155-156 | 0,62 (VII, 1:1) | -23,6° (c=1,05) | 386 |
| XXV |  | 83 | 136 | 0,15 (I, 95:5) | | 338 |

**Beispiel XXVI**

(5S)-3-(2-Methylthio-3-methyl-benzothiazol-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on Iodid



Eine gerührte Lösung von 1,35 g (4,00 mmol) der Verbindung aus Beispiel XXV in 6 ml wasserfreiem DMF wird mit 2,6 ml (40,00 mmol) Iodmethan versetzt und 23 h auf 70°C erhitzt. Danach darf die Reaktionsmischung abkühlen, man gibt 80 ml Ether zu und trennt den entstandenen Niederschlag durch Filtration ab. Nach Verrühren in 50 ml Ethanol, erneuter Filtration und Trocknen des Produkts im Hochvakuum über Sicapent erhält man 1,17 g (61%) der Titelverbindung als farblose Kristalle.

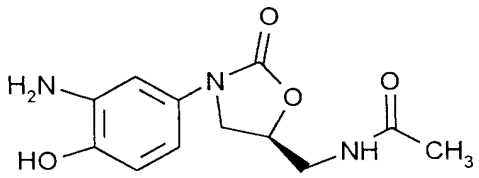
Schmp.: 149°C (Z)

MS (FAB) m/z = 352 (Kation $M^+$)

$^1$H-NMR (250 MHz, [$D_6$]DMSO): $\delta$ = 8,60 (d, J = 1 Hz, 1H, Benzothiazol H-7); 8,28 (m, 1H, NHCO); 8,20 (d, J = 10 Hz, 1H, Benzothiazol H-4); 8,02 (dd, J = 1 Hz, J = 10 Hz, 1H, Benzothiazol H-5); 4,82 (m, 1H, H-5); 4,20 (t, J = 10 Hz, 1H, H-4 cis); 4,10 (s, 3H, $NCH_3$); 3,85 (dd, J = 7 Hz, J = 10 Hz, 1H, H-4 trans); 3,46 (m, 2H, $CH_2N$); 3,12 (s, 3H, $SCH_3$); 1,85 (s, 3H, $COCH_3$).

**Beispiel XXVII**

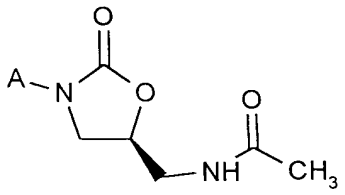
(5S)-3-(3-Amino-4-hydroxyphenyl)-5-(acetylaminomethyl)-oxazolidin-2-on

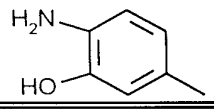


3,58 g (9,28 mmol) der Verbindung aus Beispiel XXIII und 350 mg Pd-C (10%) werden in 100 ml Methanol und 100 ml THF 3 h unter Wasserstoff (1 atm) gerührt. Es wird vom Katalysator abfiltriert, das Lösemittel abgezogen und getrocknet.
Ausbeute: 2,5 g (quant.)
$R_f$ (VII, 1:1) = 0,42
MS (CI): m/z = 265 ($M^+$)
$[\alpha]^{20}_D$ = -110,45 (c=1,0, DMSO)
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 9,0 - 9,5 (bs, 1H, OH); 8,20 (t, J = 4 Hz, 1H, NHCO); 7,05 (bs, 1H, Ph); 6,55 (bs, 2H, Ph); 4,55 - 4,70 (m, 1H, 5-H); 4,30 - 4,52 (bs, 2H, $NH_2$); 3,95 (t, J = 6 Hz, 1H, 4-H); 3,60 (dd, J= 7 Hz, J = 4 Hz, 1H, 4-H); 3,40 (t, J = 4 Hz, 2H, $CH_2N$); 1,73 (s, 3H, $COCH_3$).

Wie für Beispiel XXVII beschrieben erhält man aus den entsprechenden Ausgangsverbindungen die in Tabelle X aufgeführten Verbindungen:

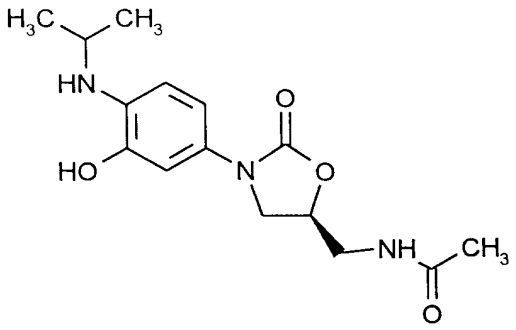
**Tabelle X:**



| Bsp.-Nr. | D | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]^{20}_D$ (DMSO) | MS (CDI, $NH_3$) m/z $(M+H)^+$ |
|---|---|---|---|---|---|---|
| XXVIII |  | quant. | 221-222 | 0,31 (VII, 1:1) | -19,89 (c=1,0) | 265 |

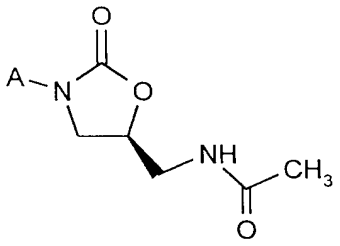
**Beispiel XXIX**

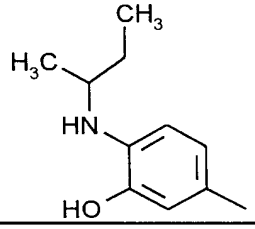
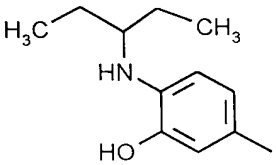
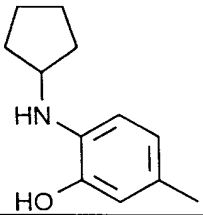
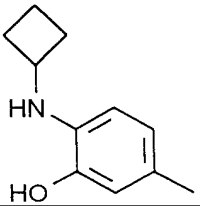
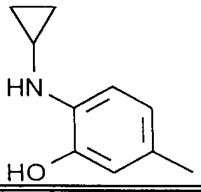
(5S)-3-(3-Hydroxy-4-(N-iso-propylamino)phenyl)-5-(acetylaminomethyl)oxazolidin-2-on



Zu einer Mischung aus 1,06 g (4,0 mmol) der Verbindung aus Beispiel XXVIII, 600 µl (8,0 mmol) Aceton und 50 ml THF werden bei 0°C 4,4 ml (4,4 mmol) einer 1 M Boran-Tetrahydrofuran-Komplex-Lösung in THF gegeben und weitere 24 h bei Raumtemperatur gerührt. Die entstandene Lösung wird mit 4 ml 1 M Natriumhydroxidlösung versetzt, getrocknet ($Na_2SO_4$) und das Lösemittel abgezogen.
Ausbeute: 1,23 g (quant.)
$R_f$ (I, 10:1) = 0,29
MS (EI):m/z = 307 ($M^+$)
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 9,50 (bs, 1H, OH), 8,25 (t, 1H, NHCO), 7,10 (d, 1H, Ar-2-H), 6,62 (dd, 1H, Ar-6-H), 6,45 (d, 1H, Ar-5-H), 4,65 (m, 1H, 5-H), 3,90-4,10 (m, 2H, ArNH, 4-H), 3,50-3,70 (m, 2H, CHN, 4-H), 3,40 (t, 2H, $CH_2N$), 1,70 (s, 3H, $COCH_3$), 1,10 (d, 6H, $CH_3$).

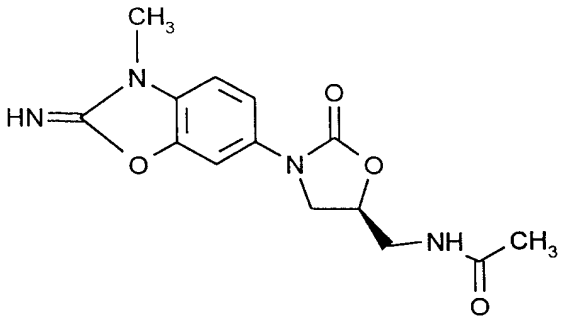
**Tabelle XI:**



| Bsp.-Nr. | A | Ausbeute | $R_f$ (Laufmittel Verhältnis) | MS (DCI, $NH_3$) m/z ($M^+$+H) |
|---|---|---|---|---|
| XXX |  | quant. | 0,69 (I, 5:1) | 322 |
| XXXI |  | quant. | 0,33 (I, 10:1) | 336 |
| XXXII |  | quant. | 0,23 (I, 10:1) | 334 |
| XXXIII |  | quant. | 0,28 (I, 10:1) | 320 |
| XXXIV |  | 8 | 0,25 (I, 10:1) | 305 |

**Beispiel XXXV**

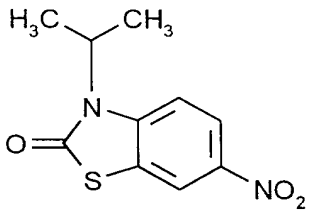
(5S)-3-(2-Imino-3-methyl-2,3-dihydrobenzoxazol-6-yl)-5-acetylaminomethyl)-oxazolidin-2-on



Eine Lösung aus 2 g (6,89 mmol) der Verbindung aus Beispiel XXVII in 30 ml Dimethylformamid wird mit 4,3 ml (69 mmol) Iodmethan versetzt und die Mischung 2 h bei 100°C gerührt. Das Lösemittel wird im Vakuum abgezogen, der Rückstand in Dichlormethan verrührt, abgesaugt und getrocknet.
Ausbeute: 2,32 g (78 %)
$R_f$ (VII, 1:1) = 0,10
MS (DCI):m/z = 305 ($M^+$+H)
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 10,0-10,5 (bs, 1H, HN=C), 8,25 (bt, 1H, NHCO), 7,95 (d, 1H, Ar-7-H), 7,62 (d, 1H, Ar-4-H), 7,55 (dd, 1H, Ar-5-H), 4,75 (m, 1H, 5-H), 4,18 (t, 1H, 4-H), 3,78 (dd, 1H, 4-H), 3,61 (s, 3H, $NCH_3$), 3,30-3,40 (m, 2H, $CH_2N$), 1,82 (s, 3H, $NCOCH_3$).

**Beispiel XXXVI**

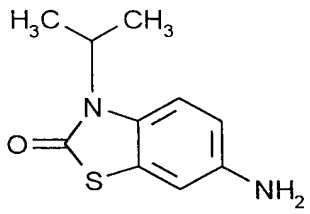
3-Isopropyl-6-nitrobenzothiazol-2-on



6-Nitrobenzothiazol-2-on (35,1 ml, 0,18 mol), Kaliumcarbonat (24,3 g, 0,18 mol) und 2-Iodopropan (153 g, 0,9 mol) in 2-Propanol (1 l) werden 24 Stunden unter Rückfluß erhitzt. Die abgekühlte Reaktionsmischung wird filtriert, das Lösungsmittel im Vakuum abgezogen, der Rückstand in Dichlormethan aufgenommen und mit Wasser gewaschen. Die organische Phase wird getrocknet ($Na_2SO_4$) und das Dichlormethan im Vakuum abgezogen. Das Rohprodukt wird durch Chromatographie (Kieselgel, Dichlormethan/Petrolether 2:1) gereinigt.
Ausbeute: 8,7 g (20 %)
Schmp.: 138 bis 142°C
$R_f$ (Dichlormethan) = 0,47
MS (CI): m/z = 256 (M+$NH_4$+)

**Beispiel XXXVII**

6-Amino-3-isopropylbenzothiazol-2-on

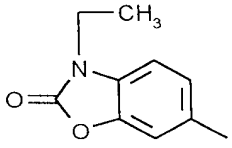


Die Verbindung aus Beispiel XXXVI (3,2 g, 138 mmol) wird in einer Mischung aus Ethanol (90 ml), Wasser (24 ml) und $CaCl_2$ (0,96 g, 8,65 mmol) suspendiert. Das Reaktionsgemisch wird unter Rückfluß erhitzt, Zink-Staub (28,8 g 0,42 mol) werden zugegeben und weitere 30 Minuten unter Rückfluß gerührt. Die Mischung wird heiß filtriert, der Rückstand gut mit Wasser gewaschen, das Filtrat eingeengt und der Rückstand in Ether kristallisiert.
Ausbeute: 2,8 g (97 %)
Schmp.: 138 bis 140°C
$R_f$ (Dichlormethan) = 0,19

In Analogie zur Vorschrift des Beispiels XXXVII werden die in Tabelle XII aufgeführten Verbindungen dargestellt:

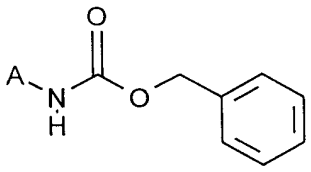
Tabelle XII:

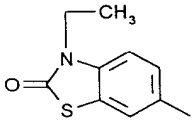
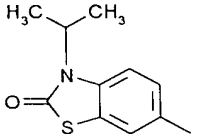
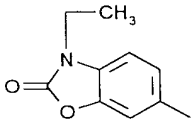
A-$NH_2$

| Bsp.-Nr. | A | Ausbeute (% d. Th.) | $R_f$ (Laufmittel, Verhältnis) |
|---|---|---|---|
| XXXVIII |  | quant. | 0,90 (VI, 10:1) |

In Analogie zur Vorschrift des Beispiels I werden die in der Tabelle XIII aufgeführten Verbindungen dargestellt:

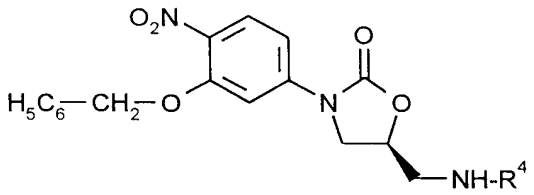
Tabelle XIII:

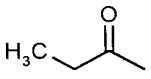
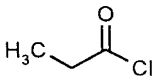
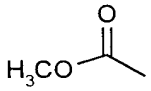
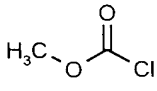
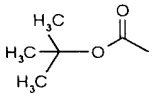


| Bsp.-Nr. | A | Ausbeute (% d. Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) |
|---|---|---|---|---|
| XXXIX |  | 87 | 163 | 0,15 ($CH_2Cl_2$) |
| XL |  | quant. | 160 | 0,70 ($CH_2Cl_2$) |
| XLI |  | 85 | - | 0,70 (VII, 95:5) |

In Analogie zur Vorschrift des Beispiels XXIII werden die in Tabelle XIV aufgeführten Verbindungen dargestellt:

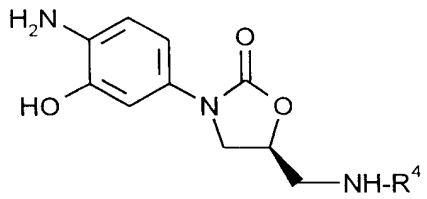
Tabelle XIV:

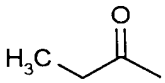
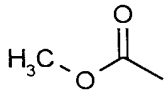
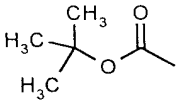


| Bsp.-Nr. | $R^4$ | Alkylierungs-mittel | Ausbeute (% d. Th.) | $R_f$ (Laufmittel, Verhältnis) | MS (CI) m/z ($M+NH_4^+$) |
|---|---|---|---|---|---|
| XLII |  |  | 99 | 0,36 (I, 10:1) | 417 |
| XLIII |  |  | 46 | 0,63 (I, 10:1) | 419 |
| XLIV |  | $BOC_2O$ | 95 | 0,80 (I, 10:1) | 461 |

In Analogie zur Vorschrift des Beispiels XXVII werden die in der Tabelle XV aufgeführten Verbindungen dargestellt

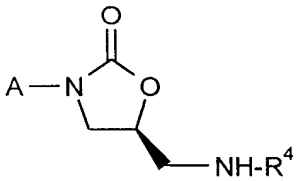
Tabelle XV:

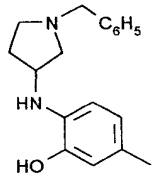
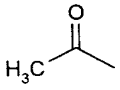
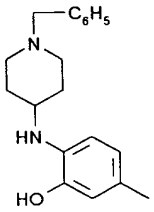
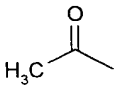
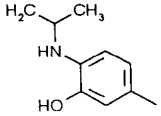
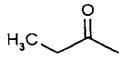
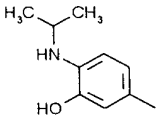
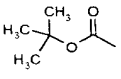
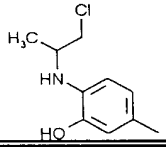
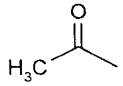



| Bsp.-Nr. | $R^4$ | Ausbeute (% d. Th.) | $R_f$ (Laufmittel, Verhältnis) | MS m/z |
|---|---|---|---|---|
| XLV |  | quant. | 0,26 (I, 10:1) | 297 ($M+NH_4^+$) |
| XLVI |  | 97 | 0,40 (I, 10:1) | 299 ($M+NH_4^+$) |
| XLVII |  | quant. | 0,28 (I, 10:1) | 323 ($M^+$) |

In Analogie zur Vorschrift des Beispiels XXIX werden die in der Tabelle XVI aufgeführten Verbindungen dargestellt:

Tabelle XVI:

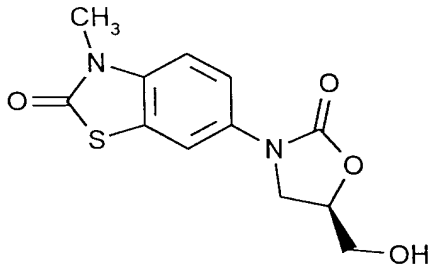


| Bsp.-Nr. | A | $R^4$ | Ausbeute (% d. Th.) | $R_f$ (Laufmittel, Verhältnis) | MS m/z |
|---|---|---|---|---|---|
| XLVIII |  |  | 31 | - | - |
| XLIX |  |  | 58 | 0,07 (I, 10:1) | 439 ($M+H^+$) |
| L |  |  | 63 | 0,35 (I, 10:1) | 322 ($M+H^+$) |
| LI |  |  | 97 | 0,57 (I, 10:1) | - |
| LII |  |  | 94 | 0,22 (I, 10:1) | 342 ($M+H^+$) |

## Herstellungsbeispiele

### Beispiel 1

(5R)-3-[3-Methyl-2-benzothiazolinon-6-yl]-5-(hydroxymethyl)-oxazolidin-2-on



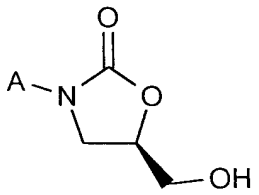
Methode A

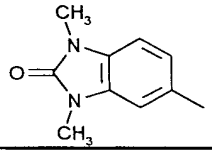
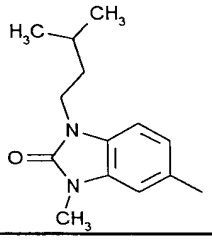
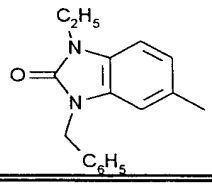
26,76 g (85,12 mmol) der Verbindung aus Beispiel I werden in 400 ml THF gelöst, mit 10 mg 1,10-Phenanthrolin-Hydrat versetzt und auf -70°C gekühlt. Nun werden langsam ca. 34 ml 2,5 N n-Butyllithium-Lösung in Hexan bis zum Farbumschlag nach rot zugetropft. Anschließend werden 12 ml (85,12 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf RT kommen, versetzt mit gesättigter Ammoniumchloridlösung und zieht im Vakuum das THF ab. Der entstandene Niederschlag wird abgesaugt, mit Wasser und Ether gewaschen und im Hochvakuum getrocknet.
Ausbeute: 17,93 g (75%)
Smp.: 166°C
$R_f$ (II, 1:1) = 0,09
MS (EI): m/z = 280 ($M^{+)}$
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 7,80 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,60 (dd, J = 6, J = 1 Hz, 1H, Benzothiazolinon 5-H); 7,32 (d, J = 6 Hz, 1H, Benzthiazolinon 4-H); 5,23 (t, J = 6 Hz, 1H, OH); 4,62 - 4,80 (m, 1H, 5-H); 4,10 (t, J = 9 Hz, 1H, 4-H); 3,85 (dd, J = 9, J = 5 Hz, 1H, 4-H); 3,48 - 3,75 (m, 2H, $CH_2O$); 3,40 (s, 3H, $CH_3$).

Methode B

9,3 g (0,03 mol) der Verbindung aus Beispiel I werden in 150 ml THF gelöst und auf -70°C gekühlt. Anschließend werden 4 ml (0,01 mol) 2,5 M n-Butyllithiumlösung in Hexan zugetropft. Danach werden gleichzeitig langsam nochmals 8 ml (0,02 mol) n-Butyllithium und 4,23 ml (0,03 mol) (R)-Glycidylbutyrat zugetropft.
Man läßt auf Raumtemperatur kommen und rührt drei Stunden nach. Die Aufarbeitung erfolgt wie für Methode A beschrieben. Ausbeute: 6 g (72 %).
Wie für Beispiel 1, Methode A, beschrieben erhält man aus den entsprechenden Carbamaten die in Tabelle 1 aufgeführten Verbindungen:

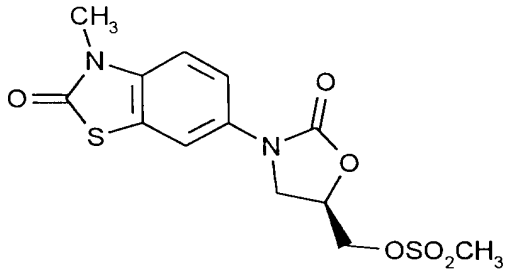
**Tabelle 1:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | Rf (Laufmittel, Verhältnis) | MS (CI) m/z ($M^+$+H) |
|---|---|---|---|---|---|
| 2 |  | 55 | 197 | 0,15 (I, 95:5) | 277 |
| 3 |  | 43 | 122 | 0,19 (I, 95:5) | 333 |
| 4 |  | 72 | 149 | 0,15 (I, 95:5) | 368 |

**Beispiel 5**

(5R)-3-(3-Methyl-2-benzothiazolinon-6-yl)-5-(methansulfonyloxymethyl)-oxazolidin-2-on

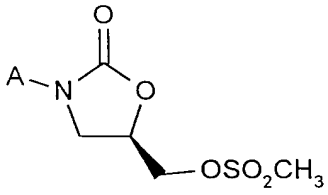


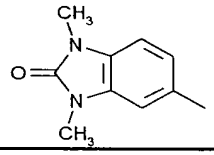
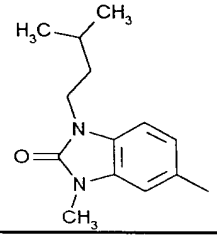
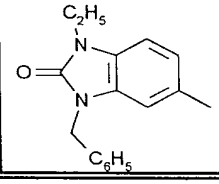
Eine auf 0°C gekühlte, gerührte Lösung von 18,72 g (66,78 mmol) der Verbindung aus Beispiel I und 13 ml (93,5 mmol) Triethylamin in 180 ml wasserfreiem Dichlormethan wird langsam mit 6,7 ml (86,82 mmol) Methansulfonsäurechlorid versetzt. Man rührt 20 min bei 0°C, weitere 5 h bei Raumtemperatur, saugt den entstandenen Niederschlag ab, wäscht

mit Wasser und Ether und trocknet im Hochvakuum.
Ausbeute: 21,45 g (89%)
Smp: 172°C
$R_f$ (I, 95:5) = 0,27
MS (FAB): m/z = 359 ($M^+$)
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 7,78 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,68 (dd, J = 6 Hz, J = 1 Hz, 1H, Benzothiazolinon 5-H); 7,35 (d, J = 6 Hz, 1H, Benzothiazolinon 4-H); 4,90 - 5,10 (m, 1H, 5-H); 4,40 - 4,60 (m, 2H, $CH_2O$); 4,20 (t, J = 9 Hz, 1H, 4-H); 3,85 (dd, J = 9 Hz, J = 5 Hz, 1H, 4-H); 3,40 (s, 3H, 4-$NCH_3$); 3,20 (s, 3H, $SO_2CH_3$).

Wie für Beispiel 5 beschrieben, erhält man aus den entsprechenden Alkoholen die in der Tabelle 2 aufgeführten Methansulfonate.

**Tabelle 2:**

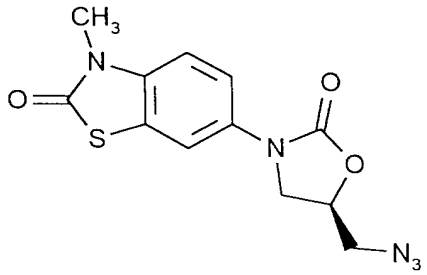



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|
| 6 |  | 78 | 188 | 0,25 (I, 95:5) | 355 a) |
| 7 |  | 76 | | 0,32 (I, 95:5) | 411 a) |
| 8 |  | 67 | 187 | 0,16 (II, 1:1) | 446 |

a) MS (EI), m/z (M)

**Beispiel 9**

(5R)-3-(3-Methyl-2-benzothiazolinon-6-yl)-5-(azidomethyl)-oxazolidin-2-on



Eine Lösung von 17,03 g (47,51 mmol) der Verbindung aus Beispiel 5 in 58 ml wasserfreiem DMF wird mit 4,02 g (61,77 mmol) Natriumazid versetzt und 5 h bei 70°C gerührt. Man läßt auf Raumtemperatur abkühlen und rührt 100 ml Eiswasser ein. Der entstandene Niederschlag wird abfiltriert, mit Wasser und Petrolether gewaschen und im Vakuum getrocknet.

Ausbeute: 12,8 g (88%)

Smp.: 129°C

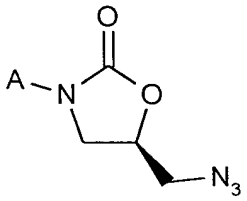
$R_f$ (I, 95:5) = 0,40

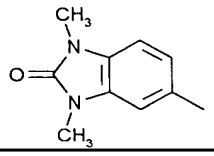
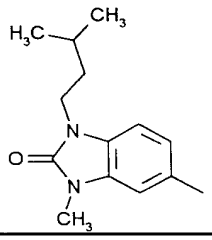
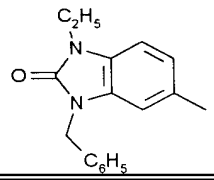
MS (EI) : m/z = 305 ($M^+$)

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 7,85 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,57 (dd, J = 6 Hz, J = 1 Hz, Benzothiazolinon 5-H); 7,34 (d, J = 6 Hz, 1H, Benzothiazolinon 4-H); 4,82 - 5,00 (m, 1H, 5-H); 4,15 (t, J = 9 Hz, 1H, 4-H); 3,65 - 3,77 (m, 3H, 4-H, $CH_2N_3$); 3,41 (s, 3H, $NCH_3$).

Wie für Beispiel 9 beschrieben erhält man aus den entsprechenden Methansulfonaten die in der Tabelle 3 aufgeführten Azide:

**Tabelle 3:**

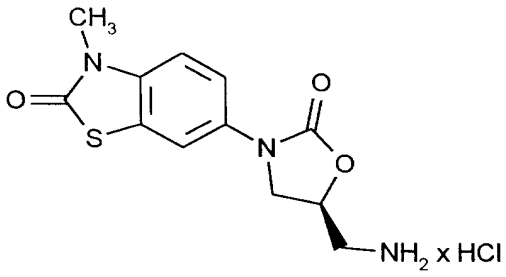


| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (FAB) m/z (M+ + H) |
|---|---|---|---|---|---|
| 10 |  | 87 | 179 | 0,33 (I, 95:5) | 302 a) |
| 11 |  | 78 | | 0,36 (I, 97:3) | 358 a) |
| 12 |  | 90 | 120 | 0,51 (IV) | 393 |

a) MS (EI), m/z ($M^+$)

**Beispiel 13**

(5S)-3-(3-Methyl-2-benzothiazolinon-6-yl)-5(aminomethyl)-oxazolidin-2-on Hydrochlorid



Eine gerührte Lösung von 12,75 g (41,76 mmol) der Verbindung aus Beispiel 9 in 30 ml 1,2-Dimethoxyethan wird auf 50°C erwärmt. Man tropft langsam 5,7 ml (50,11 mmol) Trimethylphosphit zu (Gasentwicklung) und rührt nach beende-

ter Zugabe 2 h bei 90°C nach. Nun tropft man 8,4 ml 6 N HCl zu und rührt nochmals 3 h bei 90°C nach. Man läßt auf Raumtemperatur abkühlen, trennt den Niederschlag durch Filtration ab, wäscht mit 1,2-Dimethoxyethan und trocknet im Hochvakuum über $P_2O_5$.

Ausbeute: 8,86 g (75%)

Smp.: 259°C (Zers.)

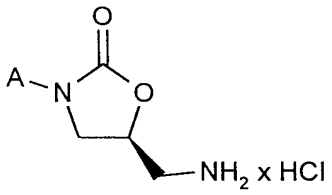
$R_f$ (III, 95:5) = 0,09

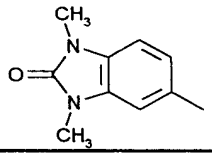
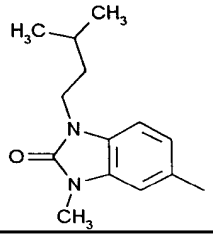
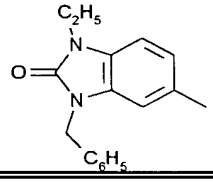
MS (EI): m/z = 279 ($M^+$)

$^1$H-NMR ([$D_6$]DMSO): δ = 8,5 (bs, 3H, NH); 7,85 (d, J = 1 Hz, 1H, Benzothiazolinon 7H); 7,65 (dd, J = 6 Hz, J = 1 Hz, 1H, Benzothiazolinon 5-H); 7,34 (d, J = 6 Hz, 1H, Benzothiazolinon 4-H); 4,90 - 5,10 (m, 1H, 5-H); 4,23 (t, J = 9 Hz, 1H, 4-H); 4,42 (dd, J = 9 Hz, J = 5 Hz, 1H, 4-H); 3,40 (s, 3H, $NCH_3$); 3,15 - 3,35 (m, 2H, $CH_2N$).

Wie für Beispiel 13 beschrieben erhält man aus den entsprechenden Aziden die in der Tabelle 4 aufgeführten Aminhydrochloride:

**Tabelle 4:**

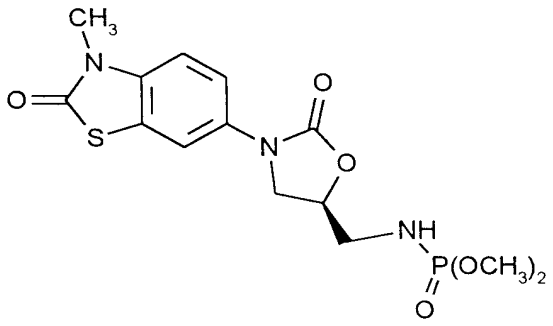



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|
| 14 |  | 92 | 272 (Z) | 0,33 (III, 8:2) | 276 [a] |
| 15 |  | 83 | (öl) | 0,12 (III, 9:1) | 333 |
| 16 |  | 95 | (Öl) | 0,5 (III, 8:2) | - |

a) MS (EI), m/z ($M^+$)

**Beispiel 17**

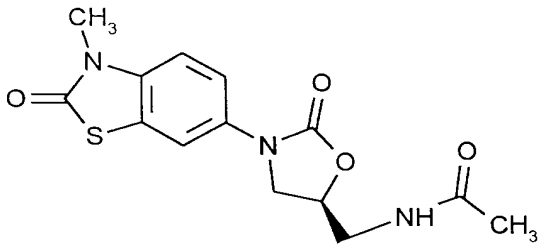
(5R)-3-[3-Methyl-2-benzothiazolinon-6-yl)-5-(dimethoxyphosphonaminomethyl)oxazolidin-2-on



Eine Losung aus 164 mg (0,5 mmol) der Verbindung aus Beispiel 9 in 3 ml 1,2-Dimethoxyethan wird auf 50°C erwärmt und langsam 0,7 ml (0,55 mmol) Trimethylphosphit zugetropft. Nach beendeter Zugabe rührt man weitere 2 h bei 90°C, zieht anschließend die Lösungsmittel ab und kristallisiert den Rückstand zweimal aus Ethanol.
Ausbeute: 32 mg (20%)
Smp.: 169°C
$R_f$ (I, 95.5) = 0,15
MS (FAB): m/z = 388 ($M^+$+H)
$^1$H-NMR ([$d_6$]DMSO): $\delta$ = 7,82 (d, J = 1 Hz, 1H, Benzthiazolinon 7-H); 7,57 (dd, J = 6 Hz, J = 1 Hz, 1H, Benzthiazolinon 5-H); 7,35 (d, J = 6 Hz, 1H, Benzthiazolinon 4-H); 5,30 - 5,50 (m, 1H, PNH); 4,60 - 4,80 (m, 1H, 5-H); 4,10 (t, J = 7 Hz, 1H, 4-H); 3,90 (dd, J = 7 Hz, J = 4 Hz, 1H, 4-H); 3,60 (d, J = 11 Hz, 3H, $POCH_3$); 3,55 (d, J = 11 Hz, 3H, $POCH_3$); 3,40 (s, 3H, $NCH_3$).

**Beispiel 18**

(5S)-3-(3-Methyl-2-benzothiazolinon-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on



Methode A:

Eine gerührte Lösung von 8,55 g (27,07 mmol) der Verbindung aus Beispiel 13 in 80 ml THF wird in einer Lösung von 1,09 g (27,34 mmol) Natriumhydroxid in 8 ml Wasser versetzt. Dazu tropft man bei 0-5°C langsam 2,81 ml (29,78 mmol) Acetanhydrid in 6 ml THF und hält pH = 9 durch gleichzeitige Zugabe einer 5 N wäßrigen NaOH-Lösung. Man rührt 1 h bei 0°C nach und dampft das THF im Vakuum ab. Der Niederschlag wird abgesaugt, mit Wasser und Ether gewaschen, und im Hochvakuum über $P_2O_5$ getrocknet.
Ausbeute: 8,39 g (96%)
Smp.: 208°C
$R_f$ (I, 95:5) = 0,21
MS (DCI, $NH_3$) m/z = 322 $(M+H)^+$

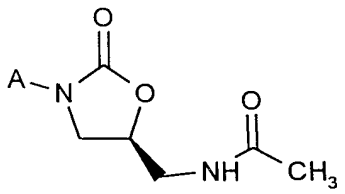
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,24 (t, J = 4 Hz, 1H, NH); 7,85 (d, J = 1 Hz, 1H, Benzthiazolinon 7-H); 7,55 (dd, J = 6 Hz, J = 1 Hz, 1H); Benzthiazolinon 5-H); 7,32 (d, J = 6 Hz, 1H, Benzthiazolinon 4-H); 4,55 - 4,80 (m, 1H, 5-H); 4,15 (t, J = 9 Hz, 1H, 4-H); 3,67 (dd, J = 9 Hz, J = 5 Hz, 1H, H-4); 3,35 - 3,50 (m, 5H, $CH_2N$, $NCH_3$); 1,83 (s, 3H, $COCH_3$).

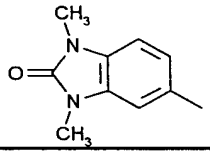
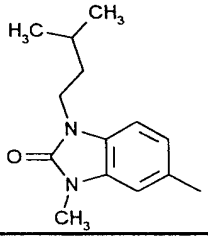
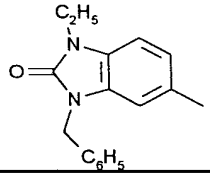
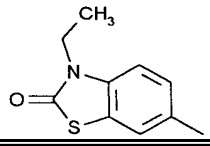
Methode B:

1,10 g (2,30 mmol) (5S)-3-(2-Methylthio-3-methyl-benzo[4,5-d]-thiazol-6-yl)-5-acetylaminomethyl-oxazolidin-2-on Iodid (Beispiel XXVI) werden in 24 ml eines Gemisches aus Dichlormethan : Methanol 4:1 gelöst. Man gibt 1,5 g Kieselgel zu und rührt 1 h bei Raumtemperatur nach. Dann gibt man 6 ml Methanol zu und dampft das Lösemittel im Vakuum ab. Der Rückstand wird auf eine Säule mit 100 g Kieselgel gegeben und mit Dichlormethan : Methanol 95:5 eluiert. Die produkthaltigen Fraktionen werden gesammelt, das Lösemittel wird im Vakuum abgedampft und der Rückstand aus Ethanol umkristallisiert. Man erhält 343 mg (46%) der Titelverbindung. Die physikalischen Daten sind identisch mit der nach Methode A erhaltenen Verbindung.

In Analogie zum Beispiel 18 erhält man die in der Tabelle 5 aufgeführten Acetamide.

## Tabelle 5:

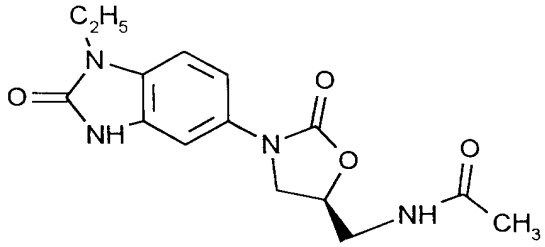


| Bsp.-Nr. | A | Methode | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (FAB) m/z ($M^+ + H$) |
|---|---|---|---|---|---|---|
| 19 |  | A | 49 | 224 (Z) | 0,36 (I, 95:5) | 318 a) |
| 20 |  | A | 37 | 142 | 0,41 (I, 9:1) | 374 a) |
| 21 |  | A | 57 | 129-132 | 0,69 (III, 8:2) | 409 |
| 22 |  | B | 5 | / | 0,12 (I, 95:5) | 335 a) |

a) MS (EI), m/z ($M^+$)

**Beispiel 23**

(5S)-3-(1-Ethyl-2-benzimidazolon-6-yl)-5-(acetylaminomethyl)-2-oxazolidinon

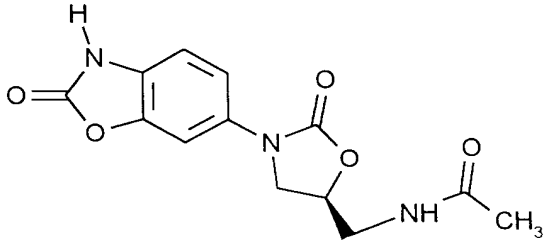


3 g (7,35 mmol) der Verbindung aus Beispiel 21 werden in 60 ml $NH_3$ bei - 40°C vorgelegt. Man gibt unter DC-Kontrolle ca. 360 mg (15 mmol) Natrium zu. Bei vollständigem Umsatz wird gesättigte Ammoniumchloridlösung zugegeben und der Ammoniak über Nacht abgedampft. Das erhaltene Rohprodukt wird an Kieselgel chromatographiert.

| | |
|---|---|
| Ausbeute: | 1,5 g (64 % der Theorie) |
| Fp: | 80 bis 85°C |
| FAB: | 319 |
| $R_F$: | 0,35 (I, 9:1) |

**Beispiel 24**

(5S)-3-(2-Benzoxazolinon-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on



1 g (3,76 mmol) der Verbindung aus Beispiel XXVII und 0,67 g (4,14 mmol) Carbonyldiimidazol in 10 ml wasserfreiem DMF werden 8 h bei Raumtemperatur gerührt. Das Lösemittel wird im Vakuum abgezogen, der Rückstand in Dichlormethan verrührt, abgesaugt und getrocknet.

Ausbeute: 0,86 g (78%)

Smp.: 219-220°C (Z)

$R_f$ (VII; 1:1) = 0,53

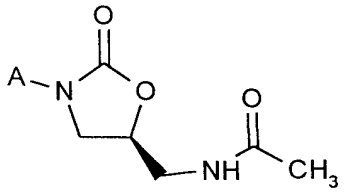
$[\alpha]_D^{20}$ = -23,213 (c = 1,0, DMSO)

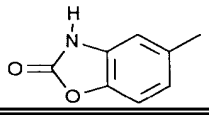
MS (FAB): m/z = 292 ($M^+$+H)

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 11,4 - 11,8 (bs, 1H, NH); 8,23 (t, J = 4 Hz, 1H, NHCO); 7,55 (d, J = 1 Hz, 1H, Benzoxazolinon 7-H); 7,20 (dd, J = 6 Hz, J = 1 Hz, 1H, Benzoxazolinon); 7,10 (d, J = 6 Hz, 1H, Benzoxazolinon 4-H); 4,60 - 4,80 (m, 1H, 5-H); 4,10 (t, J = 6 Hz, 1H, 4-H); 3,72 (dd, J = 7 Hz, J = 4 Hz,, 1H, 4-H); 3,40 (t, J = 3 Hz, 2H, $H_2CN$); 1,82 (s, 3H, $COCH_3$).

In Analogie zur Vorschrift des Beispiels 24 werden die in der Tabelle 6 aufgeführten Verbindungen hergestellt:

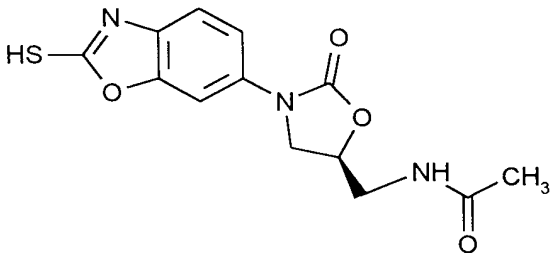
**Tabelle 6:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]^{20}_D$ (DMSO) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|---|
| 25 |  | 22 | 169 (Z) | 0,33 (VII, 2:1) | -16.4 (c=1) | 292 |

**Beispiel 26**

(5S)-3-(2-Mercaptobenzoxazol-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on



276 mg (1,04 mmol) der Verbindung aus Beispiel XXVIII und 184 mg (1,14 mmol) Kalium-O-ethyldithiocarbonat in 6 ml Ethanol werden 8 h bei 70°C gerührt. Anschließend werden 30 ml Wasser und 30 ml Essigester hinzugegeben, die organische Phase abgetrennt, die wäßrige Phase mit Essigester extrahiert, die vereinigten organischen Phasen mit ges. NaCl-Lösung gewaschen, getrocknet ($Na_2SO_4$) und die Lösemittel abgezogen. Der Rückstand wird aus Methanol umkristallisiert.

Ausbeute: 102 mg (31%)

Smp.: 239°C (Z)

$R_f$ (VIII, 1:1) = 0,41

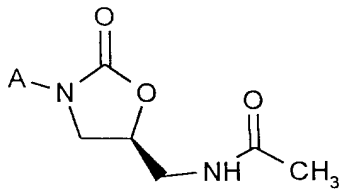
$[\alpha]^{20}_D$ = -25,15 (c=1,0, DMSO)

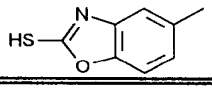
MS (CI): m/z = 307 ($M^+$)

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,25 (t, 1H, J = 4 Hz, NHCO); 7,75 (d, J = 1 Hz, 1H, Benzoxazol 7-H); 7,45 (dd, J = 6 Hz, J = 1 Hz, 1H, Benzoxazol 5-H); 7,25 (d, J = 6 Hz, 1H, Benzoxazol 4-H); 4,65 - 4,82 (m, 1H, 5-H); 4,15 (t, J = 6 Hz, 1H, 4-H); 3,75 (dd, J = 7 Hz, 4 Hz, 1H, 4-H); 3,45 (t, J = 4 Hz, 2H, $H_2CN$); 3,10 - 3,40 (bs, 1H); 1,85 (s, 3H, $COCH_3$).

In Analogie zur Vorschrift des Beispiels 26 werden die in der Tabelle 7 aufgeführten Verbindungen hergestellt:

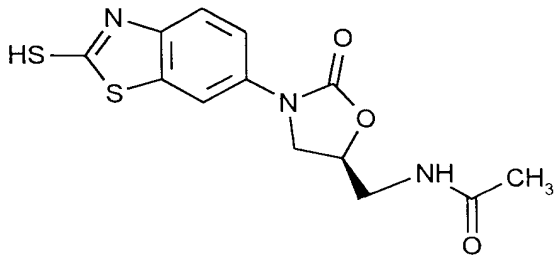
**Tabelle 7:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (CI) m/z ($M^+$ + H) |
|---|---|---|---|---|---|
| 27 |  | 33 | >250 | 0,55 (VII, 1:1) | 307 |

**Beispiel 28**

(5S)-3-(2-Mercapto-benzothiazol-6-yl)5-(acetylaminomethyl)oxazolidin-2on



Eine Lösung von 500 mg (1,21 mmol) (5S)-3-(2-Benzylthio-benzo[4,5-d]thiazol-6-yl)-5-acetylaminomethyl-oxazolidin-2-on in 2,5 ml Trifluoressigsäure und 0,56 ml Thioanisol wird 42 h auf 60°C erwärmt. Das Gemisch darf abkühlen, man versetzt mit 25 ml Ether, trennt den Niederschlag durch Filtration ab, wäscht mit 5 ml Ether und trocknet im Hochvakuum. Man erhält 59 mg (15%) der Titelverbindung als Feststoff.

Schmp.: 161°C

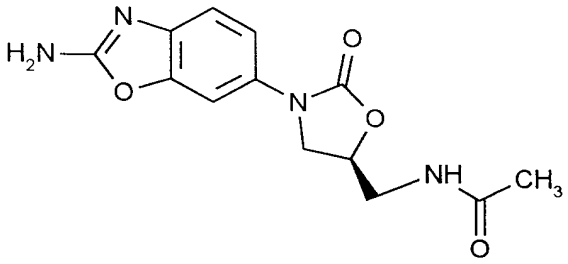
$R_f$ = 0,24 (Dichlormethan : Methanol 92:8)

MS (DCI, $NH_3$): m/z = 324 $(M+H)^+$

$^1$H-NMR (250 MHz, $D_6$-DMSO): $\delta$ = 13,73 (bs, 1H, 5H); 8,24 (m, 1H, NH); 7,86 (d, J = 1 Hz, 1H, Benzothiazol H-7); 7,63 (dd, J = 1, 10 HZ, 1H, Benzothiazol H-5); 7,30 (d, j = 10 Hz, 1H, Benzothiazol H-4); 4,74 (m, 1H, H-5); 4,11 (dd, J = 9, 9 Hz, 1H, H-4 cis); 3,76 (dd, J = 7, 9 Hz, 1H, H-4 trans); 3,42 (t, J = 6 Hz, 2H, $CH_2N$); 1,84 (s, 3H, $COCH_3$).

**Beispiel 29**

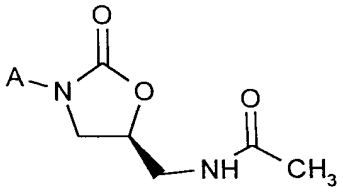
(5S)-3-(2-Aminobenzoxazol-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on

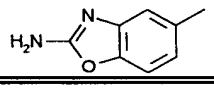


Zu einer Lösung aus 253 mg (2,41 mmol) Bromcyan in 2,5 ml Methanol und 2,5 ml Wasser werden 553 mg (2,19 mmol) der Verbindung aus Beispiel XXVIII in 10 ml Methanol gegeben und das Reaktionsgemisch 20 h bei Raumtemperatur gerührt. Das Methanol wird im Vakuum abgezogen, der ausgefallene Niederschlag abfiltriert, mit Wasser gewaschen und im Hochvakuum getrocknet.
Ausbeute: 393 mg (62%)
Smp.: 237°C
$R_f$ (VII, 1:1) = 0,4
MS (EI): m/z = 290 ($M^+$)
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,25 (t, J = 4 Hz, 1H, NHCO); 7,62 (bs, 1H, Ph); 7,50 (bs, 2H, $NH_2$); 7,30 (bs, 1H, Ph); 7,15 (bs, 1H, 7H); 4,60 - 4,78 (m, 1H, 5-H); 4,12 (Z, J= 7 Hz, 1H, 4-H); 3,70 (dd, J = 7 Hz, J = 4 Hz, 1H, 4-H); 3,35 - 3,45 (m, 2H, $CH_2N$); 1,80 (s, 3H, $CH_3CO$).

Analog Beispiel 29 werden die in Tabelle 8 aufgeführten Verbindungen hergestellt:

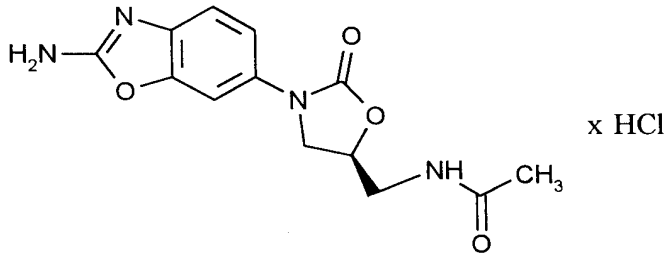
**Tabelle 8:**



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (EI) m/z ($M^+$ -Cl) |
|---|---|---|---|---|---|
| 30 |  | 56 | 219-220 | 0,42 (II, 1:1) | 290 |

**Beispiel 31**

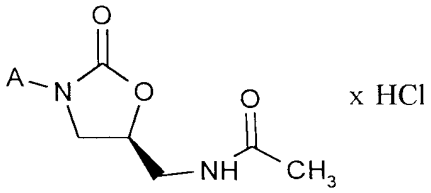
(5S)-3-(2-Aminobenzoxazol-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on Hydrochlorid

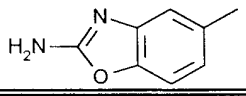



Zu einer Lösung aus 150 mg (0,52 mmol) der Verbindung aus Beispiel 29 in 35 ml Methanol werden 2,58 ml (2,58 mmol) 1 H HCl in Ether und anschließend 130 ml Ether gegeben. Der ausgefallene Niederschlag wird abgesaugt, mit Ether gewaschen und im Hochvakuum getrocknet.
Ausbeute: 170 mg (89%)
Schmp.: 226-227°C
$^1$H-NMR ([$D_6$]-DMSO): $\delta$ = 8,8 - 9,2 (bs, 1H, NH); 8,28 (t, J = 4 Hz, 1H, NHCO); 7,80 (s, 1H, Ph); 7,20 - 7,35 (m, 2H, Ph); 4,5 - 5,0 (m, 3H, 5-H, $NH_2$); 4,15 (t, J = 7 Hz, 1H, 4-H); 3,73 (dd, J = 7 Hz, J = 4 Hz, 1H, 4-H); 3,40 (t, J = 4 Hz, 2H, $CH_2N$); 1,80 (s, 3H, $CH_3CO$).

Analog Beispiel 31 werden die in Tabelle 9 aufgeführten Verbindungen dargestellt:

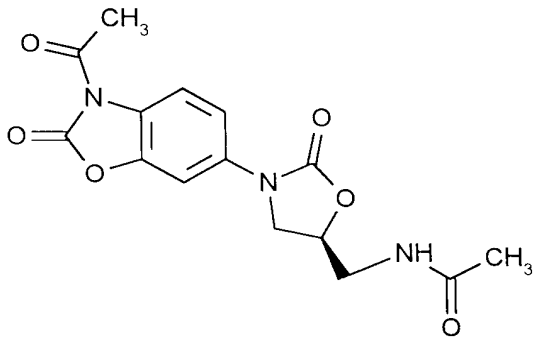
**Tabelle 9:**




| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) |
|---|---|---|---|
| 32 |  | 47 | 220 |

**Beispiel 33**

(5S)-3-(3-Acetyl-2-benzoxazolinon-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on



Zu einer Lösung aus 200 mg (0,68 mmol) der Verbindung aus Beispiel 23 in 10 ml DMF werden 16,5 ml (0,68 mmol) Natriumhydrid (80% in Paraffin) gegeben und das Reaktionsgemisch 15 min bei Raumtemperatur gerührt. Bei 0°C werden anschließend 50 µl (54 mg, 0,68 mmol) Acetylchlorid zugetropft und weitere 15 h bei 0°C gerührt. Zur Aufarbeitung wird das Lösemittel im Vakuum abgezogen, das Rohprodukt in Essigester und Wasser aufgenommen, die wäßrige Phase dreimal mit Essigester extrahiert, die vereinigten organischen Phasen mit gesättigter NaCl-Lösung gewaschen, getrocknet ($Na_2SO_4$), eingeengt und aus Methanol umkristallisiert.

Ausbeute: 54 mg (23%)

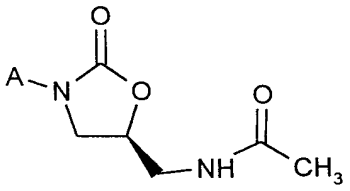
$R_f$ (VII, 1:1= = 0,62

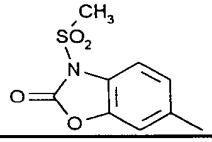
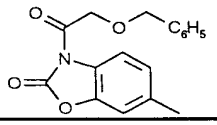
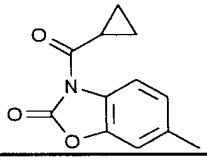
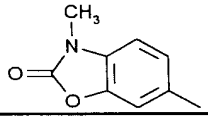
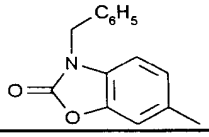
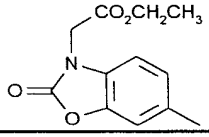
MS (EI): m/z = 333 ($M^+$)

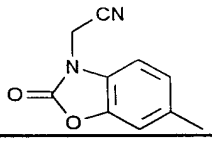
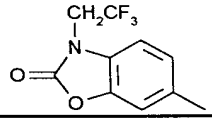
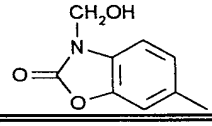
$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,25 (t, J = 4 Hz, 1H, NHCO); 7,90 (d, J = 6 Hz, 1H, Benzoxazolin 4-H); 7,72 (d, J = 1 Hz, 1H, Benzoxazolin 7-H); 7,33 (dd, J = 6 Hz, J = 1 Hz, Benzoxazolin 5-H); 4,60 - 4,80 (m, 1H, 5-H); 4,15 (t, J= 6 Hz, 1H, 4-H); 3,73 (dd, J = 7 Hz, 4 Hz, 1H, 4-H); 3,55 (t, J = 4 Hz, 2H, $CH_2N$)); 2,60 (s, 3-H, $CH_3CO$); 1,80 (s, 3H, $CH_3CON$).

In Analogie zur Vorschrift des Beispiels 33 werden die in Tabelle 10 aufgeführten Verbindungen hergestellt:

**Tabelle 10:**



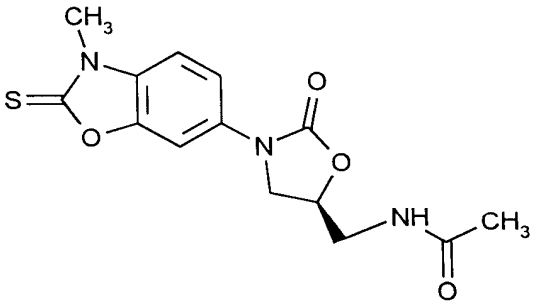
| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]_D^{20}$ (DMSO) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|---|
| 34 |  | 49 | 224-225 | 0,25 (VII, 5:1) | -17.7° (c=0,5) | 370 |
| 35 |  | 54 | 220-222 | 0,26 (VII, 5:1) | -23,2° (c=0,5) | 440 |
| 36 |  | 82 | 223-224 | 0,36 (VII, 5:1) | -22,6° (c=0,5) | 359 [a)] |
| 37 |  | 53 | 243-244 | 0,20 (VII, 5:1) | -30,6° (c=0,5) | 306 |
| 38 |  | 77 | 247-248 | 0,29 (VII, 1:1) | -19,9° (c=0,5) | 381 [a)] |
| 39 |  | 57 | 197-198 | 0,22 (VII, 5:1) | -23,0° (c=0,5) | 378 |

| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | $[\alpha]^{20}_D$ (DMSO) | MS (FAB) m/z ($M^+$ + H) |
|---|---|---|---|---|---|---|
| 40 |  | 29 | 210-212 | 0,25 (VII, 5:1) | -19,2° (c=1,0) | 331 |
| 41 |  | 82 | - | 0,60 (VII, 1:1) | - | 374 |
| 42 |  | 85 | 230-231 (Z) | 0,53 (VII, 1:1) | -20,7° (c=1,0) | 322 |

a) MS (EI), m/z ($M^+$)

**Beispiel 43**

(5S)-3-(3-Methyl-2-benzoxazolinthion-6-yl)-5-acetylaminomethyl)-oxazolidin-2-on



767,9 mg (2,9 mmol) der Verbindung aus Beispiel XXVIII und 511 mg (3,2 mmol) Kalium-O-ethyldithiocarbonat in 15 ml Ethanol werden 8 h bei 70°C gerührt. Anschließend wird das Lösemittel abgezogen, der Rückstand mit 20 ml DMF und 410 mg (28,9 mmol) Methyliodid versetzt und 20 h bei 150°C gerührt. Nach dem Abkühlen gibt man 40 ml $CH_2Cl_2$ hinzu, saugt den Niederschlag ab, wäscht mit $CH_2Cl_2$ und verkocht anschließend mit Methanol. Der Rückstand wird im Hochvakuum getrocknet.

Ausbeute: 602 mg (65%)

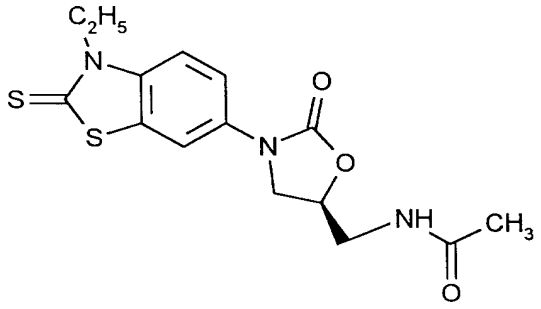
$R_f$ (VII, 1:1) = 0,44

MS (CI): m/z = 322 ($M^+$)

$^1$H-NMR ([$D_6$]DMSO: $\delta$ = 8,25 (t, J = 4 Hz, 1H, NHCO); 7,82 (s, 1H, Ph); 7,50 (s, 2H, Ph); 4,65 - 4,85 (m, 1H, 5-H); 4,15 (t, J = 7 Hz, 1H, 4-H); 3,25 (dd, J = 7 Hz, J = 4 Hz, 1H, 4-H); 3,14 (s, 3H, $NCH_3$); 3,40 - 3,50 (m, 2H, $CH_2N$); 1,82 (s, 3H, $CH_3CO$).

**Beispiel 44**

(5S)-3-(3-Ethyl-benzothioazolinthion-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on



Eine gerührte Lösung von 303 mg (0,90 mmol) (5S)-3-(2-Methylthio-benzo[4,5-d]thiazol-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on (Beispiel XXVI) in 3 ml wasserfreiem DMF wird mit 0,72 ml (9,00 mmol) Iodethan versetzt und 23 h auf 100°C (Badtemperatur) erhitzt. Das Reaktionsgemisch darf abkühlen, man gibt 30 ml Ether zu und trennt den entstandenen honigartigen Niederschlag durch Dekandieren ab. Nach chromatographischer Reinigung an 58 g Kieselgel (Dichlormethan : Methanol 95:5) erhält man 74 mg (25%) der Titelverbindung als Kristalle.

Schmp.: 224°C

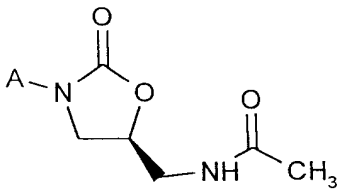
$R_f$ = 0,15 (Dichlormethan : Methanol 95:5)

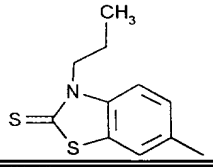
MS (EI): m/z = 351$(M)^+$

$^1$H-NMR ([$D_6$]DMSO): $\delta$ = 8,23 (m, 1H, NHCO); 7,96 (d, J = 1 Hz, 1H, Benzothiazolon H-7); 7,73 (dd, J = 1, 9 Hz, 1H, Benzothiazolon H-5); 7,63 (d, J = 9 Hz, 1H, Benzothiazolon H-4); 4,76 (m, 1H, H-5); 4,46 (q, J = 7 Hz, 2H, $CH_3\underline{CH_2}$); 4,17 (dd, J = 10, 10 Hz, 1H, H-4 cis); 3,80 (m, 1H, H-4 cis); 3,46 (m, 2H, $CH_2N$); 1,83 (s, 3H, $COCH_3$); 1,28 (t, J = 7 Hz, 3H, $\underline{CH_3}CH_2$).

Wie für Beispiel 44 beschrieben erhält man analog die in Tabelle 11 aufgeführten Verbindungen:

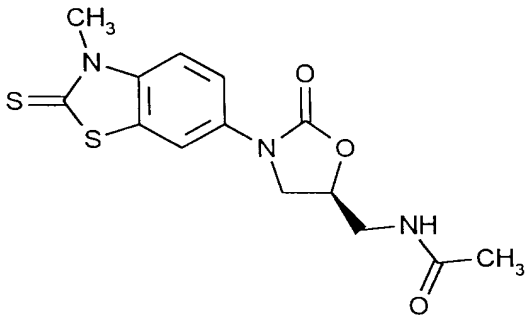
**Tabelle 11**:



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | Schmp. (°C) | $R_f$ (Laufmittel, Verhältnis) | MS (EI) m/z $(M + H)^+$ |
|---|---|---|---|---|---|
| 45 |  | 16 | 197 | 0,14 (I, 95:5) | 366 |

**Beispiel 46**

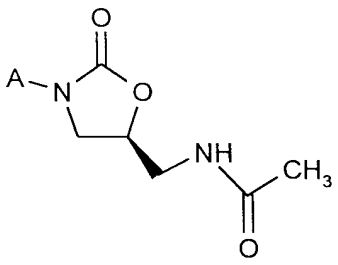
(5S)-3-(3-Methyl-benzothiazolinthion-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on

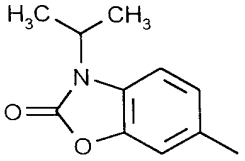
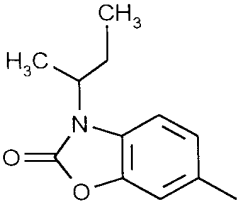
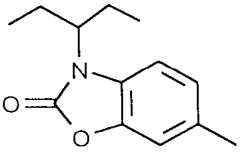
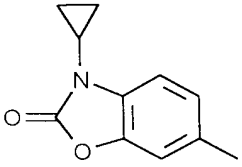


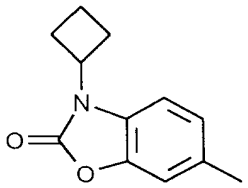
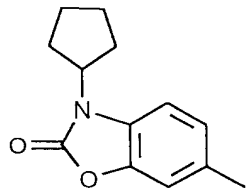
83 mg (0,17 mmol) der Verbindung aus Beispiel XXVI werden unter Rühren im Vakuum (1 mm) in Sustanz innerhalb von 1,5 h von 125°C auf 150°C erhitzt. Der Rückstand darf abkühlen und wird gut mit 250 ml Wasser gewaschen, mit 15 ml Ethylacetat und 5 ml Ethanol gut gerührt und über Sicapent im Hochvakuum getrocknet. Man erhält 48 mg (83%) der Titelverbindung als farblose Kristalle.
Schmp.: 253°C (Z)
$R_f$ = 0,10 (Dichlormethan : Methanol 95:5)
MS (FAB): m/z = 338 $(M+H)^+$
$^1$H-NMR (200 MHz, $D_6$-DMSO): $\delta$ = 8,28 (m, 1H, NHCO); 7,91 (d, J = 1Hz, 1H, Benzothiazolinthion H-7); 7,72 (dd, J = 1, 9 Hz, 1H, Benzothiazolinthion H-5); 7,56 (d, J = 9 Hz, 1H, Benzothiazolinthion H-4); 4,78 (m, 1H, H-5); 4,15 (dd, J= 10, 10 Hz, 1H, H-4 cis); 3,75 (m, 4H, $CH_3$, H-4 trans); 3,43 (m, 2H, $CH_2N$); 1,85 (s, 3H, $COCH_3$).

In Analogie zur Vorschrift des Beispiels 24 werden die in der Tabelle aufgeführten Verbindungen dargestellt.

**Tabelle 12**

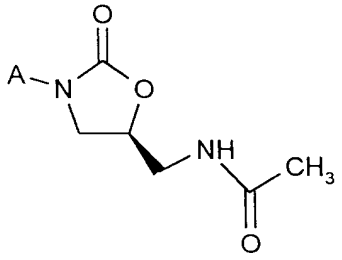


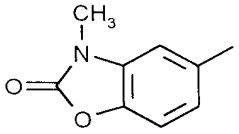
| Bsp.-Nr. | A | Ausbeute | $R_f$ Laufmittel, Verhältnis | MS (DCl) m/z ($M^+$+H) |
|---|---|---|---|---|
| 47 |  | quant. | 0,44 (I, 10:1) | 324 |
| 48 |  | 78 | 0,71 (I, 5:1) | 348 |
| 49 |  | 73 | 0,16 (I, 10:1) | 362 |
| 50 |  | 62 | 0,38 (I-10:1) | 322 |

| Bsp.-Nr. | A | Ausbeute | $R_f$ Laufmittel, Verhältnis | MS (DCI) m/z ($M^+$+H) |
|---|---|---|---|---|
| 51 |  | 77 | 0,23 (I, 10:1) | 346 |
| 52 |  | 86 | 0,22 (I, 10:1) | 360 |

In Analogie zur Vorschrift des Beispiels 33 werden die in der Tabelle aufgeführten Verbindungen dargestellt.

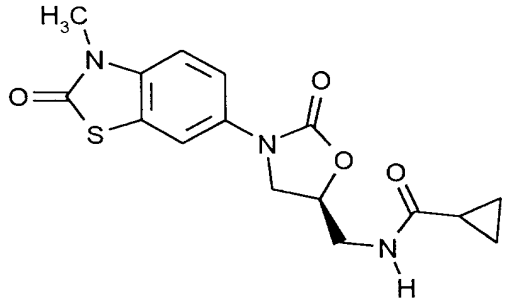
**Tabelle 13**



| Bsp.-Nr. | A | Ausbeute (% d.Th) | $R_f$ Laufmittel, Verhältnis | MS (DCI) m/z ($M^+$+H) |
|---|---|---|---|---|
| 53 |  | 50 | 0,14 (VII, 5:1) | 306 |

**Beispiel 54**

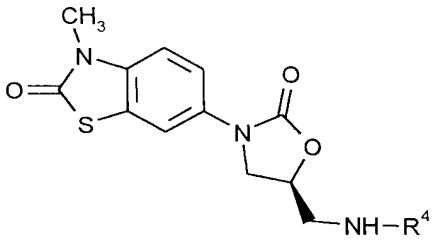
(5S)-3-(3-Methyl-2-benzothiazolinon-6-yl)-5-(cyclopropylcarbonylaminomethyl)-oxazolidin-2-on

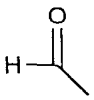
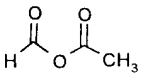
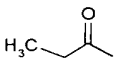
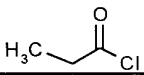
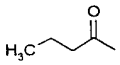
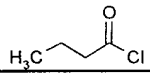
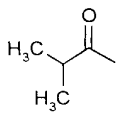
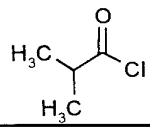
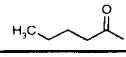
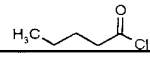
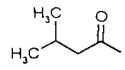
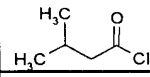
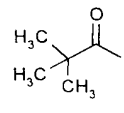
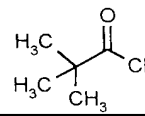
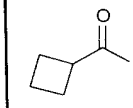
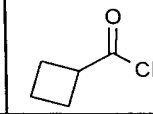
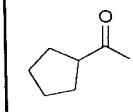
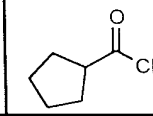
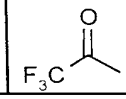


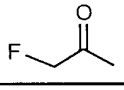
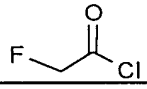
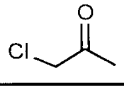
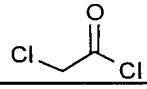
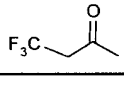
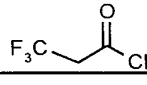
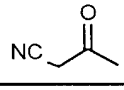
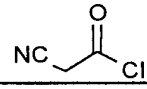
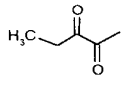
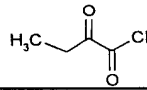
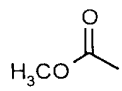
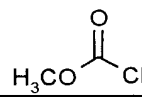
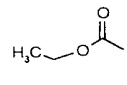
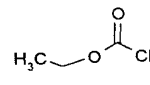
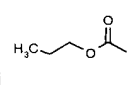
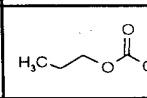
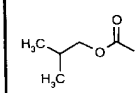
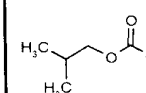
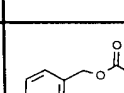
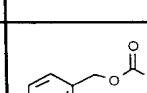
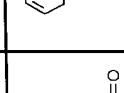
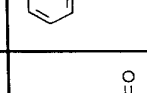
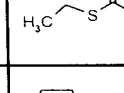
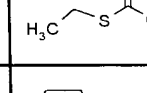
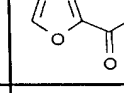
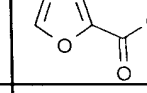
4,74 g (0,015 mol) (5S)-3-(3-Methyl-2-benzothiazolinon-6-yl)-5-(aminomethyl)-oxazolidin-2-on Hydrochlorid (Beispiel 13) werden in 150 ml Dichlormethan bei ca. 5°C unter Argon vorgelegt. Nacheinander werden 4,5 ml (0,033 mol) Triethylamin und 1,35 ml (0,015 mol) Cyclopropancarbonsäurechlorid zugetropft. Man rührt eine Stunde bei Raumtemperatur, versetzt mit Wasser, trennt die organische Phase ab und zieht das Lösemittel ab. Das erhaltene Rohprodukt wird an Kieselgel (Laufmittel:Dichlormethan/Methanol 100:2) gereinigt und anschließend mit Dichlormethan/Petrolether verrieben.
Ausbeute: 5,1 g (98 %)
Schmelzpunkt: 190-192°C
$R_f$ (I, 100:2) = 0,15
MS (DCI, $NH_3$):m/z = 348 $(M+H)^+$

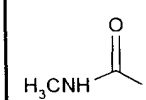
In Analogie zur Vorschrift des Beispiels 54 werden die in der Tabelle 14 aufgeführten Verbindungen dargestellt.

**Tabelle 14**



| Bsp.-Nr. | $R^4$ | Acylierungs-mittel | Ausbeute (% d.Th.) | Schmp. (°C | $R_f$(Lauf-mittel, Verhält-nis | MS(Cl) m/z ($M^+$+H) |
|---|---|---|---|---|---|---|
| 55 |  |  | 26 | 182-184 | 0,13 (I, 100:5) | 325[a] |
| 56 |  |  | 58 | 186-188 | 0,12 (I,100:2) | 336 |
| 57 |  |  | 76 | 185-188 | 0,25 (I, 100:5) | 350 |
| 58 |  |  | 79 | 218-220 | 0,29 (I, 100:5) | 350 |
| 59 |  |  | 68 | 190-192 | 0,24 (I,100:5) | 364 |
| 60 |  |  | 63 | 213-215 | 0,28 (I,100:5) | 364 |
| 61 |  |  | 69 | - | 0,15 (I, 100:5) | 364 |
| 62 |  |  | 74 | 195-197 | 0,20 (I, 100:5) | 379[a] |
| 63 |  |  | 74 | 211-213 | 0,39 (I, 100:5) | 376 |
| 64 |  | $(F_3CCO)_2O$ | 50 | 198-200 | 0,14 (I, 100:2) | 375[b] |

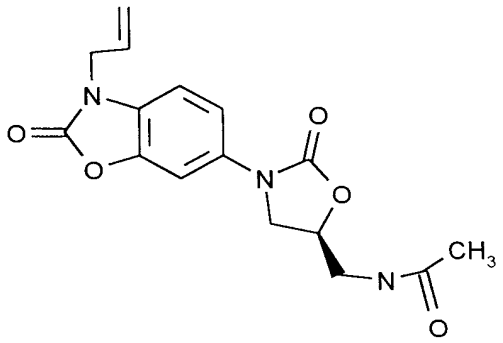
| Bsp.-Nr. | $R^4$ | Acylierungs-mittel | Ausbeute (% d.Th.) | Schmp. (°C | $R_f$(Lauf-mittel, Verhält-nis | MS(Cl) m/z ($M^+$+H) |
|---|---|---|---|---|---|---|
| 65 |  |  | 52 | 208-210 | 0,40 (I, 100:5) | 339[b] |
| 66 |  |  | 45 | 192-194 | 0,48 (I, 100:5) | 373[a] |
| 67 |  |  | 37 | 106-108 | 0,37 (I, 100:5) | 407[a] |
| 68 |  |  | 29 | 113-115 | 0,10 (I, 100:2) | - |
| 69 |  |  | 26 | 230-232 | 0,26 (I, 100:5) | 397[a] |
| 70 |  |  | 48 | 173-175 | 0,13 (I, 100:2) | 337[b] |
| 71 |  |  | 51 | 143-145 | 0,40 (I,100:5) | 369[a] |
| 72 |  |  | 41 | 148-150 | 0,33 (I, 100:5) | 383[a] |
| 73 |  |  | 46 | 168-170 | 0,40 (I,100:5) | 397[a] |
| 74 |  |  | 25 | 183-185 | 0,59 (I, 100:5) | 414 |
| 75 |  |  | 41 | 181-183 | 0,56 (I, 100:5) | 385[a] |
| 76 |  |  | 31 | 187-189 | 0,13 (I, 100:2) | 391[a] |
| 77 |  |  | 49 | 228-230 | 0,25 (I, 100:2) | 406[a] |

| Bsp.-Nr. | $R^4$ | Acylierungsmittel | Ausbeute (% d.Th.) | Schmp. (°C | $R_f$(Laufmittel, Verhältnis | MS(Cl) m/z ($M^+$+H) |
|---|---|---|---|---|---|---|
| 78 |  | $H_3C$-NCO | 85 | 188-191 | 0,39 (I, 9:1) | 337 |
| 79 | $H_3C$-$SO_2$- | $H_3C$-$SO_2Cl$ | 35 | 188-190 | 0,27 (I, 100:5) | 375[a] |

a) MS (Cl, $NH_3$):m/z ($M+NH_4^+$)
b) MS (EI):m/z ($M^+$)

**Beispiel 80**

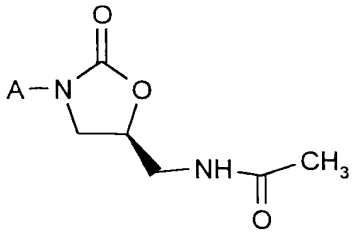
(5S)-3-(3-Allyl-2-benzoxazolinon-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on

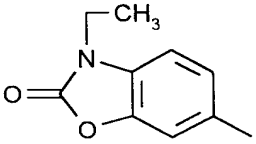
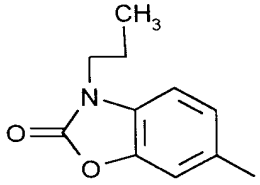
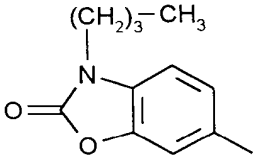
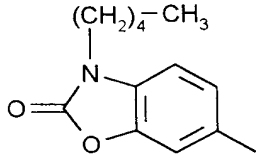
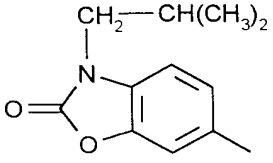


Eine Lösung aus 174 mg (0,6 mmol) der Verbindung aus Beispiel 23 und 140 µl (0,9 mmol) Diazobicycloundecen (DBU) in 10 ml DMF wird 1 h bei 40 bis 50°C gerührt. Anschließend werden 50 µl (0,6 mmol) Allylbromid hinzugegeben und die Mischung weitere 14 h bei 100°C gerührt. Das Lösemittel wird im Vakuum abgezogen und der Rückstand durch Chromatographie gereinigt.
Ausbeute: 155 mg (78 %)
$R_f$ (I, 10:1) = 0,33
MS (EI):m/z = 331 ($M^+$)
$^1$H-NMR ([$D_6$]DMSO): δ = 8,25 (bt, 1H, NHCO), 7,70 (d, 1H, Benzoxazolin 7-H), 7,25 (dd, 1H, Benzoxazolin 5-H), 7,15 (d, 1H, Benzoxazolin 4-H), 5,80-6,05 (m, 1H, C=CH), 5,10-5,70 (m, 2H, $C=CH_2$), 4,80 (m, 1H, 5-H), 4,45 (d, 2H, $CH_2C$=C), 4,10 (t, 1H, 4-H), 3,70 (dd, 1H, 4-H), 3,40 (bt, 2H, $CH_2N$), 1,80 (s, 3H, $COCH_3$).

In Analogie zum Beispiel 80 wurden die in Tabelle 15 aufgeführten Verbindungen dargestellt.

## Tabelle 15



| Bsp.-Nr. | A | Ausbeute (% d.Th.) | $R_f$ (Laufmittel, Verhältnis) | MS (DCI) m/z ($M^+$+H) |
|---|---|---|---|---|
| 81 |  | 49 | 0,37 (I, 10:1) | 320 |
| 82 |  | 69 | 0,23 (I, 10:1) | 334 |
| 83 |  | 50 | 0,26 (I, 10:1) | 348 |
| 84 |  | 59 | 0,28 (I, 10:1) | 362 |
| 85 |  | 24 | 0,25 (I, 10:1) | 348 |