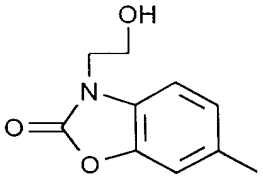
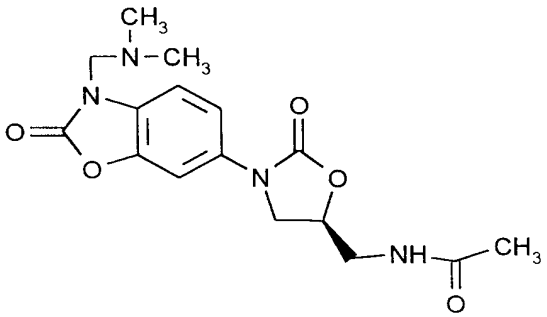
Bsp.-Nr.	A	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis)	MS (DCI) m/z (M^++H)
86		51	0,10 (I, 10:1)	336

Beispiel 87

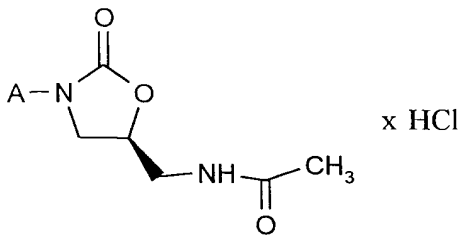
(5S)-3-(3-Dimethylaminomethyl-2-benzoxazolinon-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on



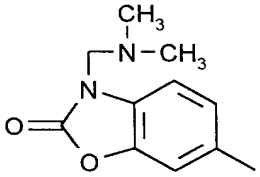
Eine Mischung aus 290 mg (1,0 mmol) der Verbindung aus Beispiel 23, 140 µl einer 30 % Formaldehyd-Lösung in Wasser, 150 µl einer 51 % Dimethylamin-Lösung in Wasser und 10 ml Ethanol wird 16 h bei 80°C gerührt. Der Niederschlag wird bei Raumtemperatur abfiltriert, mit Petrolether gewaschen und im Hochvakuum getrocknet.
Ausbeute: 86 %
R_f (II, 5:1) = 0,24
MS (DCI, NH_3): m/z = 349 (M^+ +H)
^{1}H-NMR ([D_6]DMSO): δ = 8,25 (bt, 1H, NHCO), 7,65 (d, 1H, Ar 7-H), 7,40 (d, 1H, Ar 4-H); 7,25 (dd, 1H, Ar 5-H), 4,70 (m, 1H, 5-H), 4,60 (s, 2H, NCH_2N), 4,75 (t, 1H, 4-H), 3,75 (dd, 1H, 4-H), 3,40 (t, 2H, CH_2N), 2,30 (s, 6H, NCH_3), 1,80 (s, 3H, $COCH_3$).

Analog Beispiel 31 werden die in Tabelle 16 aufgeführten Verbindung dargestellt.

Tabelle 16

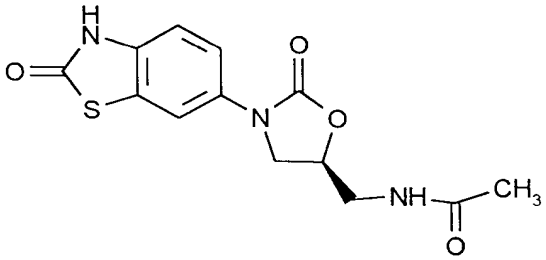


x HCl

Bsp.-Nr.	A	Ausbeute (% d. Th.)
88		97

Beispiel 89

(5S)-3-(2-Benzothiazolinon-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on



Eine Mischung aus 95 g (0,28 mol) der Verbindung aus Beispiel XXV und 200 g (0,37 mol) Oxone® (Kaliummonopersulfat Tripelsalz) in 5 l Wasser wird 24 h bei Raumtemperatur gerührt. Nach Zugabe von 1 l 2-Propanol wird der Niederschlag abgesaugt und der Rückstand durch Chromatographie gereinigt. Man erhält 84,6 g (81 %) (5S)-3-(2-Methylsulfonyl-2-benzothiazolinon-6-yl)-5-(acetylaminomethyl)-oxazolidinon. 2 g (5,4 mmol) dieser Verbindung werden in 50 ml Wasser und 10 ml Triethylamin 14 h zum Rückfluß erhitzt. Nach dem Abziehen der flüchtigen Bestandteile wird der Rückstand durch Chromatographie gereinigt.

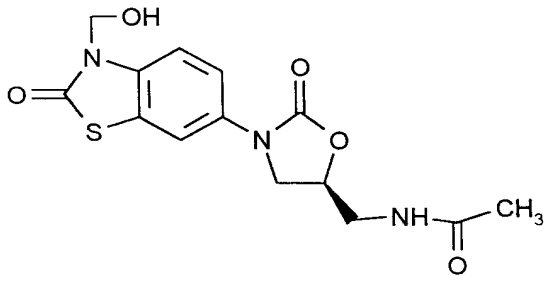
Ausbeute: 1,15 g (69 %)

Schmp.: 223°C

MS (CI), m/z = 325 ($M^+NH_4^+$)

Beispiel 90

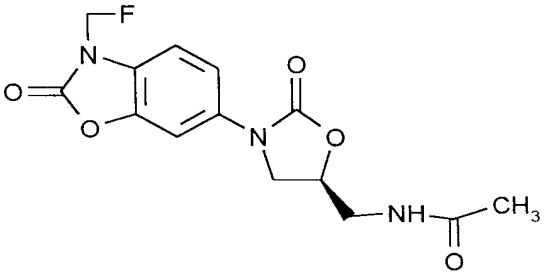
(5S)-3-(3-Hydroxymethyl-2-benzothiazolinon-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on



Eine Mischung aus 308 mg (1,0 mmol) der Verbindung aus Beispiel 89 und 0,13 ml 37 % Formaldehyd-Lösung in 1 ml Wasser wird 14 h bei 70-80°C gerührt. Der entstandene Niederschlag wird abgesaugt, mit Wasser gewaschen und getrocknet.
Ausbeute: 280 mg (83 %)
Schmp.: 192°C

Beispiel 91

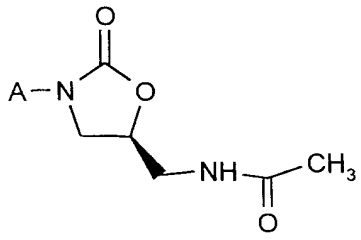
(5S)-3-(3-Fluormethyl-2-benzoxazolinon-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on

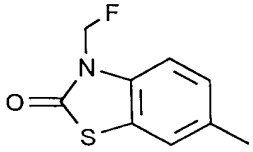


Zu einer Suspension von 100 ml (311 mmol) der Verbindung aus Beispiel 42 und 10 ml Dichlormethan werden bei -50°C 61 µl (466 mmol) Diethylaminoschwefeltrifluorid (DAST) gegeben. Man läßt auf Raumtemperatur kommen, rührt weitere 52 h, versetzt mit 5 ml gesättigter $NaHCO_3$-Lösung, rührt 10 min und wäscht dann die organische Phase mit Wasser. Der dabei ausgefallene Niederschlag wird abgesaugt, die organische Phase getrocknet (Na_2SO_4) und eingedampft. Ausbeute: 25 mg (25 %)
R_f = 0,22 (VII, 5:1)
MS (EI): m/z = 323 (M^+)
^{1}H-NMR (200 MHz, [D_6]DMSO): δ = 8,25 (bs, 1H, NHCO), 7,72 (d, 1H, Ar-H-2), 7,55 (d, 1H, Ar-H-4), 7,32 (dd, 1H, Ar-H-5), 6,05 (d, 2H, CH_2F), 4,70 (m, 1H, H-5), 4,10 (t, 1H, H-4), 3,75 (d, 1H, H-4), 3,40 (m, 2H, CH_2N), 1,85 (s, 3H, $COCH_3$).

In Analogie zur Vorschrift des Beispiels 91 erhält man die in der Tabelle 17 aufgeführten Verbindungen.

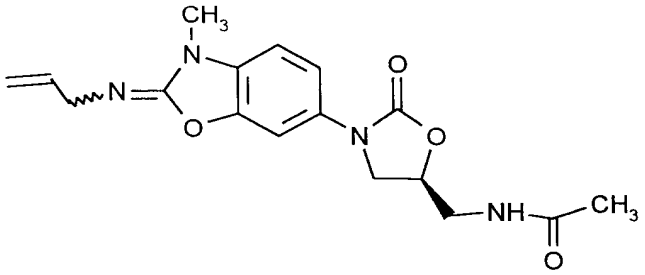
Tabelle 17



Bsp.-Nr.	A	Ausbeute (% d. Th.)	Schmp. (°C)	R_f (Laufmittel, Verhältnis
92		74	185	0,54 (I, 9:1)

Beispiel 93

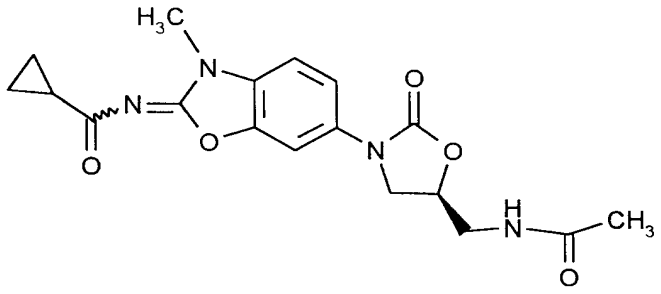
(5S)-3-(2-(Allylimino)-3-methyl-2,3-dihydrobenzoxazol-6-yl)-5-(acetylaminomethyl)oxazolidin-2-on



Eine Mischung aus 0,30 g (0,694 mol) der Verbindung aus Beispiel XXXV, 0,29 g (3,33 mol) Allylbromid und 0,38 g (2,77 mol) wasserfreies Kaliumcarbonat in 4 ml Ethanol wird 11 h unter Rückfluß erhitzt. Zur Aufarbeitung wird abgesaugt, das Filtrat im Vakuum eingeengt, getrocknet und durch Chromatographie gereinigt. Das so erhaltene Öl wird in Essigester gelöst und mit Petrolether das Produkt gefällt.
Ausbeute: 0,015 g (6 %)
R_f (VII, 1:1) = 0,47
MS (EI): m/z = 344 (M^+)
^{1}H-NMR ([D_6]DMSO): δ = 8,24 (t, 1H, NHCO), 7,52 (d, 1H, Ar 7-H), 7,15 (dd, 1H, Ar 5-H), 7,03 (d, 1H, Ar 4-H), 5,72-6,07 (m, 1H, HC=C), 5,22 (dq, 1H H_2C=C), 5,03 (dq, 1H, H_EC=C), 4,70 (m, 1H, 5-H), 4,10 (t, 1H, 4-H), 3,98 (m, 2H, CH_2N), 3,72 (dd, 1H, 4-H), 3,40 (t, 2H, CH_2N), 3,33 (s, 3H, NCH_3), 1,82 (s, 3H, $COCH_3$).

Beispiel 94

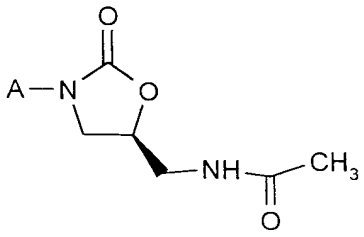
(5S)-3-(2-Cyclopropylcarbonylimino-3-methyl-2,3-dihydrobenzoxazol-6-yl)-5-(acetylaminomethyl)-oxazolidin-2-on

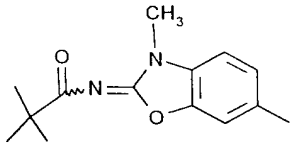
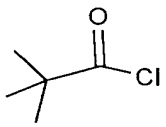
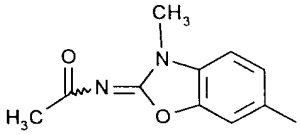
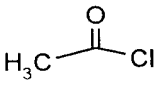
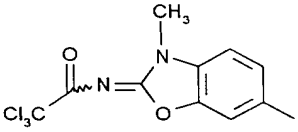
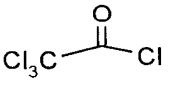
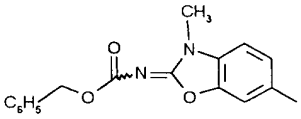
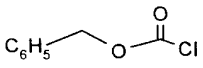
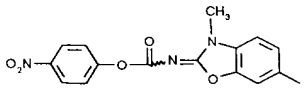
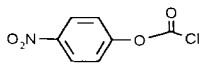
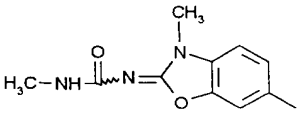
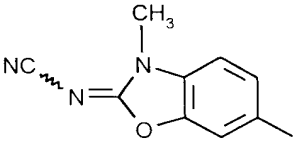


Zu einer Suspension von 304 mg (0,703 mmol) der Verbindung aus Beispiel XXXV in 10 ml THF werden 310 µl (2,2 mmol) Triethylamin gegeben und anschließend bei 0°C 100 µl (11 mmol) Cyclopropancarbonsäurechlorid zugetropft. Nach 1 h gibt man die Mischung auf Eiswasser, sättigt die wäßrige Phase mit Natriumchlorid, extrahiert dreimal mit Essigester, trocknet (Na_2SO_4), zieht die Lösungsmittel ab und kristallisiert aus Dichlormethan.
Ausbeute: 196 mg (75 %)
R_f = 0,45 (VII, 1:1)
MS (DCI/NH_3): m/z = 373 (M^++H)
^{1}H-NMR (200 MHz, [D_6]DMSO): δ = 8,25 (bt, 1H, NHCO), 7,75 (s, 1H, Ar), 7,40 (bs, 2H, Ar), 4,75 (m, 1H, H-5), 4,15 (t, 1H, H-4), 3,40 (m, 5H, CH_2N, CH_3), 1:90 (s, 3H, $COCH_3$), 1,70 (m, 1H, Cpr-H), 0,70-0,95 (m, 4H, Cpr-H).

In Analogie zur Vorschrift des Beispiels 94 werden die in der Tabelle 18 aufgeführten Verbindungen dargestellt.

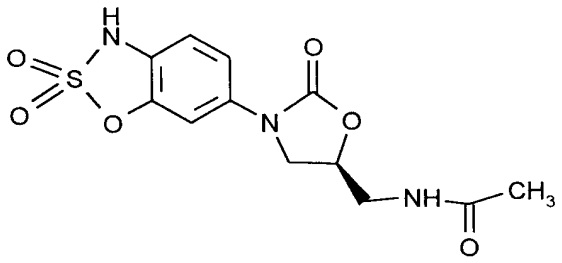
Tabelle 18



Bsp.-Nr.	A	Acylierungsmittel	Ausbeute (% d. Th.)	R_f (Laufmittel, Verhältnis)	MS (Cl) m/z (M^++H)
95			79	0,53 (VII, 1:1)	389
96			36	0,35 (VII, 1:1)	347
97			38	0,53 (VII, 1:1)	449
98			32	0,43 (VII, 1:1)	439
99			62	0,44 (VII, 1:1)	470
100		H_3C-NCO	46	0,26 (VII, 1:1)	362
101		BrCN	44	0,37 (VII, 1:1)	330

Beispiel 102

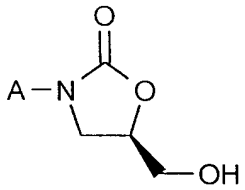
(5S)-3-(3-Aza-1-oxa-2-thiaindan-2-dioxid-6-yl)-5-(acetylaminomethyl)ozazolidin-2-on

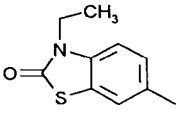
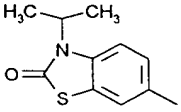
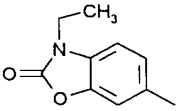


Zu einer Mischung aus 0,5 g (1,88 mmol) der Verbindung aus Beispiel 23, 0,63 ml (4,52 mmol) Triethylamin und 20 ml wasserfreiem Dichlormethan wird bei -5°C tropfenweise eine Lösung aus 0,17 ml (2,07 mmol) Sulforylchlorid in 5 ml Dichlormethan gegeben. Man rührt weitere 1 h bei -5°C, anschließend 14 h bei Raumtemperatur und versetzt dann mit Wasser. Die organische Phase wird dreimal mit Dichlormethan gewaschen, die vereinigten wäßrigen Phasen mit Natriumchlorid gesättigt und viermal mit Essigester extrahiert. Die Essigester-Phasen werden getrocknet (Na_2SO_4) und im Vakuum das Lösemittel abgezogen.
Ausbeute: 98 mg (16%)
R_f (VII, 1:1) = 0,17
MS (FAB): m/z = 326 (M^+-H)
^{1}H-NMR ([D_6]DMSO): δ = 8,25 (t, 1H, NHCO), 7,50 (d, 1H, Ar 7-H), 7,27 (dd, 1H, Ar 5-H), 7,05 (d, 1H, Ar 4-H), 4,70 (m, 1H, 5-H), 4,05 (t, 1H, 4-H), 3,65 (dd, 1H, 4-H), 3,40 (t, 1H, CH_2N), 1,80 (s, 3H, $COCH_3$).

In Analogie zur Vorschrift des Beispiels 1 werden die in der Tabelle 19 aufgeführten Verbindungen dargestellt:

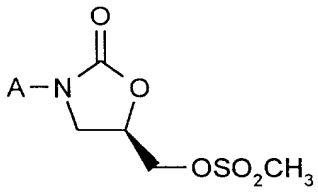
Tabelle 19

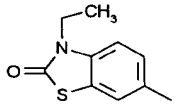
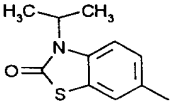
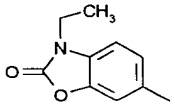


Bsp.-Nr.	A	Ausbeute (% d. Th.)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
103		76	156	0,32 (I, 100:5)	312 ($M+NH_4^+$)
104		62	157	0,33 (I, 100:5)	326 ($M+NH_4^+$)
105		50	-	0,12 (II, 1:1)	296 ($M+NH_4^+$)

In Analogie zur Vorschrift des Beispiels 5 werden die in der Tabelle 20 aufgeführten Verbindungen dargestellt:

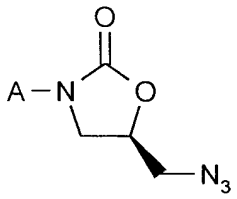
Tabelle 20

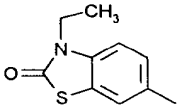
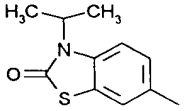
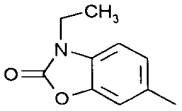


Bsp.-Nr.	A	Ausbeute (% d. Th.)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
106		86	150	0,52 (I, 100:5)	-
107		quant.	-	0,58 (I, 100:5)	-
108		95	-	0,31 (VII, 5:1)	357 ($M+H^+$)

In Analogie zur Vorschrift des Beispiels 9 werden die in der Tabelle 21 aufgeführten Verbindungen dargestellt:

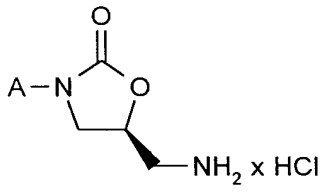
Tabelle 21

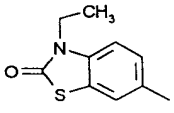
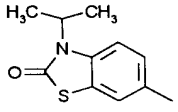
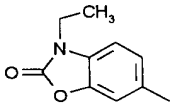


Bsp.-Nr.	A	Ausbeute (% d. Th.)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
109		93	180-183	0,69 (I, 100:5)	-
110		91	-	0,69 (I, 100:5)	-
111		88	-	0,27 (VII, 5:1)	304 ($M+H^+$)

In Analogie zur Vorschrift des Beispiels 13 werden die in der Tabelle 22 aufgeführten Verbindungen dargestellt:

Tabelle 22

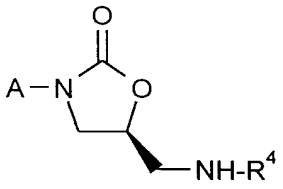


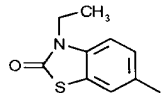
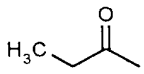
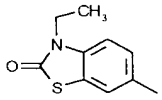
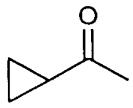
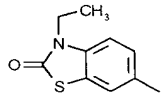
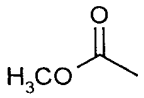
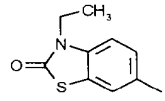
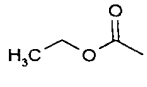
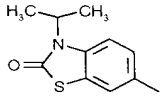
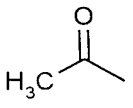
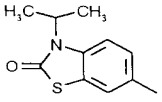
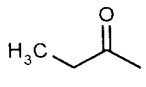
Bsp.-Nr.	A	Ausbeute (% d. Th.)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
112		91	258 (Z)	0,25 (I, 9:1)	311 ($M+NH_4^+$)
113		90	231 (Z)	0,19 (I, 9:1)	325 ($M+NH_4^+$)
114[a]		quant.	-	0,21 (I, 10:1)	295 ($M+NH_4^+$)

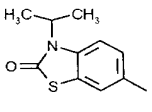
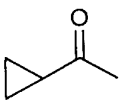
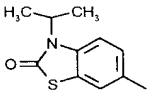
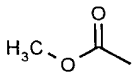
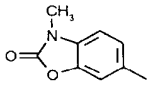
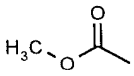
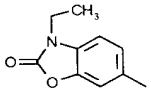
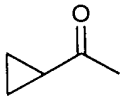
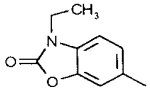
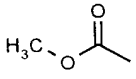
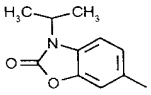
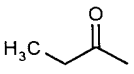
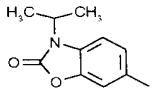
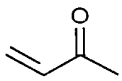
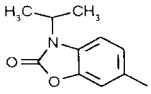
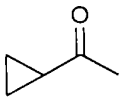
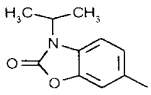
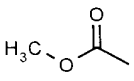
[a] isoliert als freies Amin in Analogie zur Vorschrift des Beispiels XXVII

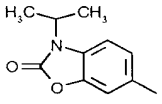
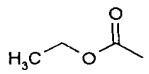
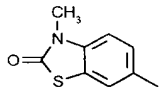
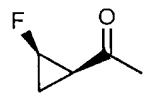
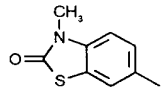
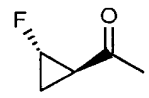
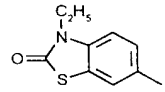
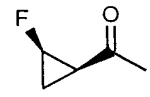
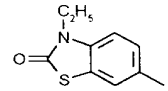
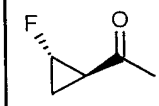
In Analogie zur Vorschrift des Beispiels 54 werden die in der Tabelle 23 aufgeführten Verbindungen dargestellt:

Tabelle 23:



Bsp.-Nr.	A	R^4	Ausbeute (%)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
115			73	175	0,26 (I, 100:5)	350 ($M+H^+$)
116			74	191	0,28 (I, 100:5)	362 ($M+H^+$)
117			55	142	0,50 (I, 100:5)	352 ($M+H^+$)
118			51	129	0,45 (I, 100:5)	383 ($M+H^+$)
119			64	132	0,20 (I, 100:5)	367 ($M+H^+$)
120			69	143	0,35 (I, 100:5)	363 (M^+)

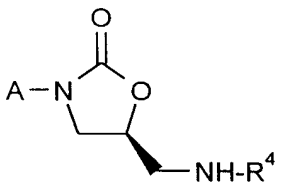
Bsp.-Nr.	A	R^4	Ausbeute (%)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
121			57	143	0,38 (I, 100:5)	375 (M^+)
122			64	151	0,39 (I, 100:5)	383 ($M+NH_4^+$)
123			53	-	0,40 (I, 10:1)	339 ($M+H^+$)
124			69	-	0,46 (I, 10:1)	346 ($M+H^+$)
125			48	-	0,43 (I, 10:1)	353 ($M+H^+$)
126			82	-	0,44 (I, 10:1)	334 ($M+H^+$)
127			90	-	0,45 (I, 10:1)	348 ($M+H^+$)
128			86	-	0,45 (I, 10:1)	360 ($M+H^+$)
129			85	-	0,49 (I, 10:1)	350 ($M+H^+$)

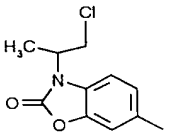
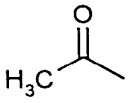
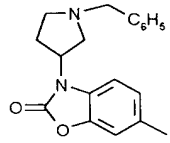
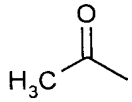
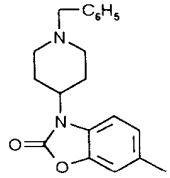
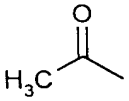
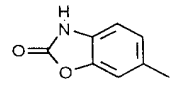
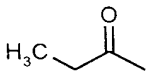
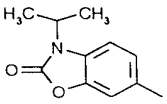
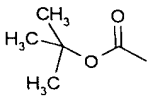
Bsp.-Nr.	A	R^4	Ausbeute (%)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
130			48	-	0,71 (I, 10:1)	443 ($M+NH_4^+$)
131[a]		 (rac)	57	-	0,26 (I, 100:5)	366 ($M+H^+$)
132[a]		 (rac)	56	-	0,31 (I, 100:5)	366 ($M+H^+$)
133[a]		 (rac)	37	209	0,37 (I, 100:5)	397 ($M+NH_4^+$)
134[a]		 (rac)	72	182	0,34 (I, 100:5)	397 ($M+NH_4^+$)

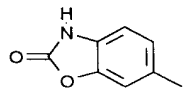
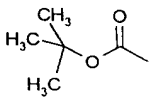
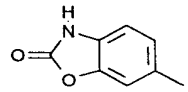
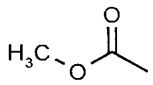
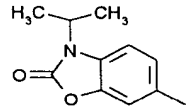
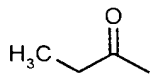
[a] dargestellt aus den entsprechenden Carbonsäuren mit 1-Hydroxybenzotriazol (HOBT), N-Ethyl-N'-(3-dimethylamino)carbodiimid (EDC)

In Analogie zur Vorschrift des Beispiels 24 werden die in der Tabelle 24 aufgeführten Verbindungen dargestellt:

Tabelle 24:

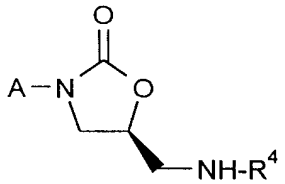


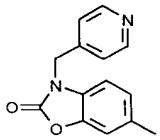
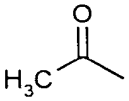
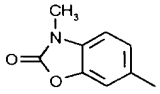
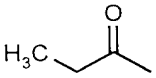
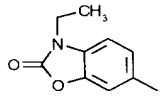
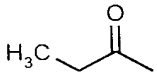
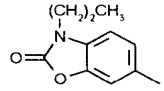
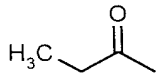
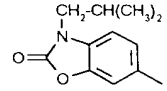
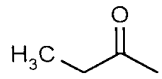
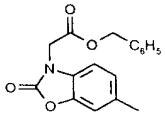
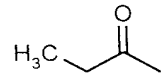
Bsp.-Nr.	A	R^4	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis)	MS m/z
135			65	0,29 (I, 10:1)	368 ($M+H^+$)
136			93	0,44 (I, 10:1)	-
137			quant.	0,13 (I, 10:1)	465 ($M+H^+$)
138			79	0,26 (I, 10:1)	323 ($M+NH_4^+$)
139			96	0,71 (I, 10:1)	409 ($M+NH_4^+$)

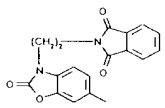
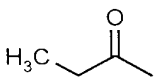
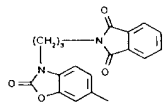
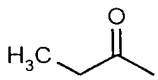
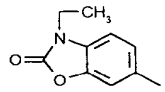
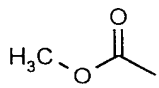
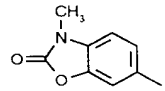
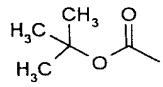
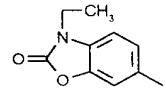
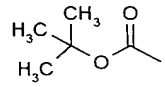
Bsp.-Nr.	A	R^4	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis	MS m/z
140			49	0,34 (I, 10:1)	367 ($M+NH_4^+$)
141			66	-	325 ($M+NH_4^+$)
142			82	0,38 (I, 10:1)	348 ($M+H^+$)

In Analogie zur Vorschrift des Beispiels 80 werden die in der Tabelle 25 aufgeführten Verbindungen dargestellt:

Tabelle 25:

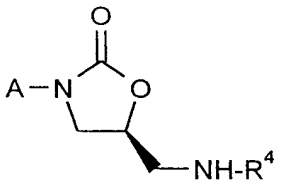


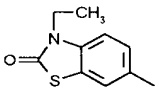
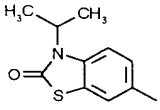
Bsp.-Nr.	A	R^4	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis)	MS m/z
143			65	0,32 (I, 10:1)	397 ($M+H^+$)
144			74	0,52 (I, 10:1)	337 ($M+H^+$)
145			64	0,37 (I, 10:1)	351 ($M+NH_4^+$)
146			85	0,32 (I, 10:1)	365 ($M+NH_4^+$)
147			36	-	379 ($M+NH_4^+$)
148			76	0,81 (I, 10:1)	454 ($M+H^+$)

Bsp.-Nr.	A	R^4	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis)	MS m/z
149			41	0,31 (I, 10:1)	496 ($M+NH_4^+$)
150			73	0,30 (I, 10:1)	493 ($M+H^+$)
151			90	0,43 (I, 10:1)	353 ($M+H^+$)
152			23	0,49 (I, 10:1)	381 ($M+H^+$)
153			63	0,48 (I, 10:1)	395 ($M+NH_4^+$)

In Analogie zur Vorschrift des Beispiels V werden die in der Tabelle 26 aufgeführten Verbindungen dargestellt:

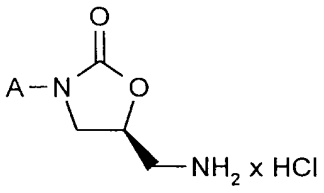
Tabelle 26:

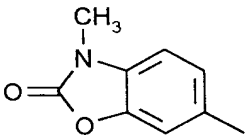
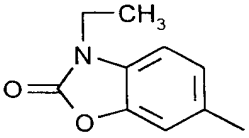
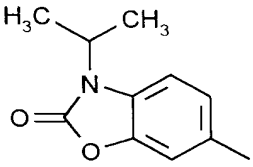


Bsp.-Nr.	A	R^4	Ausbeute (% d. Th.)	Schmp. (°C)	R_f (Laufmittel, Verhältnis)	MS m/z
154			31	166	0,61 (I, 9:1)	353 ($M+NH_4^+$)
155			63	120	0,65 (I, 9:1)	350 ($M+H^+$)

In Analogie zur Vorschrift des Beispiels 31 werden unter Verwendung von 4 N HCl in Dioxan die in Tabelle 27 aufgeführten Verbindungen dargestellt:

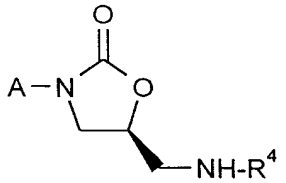
Tabelle 27:

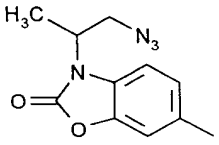
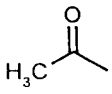


Bsp.-Nr.	A	Ausbeute (% d. Th.)	MS m/z
156		70	-
157		93	278 (M^+-Cl)
158		97	309 ($M+NH_4^+$-Cl)

In Analogie zur Vorschrift des Beispiels 9 werden die in der Tabelle 28 aufgeführten Verbindungen dargestellt:

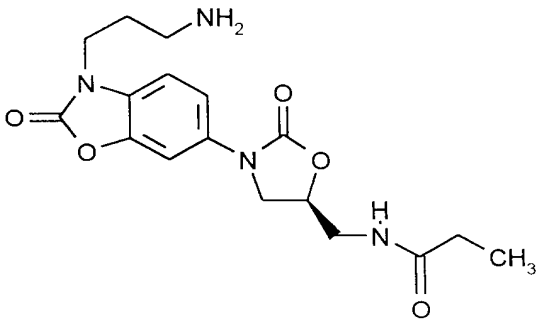
Tabelle 28:



Bsp.-Nr.	A	R^4	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis	MS m/z
159			95	0,29 (I, 10:1)	392 ($M+NH_4^+$)

Beispiel 160

(5S)-3-(3-(3-Aminopropyl)-2-benzoxazolinon-6-yl)-5-(propionylaminomethyl)-2-oxazolidinon



Eine Suspension der Verbindung aus Beispiel 150 (328 mg, 0,67 mmol) in Ethanol (20 ml) wird mit 40 % Methylamin (in H_2O, 320 µl, 4,1 mmol) versetzt und 3 Stunden bei 70°C gerührt, anschließend 1 Stunde unter Rückfluß erhitzt. Der ausgefallene Niederschlag wird abgesaugt und getrocknet.

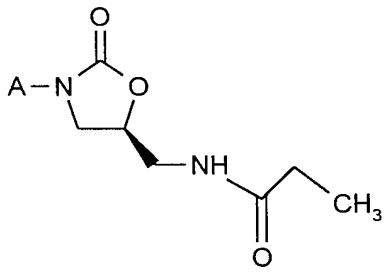
Ausbeute: 123 mg (51 %)

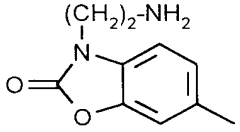
R_f (I, 10:1) = 0,21

^{1}H-NMR (200 MHz, [D_6]DMSO): δ = 8,10 (bt, 1H, NH), 7,18 (d, 1H, Ar-H), 7,08 (d, 1H, Ar-H), 6,81 (dd, 1H, Ar-H), 6,60 (bs, 2H, NH_2), 4,70 (m, 1H, 5-H), 4,10 (t, 1H, 4-H), 3,70 (dd, 1H, 4-H), 3,40 (m, 4H, CH_2N), 3,20 (m, 2H, CH_2N), 2,10 (q, 2H, $COCH_2$), 190 (m, 2H, CH_2), 0,95 (t, 3H, CH).

In Analogie zur Vorschrift des Beispiels 160 werden die in der Tabelle 29 aufgeführten Verbindungen dargestellt:

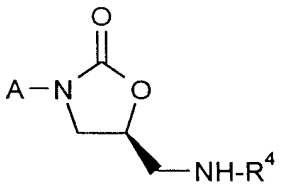
Tabelle 29:

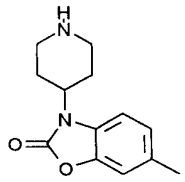
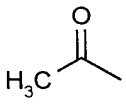
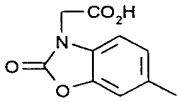
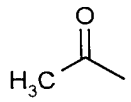
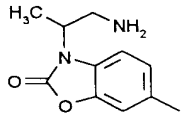
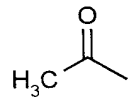


Bsp.-Nr.	A	Ausbeute (% d.Th.)	R_f (Laufmittel, Verhältnis)	MS m/z
161		17	0,30 (I, 10:1)	347 ($M+H^+$)

In Analogie zur Vorschrift des Beispiels XXXVII werden die in der Tabelle 30 aufgeführten Verbindungen dargestellt:

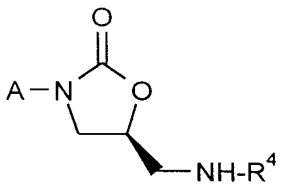
Tabelle 30:

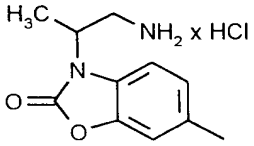
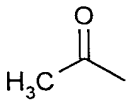
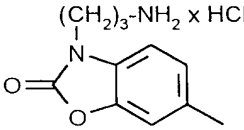
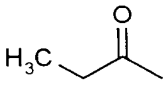
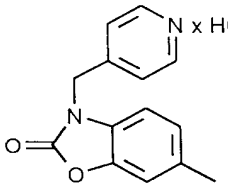
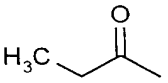


Bsp.-Nr.	A	R^4	Ausbeute (% d. Th.)	R_f (Laufmittel, Verhältnis)	MS m/z
162			13	0,01 (I, 10:1)	375 ($M+H^+$)
163			32	0,01 (I, 10:1)	364 ($M+H^+$)
			quant.	0,11 (I, 100:1)	-

In Analogie zur Vorschrift des Beispiels 31 werden die in der Tabelle 31 aufgeführten Verbindungen dargestellt:

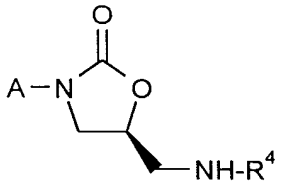
Tabelle 31:

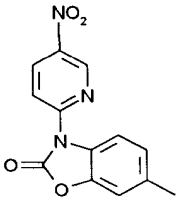
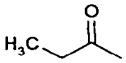


Bsp.-Nr.	A	R^4	Ausbeute (% d. Th.)	MS m/z
165			25	-
166			60	363 ($M+H^+$)
167			31	-

In Analogie zur Vorschrift des Beispiels 33 werden die in der Tabelle 32 aufgeführten Verbindungen dargestellt:

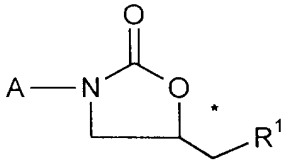
Tabelle 32:



Bsp.-Nr.	A	R^4	Ausbeute (% d. Th.)	R_f (Laufmittel, Verhältnis)	MS m/z
168			43	0,55 (I, 10:1)	445 ($M+NH_4^+$)

Patentansprüche

1. Verbindungen 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-R^6, P(O)(OR^7)(OR^8) oder -SO_2-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

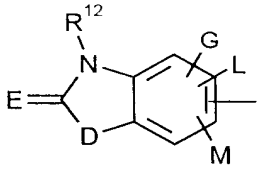
R^{10} und R^{11} gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
oder

R^6 einen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeutet, der gegebenenfalls durchgeradkettiges 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



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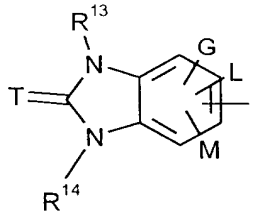

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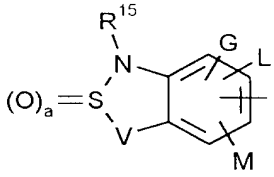
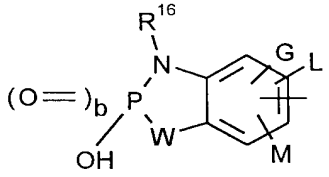


oder

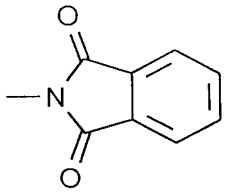


steht,
worin

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-$NR^{17}R^{18}$ 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, die 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 $-(CO)_c-NR^{19}R^{20}$, $R^{21}-N-SO_2-R^{22}$, $R^{23}R^{24}-N-SO_2-$, $R^{25}-S(O)_d-$ oder



substituiert sind,
worin

c eine Zahl 0 oder 1 bedeutet,

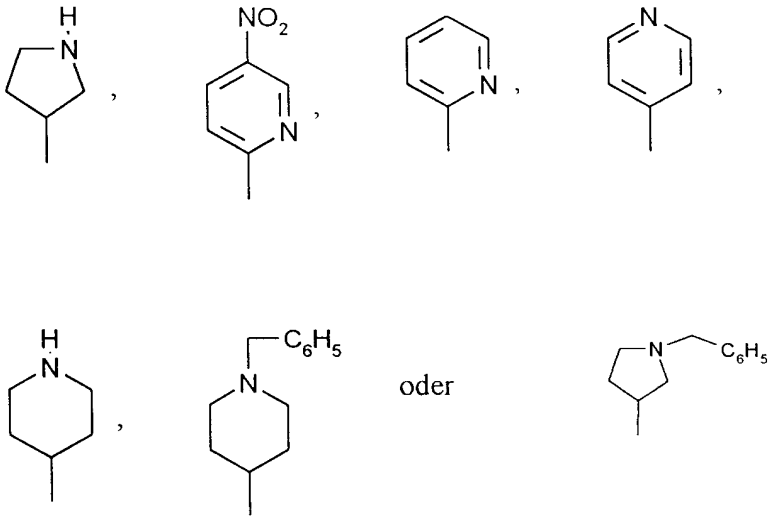
R^{19}, R^{20} und R^{21} die oben angegebene Bedeutung von R^{17} und R^{18} haben und mit dieser gleich oder verschieden sind,
oder gemeinsam mit dem Stickstoffatom einen 5- bis 6-gliedrigen, gesättigten Heterocyclus mit gegebenenfalls einem weiteren Heteroatom aus der Serie N, S und/oder O bilden, 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,
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} 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 angegebenen 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 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 tautomeren Formen, Isomere und Salze.

2. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß

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 6 Kohlenstoffatomen oder Benzyl bedeutet,
R^3	geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, 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 6 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_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

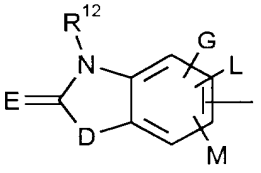
R^{10} und R^{11} gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, oder

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



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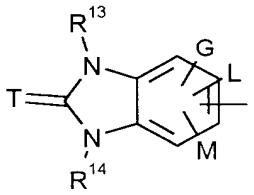

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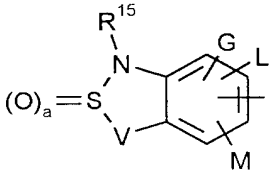

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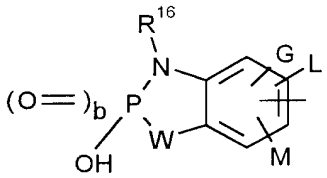
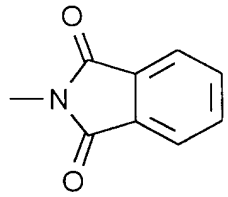


steht,
worin

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, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 5 Kohlenstoffatomen, Phenyl, Naphthyl, 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,

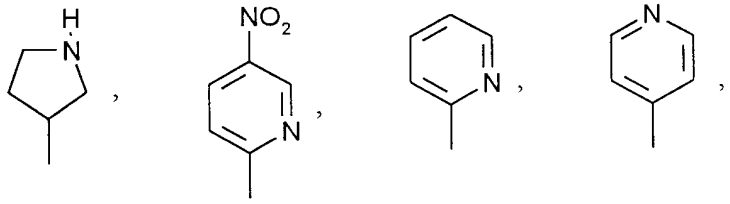
R^{19}, R^{20} und R^{21} — die oben angegebene Bedeutung von R^{17} und R^{18} haben und mit dieser gleich oder verschieden sind,
oder gemeinsam mit dem Stickstoffatom einen Morpholinyl-, Pyrrolidinyl-, Piperazinyl-oder Piperidylring bilden, die gegebenenfalls, auch über die freie N-Funktion, durch Methyl, Ethyl oder Acetyl substituiert sind,

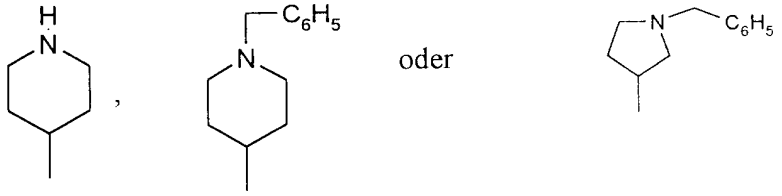
R^{23} und R^{24} — die oben angegebene Bedeutung von R^{17} und R^{18} haben und mit dieser gleich oder verschieden sind,

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





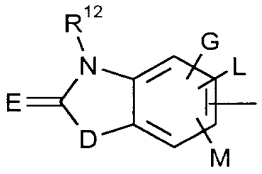
bedeutet oder
eine Gruppe der Formel $-COCCl_3$ oder geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Trifluormethyl, Trichlormethyl oder eine Gruppe der Formel $-OR^{26}$ substituiert ist,
worin

R^{26}	Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Phenyl oder Naphthyl substituiertist, 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, Isomere und Salze.

3. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß

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 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 $-CO\text{-}R^6$, $P(O)(OR^7)(OR^8)$ oder $-SO_2R^9$ bedeutet, worin
R^6	Cyclopropyl, Fluor-substituiertes Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluorethyl oder geradkertiges 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



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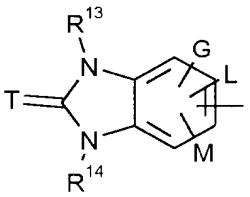

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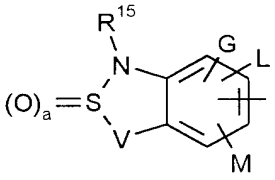

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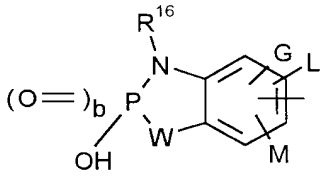
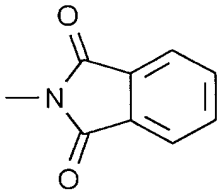


steht,
worin

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, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 4 Kohlenstoffatomen, Phenyl, 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 ist,
worin

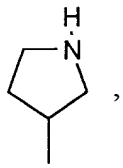
c eine Zahl 0 oder 1 bedeutet,

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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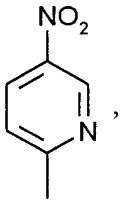
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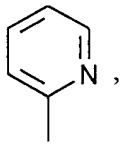
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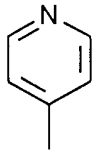
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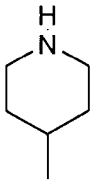
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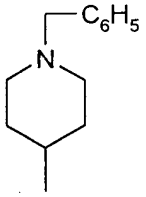
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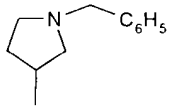


bedeutet oder
eine Gruppe der Formel $-COCCl_3$ oder geradkettiges oder verzweigtes Acyl mit bis zu 4 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Trifluormethyl, Trichlormethyl, eine Gruppe der Formel $-OR^{26}$ substituiert ist,
worin

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, Isomere und Salze.

4. Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß
G, L und M für Wasserstoff stehen,
und der Oxazolidinonrest in den Positionen 5 oder 6 an den Phenylring angebunden ist.

5. Verfahren zur Herstellung von Verbindungen der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß man

[A] Verbindungen der allgemeinen Formeln (II) oder (III)

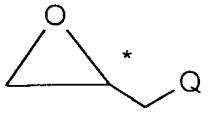
$$A\text{-}N{=}C{=}O \qquad (II)$$

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)

$$A\text{-}NH\text{-}CO_2\text{-}Y \qquad (Va)$$

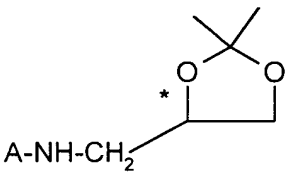
in welcher

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

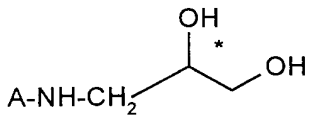
[D] Verbindungen der allgemeinen Formel (VI)



(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)



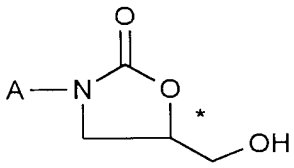
(VII)

in welcher

A die oben angegebene Bedeutung hat,
herstellt,
und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert,

oder

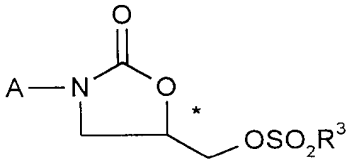
[E] zunächst Verbindungen der allgemeinen Formel (Ia)



(Ia)

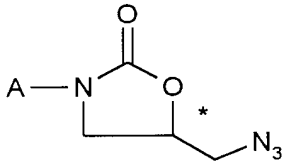
in welcher

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)

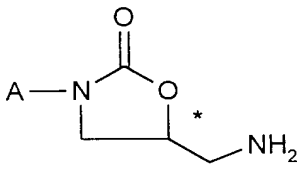
in welcher
A und R^3 die oben angegebene Bedeutung haben, überführt,
anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (Ic)



(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

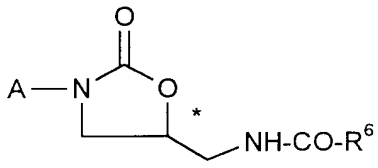
A die oben angegebene Bedeutung hat,
überführt,
und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (VIII)

$$R^{36}\text{-}CO\text{-}R^{6} \qquad \text{(VIII)}$$

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)

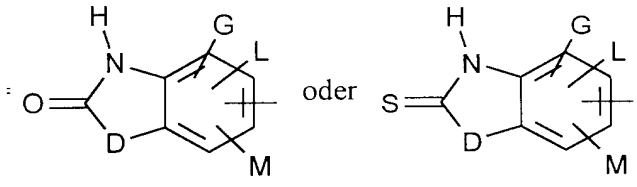


(Ie)

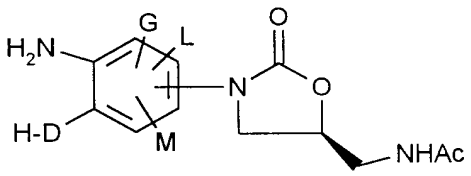
in welcher
A und R^6 die oben angegebene Bedeutung haben,
herstellt,

oder

[F] im Fall A =

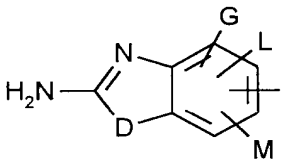


Verbindungen der allgemeinen Formel (IX)



(IX)

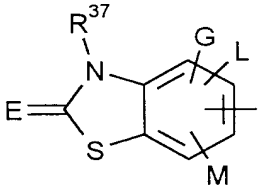
in welcher
G, L, M und D die oben angegebene Bedeutung haben, entweder mit Carbonyldiimidazol bzw. Thiocarbonyldiimidazol in Dimethylformamid oder durch Umsetzung mit $KS\text{-}CO_2\text{-}C_2H_5$ / CH_3OH und anschließender Zugabe von Wasser cyclisiert,
im Fall A =



die Verbindungen der allgemeinen Formel (IX) mit BrCN / H_2O / CH_3OH umsetzt,
oder

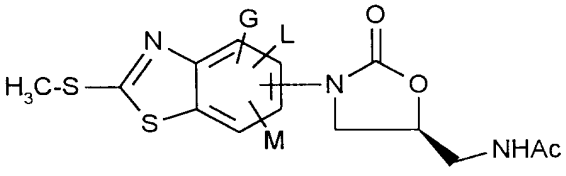
[G] im Fall $R^{12} \neq H$, ausgehend von den Verbindungen mit R^1 = $NH\text{-}COCH_3$ eine Acylierung oder eine Alkylierung unter Doppelbindungsverschiebung durchführt, oder

Verbindungen der allgemeinen Formel (I) mit dem Rest



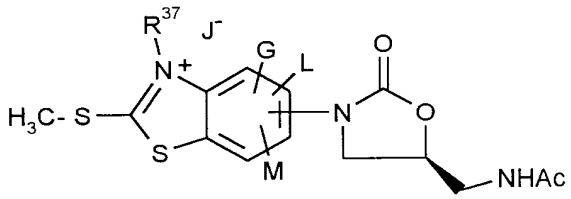
worin

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.

6. Verwendung der Verbindungen nach den Ansprüchen 1 bis 4 zur Herstellung von Arzneimitteln.

7. Arzneimittel, enthaltend Verbindungen gemäß den Ansprüchen 1 bis 4.

Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung
EP 96 10 5539

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int.Cl.6)
D,X	EP-A-0 609 441 (EISAI CO LTD) 10.August 1994 Siehe u.a. Seite 6, Formel B ---	1-7	C07D417/04 A61K31/425 C07D413/04 C07D263/58
D,Y	EP-A-0 609 905 (UPJOHN CO) 10.August 1994 Siehe Ansprüche ---	1-7	C07D419/04 C07F9/6584 C07F9/6558
D,Y	EP-A-0 311 090 (DU PONT) 12.April 1989 Siehe Ansprüche ---	1-7	C07D417/14 C07D413/06
Y,D	J. MED. CHEM., Bd. 35, 1992, Seiten 1156-1165, XP002009380 PARK ET AL.: "Antibacterials. Synthesis and ..." * das ganze Dokument * -----	1-7	

RECHERCHIERTE SACHGEBIETE (Int.Cl.6)

C07D
A61K

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

Recherchenort	Abschlußdatum der Recherche	Prüfer
MÜNCHEN	25.Juli 1996	Steendijk, 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
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EPO FORM 1503 03.82 (P04C03)

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) **Internationale Patentklassifikation** 6 :
C07D 413/14, A61K 31/42, 31/445, 31/44, 31/505

A1

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(43) **Internationales Veröffentlichungsdatum:** 30. Januar 1997 (30.01.97)

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(22) **Internationales Anmeldedatum:** 4. Juli 1996 (04.07.96)

(30) **Prioritätsdaten:**
195 24 765.5 7. Juli 1995 (07.07.95) DE

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(72) **Erfinder; und**
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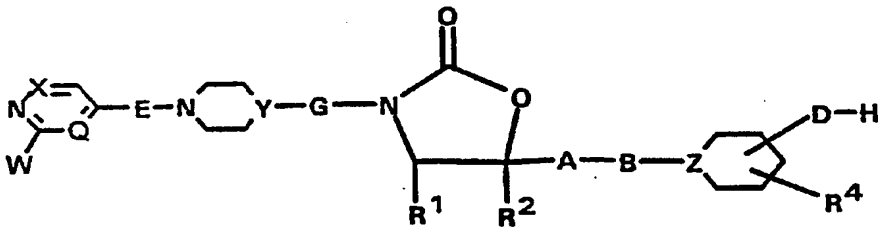
(74) **Gemeinsamer Vertreter:** BOEHRINGER MANNHEIM GMBH; Patentabteilung, D-68298 Mannheim (DE).

(81) **Bestimmungsstaaten:** AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO Patent (KE, LS, MW, SD, SZ, UG), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, 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).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) **Title:** NEW OXAZOLIDINONE DERIVATIVES, PROCESS FOR PREPARING THE SAME AND MEDICAMENTS THAT CONTAIN THESE COMPOUNDS

(54) **Bezeichnung:** NEUE OXAZOLIDINONDERIVATE, VERFAHREN ZU DEREN HERSTELLUNG UND DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL



(I)

(57) **Abstract**

New oxazolidinone derivatives are disclosed, as well as a process for preparing the same and medicaments that contain these substances. The disclosed compounds have general formula (I), in which X, Y and Q independently represent nitrogen or CH; W stands for hydrogen or NR^0R^{00}; Z stands for nitrogen, CH or C-OH; A, E and G independently represent the valence dash or an alkylene chain $-(CH_2)_n-$; B stands for a valence dash and, when Z equals N, it may also stand for a carbonyl group; D stands for a side chain having the form $-(CHR^3)_m-COO-$ or $=CR^3-COO-$; n equals 1 to 5; m equals 0.1; R^1, R^2 independently represent hydrogen, lower alkyl or aryl, or form together a carbocyclic five- or six-membered ring; R^3 stands for hydrogen or a group $-OR^5$ or $-NR^6R^7$; R^4 stands for hydrogen or a group $-OR^5$; R^5 stands for hydrogen, lower alkyl, aryl or arylalkyl; R^6 stands for hydrogen, lower alkyl or arylalkyl; R^7 stands for hydrogen, lower alkyl, arylalkyl, acyl, alkylsulphonyl or arylsulphonyl.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft neue Oxazolidinonderivate, Verfahren zu deren Herstellung sowie Arzneimittel, die diese Substanzen enthalten. Gegenstand der vorliegenden Erfindung sind Verbindungen der allgemeinen Formel (I), in der X, Y und Q unabhängig voneinander Stickstoff oder CH bedeuten; W Wasserstoff oder NR^0R^{00} bedeutet; Z Stickstoff, CH oder C-OH bedeutet; A, E und G unabhängig voneinander den Valenzstrich oder eine Alkylenkette $-(CH_2)_n-$ bedeuten; B Valenzstrich und für den Fall, daß Z gleich N ist, auch die Carbonylgruppe bedeutet; D eine Seitenkette der Form $-(CHR^3)_m-COO-$ oder $=CR^3-COO-$ bedeutet; n = 1-5 bedeutet; m = 0,1 bedeutet; R^1, R^2 unabhängig voneinander Wasserstoff, niederes Alkyl oder Aryl bedeuten, oder zusammen einen carbocyclischen fünf- oder sechsgliedrigen Ring bilden; R^3 Wasserstoff oder eine Gruppe $-OR^5$ oder $-NR^6R^7$ bedeutet; R^4 Wasserstoff oder eine Gruppe $-OR^5$ bedeutet; R^5 Wasserstoff, niederes Alkyl, Aryl oder Arylalkyl bedeutet; R^6 Wasserstoff, niederes Alkyl oder Arylalkyl bedeutet; R^7 Wasserstoff, niederes Alkyl, Arylalkyl, Acyl, Alkylsulfonyl oder Arylsulfonyl bedeutet.

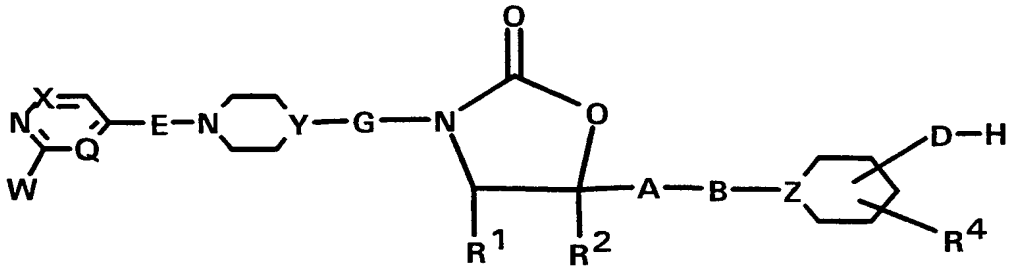
Neue Oxazolidinonderivate, Verfahren zu deren Herstellung und diese Verbindungen enthaltende Arzneimittel

Es ist bekannt, daß Verbindungen, die eine basische und eine Säuregruppe tragen, in der Lage sind, die Blutplättchen-Aggregation zu hemmen, wenn die basische und Säuregruppe in den Verbindungen einen ganz bestimmten Abstand einnehmen (Drugs of the Future 19(2):135-159 (1994). In den Patentschriften WO 93/14077, EP-A-0 537-980, EP-A-0 542 363, WO 94/22834, WO 94/22835 und EP 0623615A1 sind Verbindungen mit antiaggregatorischer Wirkung an den Blutplättchen beschrieben.

Die vorliegende Erfindung betrifft neue Oxazolidinonderivate, Verfahren zu deren Herstellung sowie Arzneimittel, die diese Substanzen enthalten.

Es wurde nun gefunden, daß Oxazolidinonderivate effektiv die Aggregation der Blutblättchen hemmen und damit zur Behandlung von Krankheiten eingesetzt werden können, die auf thromboembolische Ereignisse zurückzuführen sind, wie Schlaganfall, Myocardinfarkt oder arterielle Verschlußkrankheiten, sowie Entzündungen, Osteoporose oder Tumorerkrankungen.

Gegenstand der vorliegenden Erfindung sind Verbindungen der allgemeinen Formel I,



(I)

in der

X, Y und Q unabhängig voneinander Stickstoff oder CH bedeuten,

W Wasserstoff oder NR^0R^{00} bedeutet

Z Stickstoff, CH oder C-OH bedeutet,

A, E und G unabhängig von einander den Valenzstrich oder eine Alkylenkette $-(CH_2)_n-$ bedeuten,

B Valenzstrich und für den Fall, daß Z gleich N ist, auch die Carbonylgruppe bedeutet,

D eine Seitenkette der Form $-(CHR^3)_m-COO-$ oder $=CR^3-COO-$ bedeutet,

n = 1-5 bedeutet,

m = 0,1 bedeutet,

R^1, R^2 unabhängig voneinander Wasserstoff, niederes Alkyl oder Aryl bedeuten, oder zusammen einen carbocyclischen fünf- oder sechsgliedrigen Ring bilden,

R^3 Wasserstoff oder eine Gruppe $-OR^5$ oder $-NR^6R^7$ bedeutet,

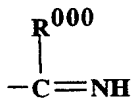
R^4 Wasserstoff oder eine Gruppe $-OR^5$ bedeutet,

R^5 Wasserstoff, niederes Alkyl, Aryl oder Arylalkyl bedeutet,

R^6 Wasserstoff, niederes Alkyl oder Arylalkyl bedeutet,

R^7 Wasserstoff, niederes Alkyl, Arylalkyl, Acyl, Alkylsulfonyl oder Arylsulfonyl bedeutet,

R^0, R^{00} unabhängig voneinander Wasserstoff, niederes Alkyl, Aryl, Arylalkyl, Hetaryl, Acyl oder einen gegebenenfalls substituierten carbocyclischen oder heterocyclischen Ring bedeuten, oder zusammen mit dem Stickstoff an dem sie gebunden sind, einen gegebenenfalls substituierten fünf- oder sechsgliedrigen Ring bilden, der noch 1 bis 3 weitere Heteroatome enthalten kann, oder eine Gruppe



bedeuten,

R^{000} Wasserstoff, niederes Alkyl, Arylalkyl oder eine Gruppe NHR^{0000} bedeutet,

R^{0000} Wasserstoff, niederes Alkyl, Arylalkyl, Acyl, Alkylsulfonyl oder Arylsulfonyl bedeutet,

sowie deren pharmakologisch unbedenklichen Salze.

Niederes Alkyl soll in allen Fällen eine geradkettige oder verzweigte C_1-C_6-Alkylgruppe wie z.B. Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl oder Hexyl, insbesondere Methyl, Ethyl, Propyl, Isobutyl und Pentyl darstellen.

Aryl bedeutet in der Regel den gegebenenfalls ein- oder mehrfach substituierten Phenylrest.

Arylalkyl bedeutet in der Regel einen unsubstituierten oder ein- oder mehrfach substituierten Benzyl-, Phenethyl-, Phenylpropyl-, Phenylbutyl- oder Phenylpentylrest, vorzugsweise einen Benzyl-, Phenethyl- oder Phenylpentylrest. Als Substituenten kommen C_1-C_6-Alkylreste, vorzugsweise Methyl-, Ethyl- oder Isopropyl, sowie Chlor, Brom, Fluor, oder Hydroxy-, Methoxy-, Benzyloxy-, Acetyloxy-, Carboxy-, Ethoxycarbonyl-, Aminocarbonyl-, Methylaminocarbonyl-, Dimethylaminocarbonyl-, Cyano-, Amino-, Methylamino-, Dimethylamino-, Benzylamino-, Acetylamino-, Benzoylamino- und Amidinogruppen infrage.

Acyl bedeutet in der Regel den Formyl-, Acetyl-, Propionyl-, Butyryl- oder Benzoylrest, insbesondere den Acetyl oder Benzoylrest.

Alkylsulfonyl bedeutet in der Regel den Methansulfonyl, Ethansulfonyl-, Propansulfonyl oder den Butansulfonylrest, insbesondere der Butansulfonylrest.

Arylsulfonyl bedeutet in der Regel den Benzol- oder Toluolsulfonsäurerest.

Falls die Reste R^1 und R^2 zusammen einen carboclyclischen fünf- oder sechsgliedrigen Ring bilden, handelt es sich um einen gesättigten oder ungesättigten, gegebenenfalls durch niederes Alkyl einfach oder zweifach substituierten 5-6-gliedrigen Ring, wie den Cyclopentyl-, Cyclohexyl-, Cyclopentenyl- oder Cyclohexenylring.

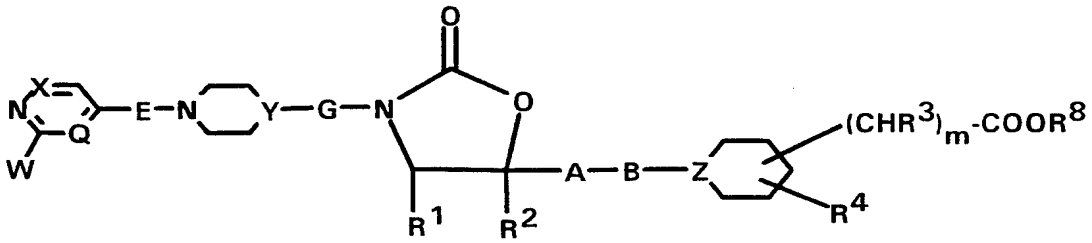
Verbindungen der allgemeinen Formel I enthalten mindestens ein asymmetrisches Kohlenstoffatom, daher sind auch optisch aktive Verbindungen der allgemeinen Formel I

Gegenstand der vorliegenden Anmeldung. Gegenstand der vorliegenden Anmeldung sind weiterhin Konformationsisomere von Verbindungen der allgemeinen Formel I, die gegebenenfalls auftreten können.

Bevorzugte Verbindungen sind Verbindungen der Formel I, in der die Gruppe A-B eine Gruppe $(CH_2)_{1-3}$ oder $(CH_2)_{1-3}$-CO darstellt und E, G, Q, W, X, Y, Z, D, R^1, R^2 und R^4 die angegebene Bedeutung haben.

Insbesondere sind Verbindungen der Formel I bevorzugt, in der A-B die Gruppe Methylen, Ethylen, Carbonyl oder Methylencarbonyl und E, G, Q, W, X, Y und Z Stickstoff bedeuten.

Verbindungen der allgemeinen Formel I werden nach an sich bekannten Verfahren durch Hydrolyse eines Esters der allgemeinen Formel II,

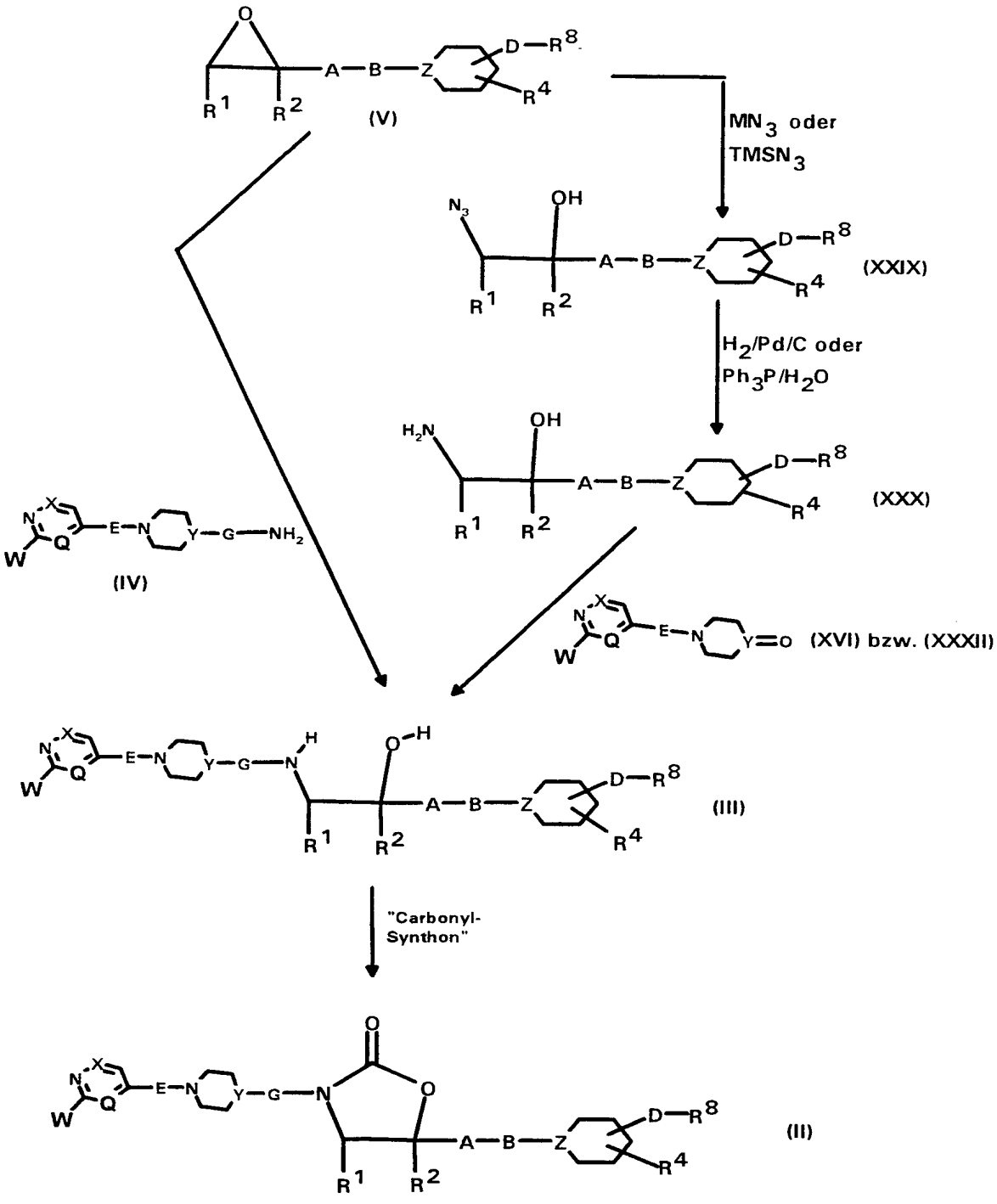


(II)

in der R^1, R^2, R^3, R^4, A, B, E, G, Q, W, X, Y, Z und m die oben angegebenen Bedeutungen besitzen und R^8 Methyl, Ethyl tert.-Butyl, Phenyl oder Benzyl bedeutet, hergestellt.

Verbindungen der allgemeinen Formel II werden nach dem im Schema 1 skizzierten Reaktionsweg hergestellt.

SCHEMA 1

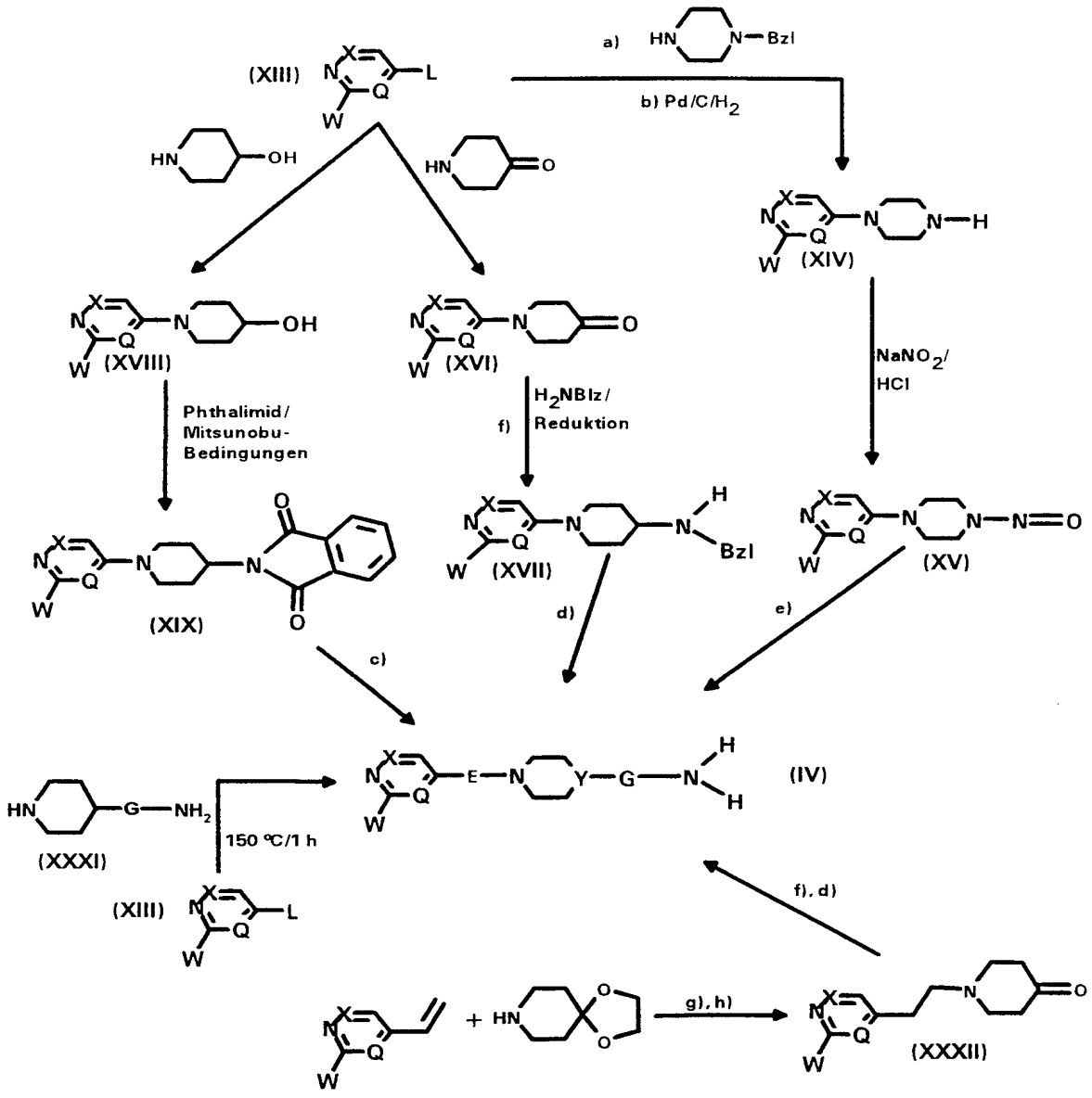

(V)
MN_3 oder
$TMSN_3$
(XXIX)
H_2/Pd/C oder
Ph_3P/H_2O
(XXX)
(IV)
(XVI) bzw. (XXXII)
(III)
"Carbonyl-
Synthon"
(II)

Schema 1

Im Schema 1 besitzen R^1, R^2, R^4, R^8, A, B, D, E, G, Q, W, X, Y und Z die obengenannten Bedeutungen. „Carbonyl-Synthon" bedeutet in der Regel Phosgen, Diphosgen, Triphosgen, Carbonyldiimidazol, Kohlensäuredimethyldiethyl oder -diphenylester, Chlorameisensäuremethyl- oder -ethylester, insbesondere Carbonyldimidazol, Kohlensäurediethylester oder Chlorameisensäureethylester. MN_3 Bedeutet ein Metallazid wie Lithium-, Natrium-, Kalium- Tributylzinn- oder Magnesiumazid, insbesondere Lithium- oder Natrium-azid. $TMSN_3$ ist die Abkürzung für Trimethylsilylazid.

Verbindungen der allgemeinen Formel IV können nach den im Schema 2 wiedergegebenen Reaktionswegen hergestellt werden.

SCHEMA 2



c) Hydrolyse des Phthalimids; d) Hydrierung der Benzylgruppen; e) Reduktion der Nitroso-Gruppe;

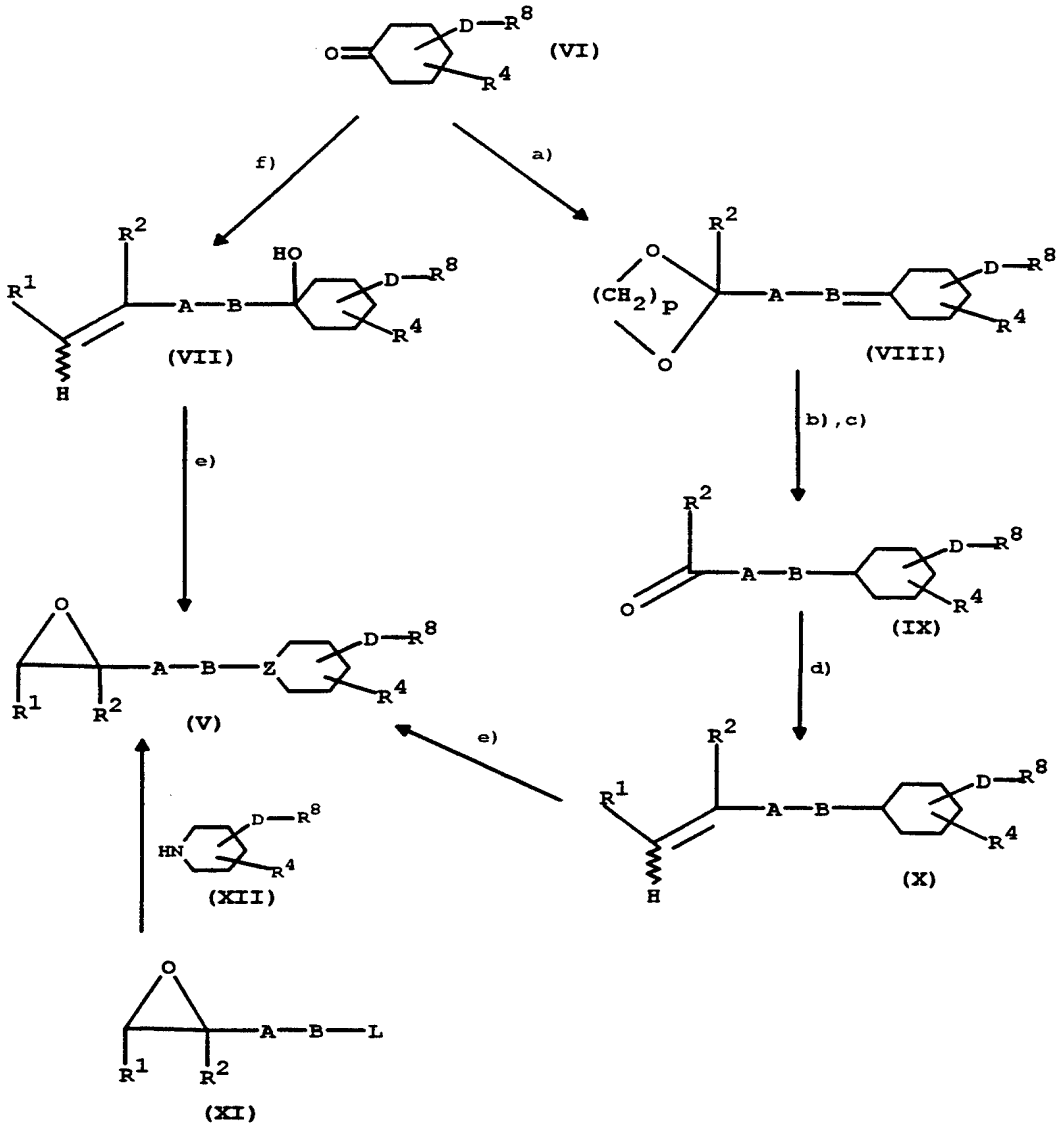
g) AcOH/100 °C/3 h; h) HCl/THF/H_2O

Schema 2

Im Schema 2 besitzten E, G, Q, X und W die oben angegebenen Bedeutungen; L bedeutet in der Regel eine Abgangsgruppe wie Chlor, Brom, Iod, Mesylat, Triflat oder Tosylat, insbesondere Chlor oder Tosylat.

Verbindungen der allgemeinen Formel V sind über Reaktionswege zugänglich, die im Schema 3 wiedergegeben sind.

SCHEMA 3

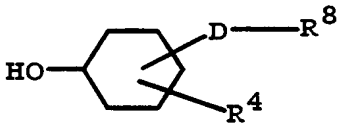


a) Wittig-Reaktion; b) Pd/C/H_2; c) Ketalspaltung; d) Wittig-Reaktion; e) Epoxydierung; f) Metallorganische Reaktion

Schema 3

Im Schema 3 besitzen R^1, R^2, R^3, R^4, A, B und L die oben angegebenen Bedeutungen und für den Fall, daß B die Carbonylgruppe bedeutet, kann L auch die Hydroxylgruppe bedeuten; p bedeutet die Zahl 1 oder 2.

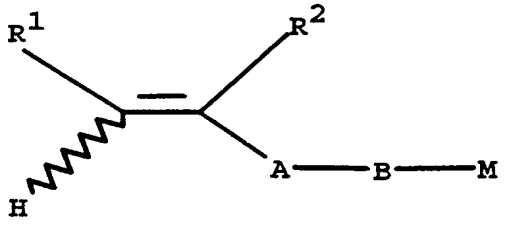
Verbindungen der allgemeinen Formel VI sind zum Teil käuflich erwerblich und lassen sich in speziellen Fällen durch Oxidation eines Alkohols der allgemeinen Formel XX,



(XX)

in der D, R^4 und R^8 die oben angegebenen Bedeutungen besitzen, erhalten.

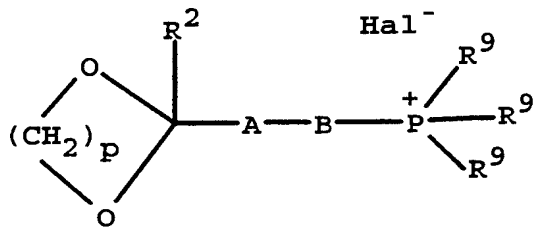
Verbindungen der allgemeinen Formel VII lassen sich dadurch herstellen, daß man eine Verbindung der allgemeinen Formel VI mit einer metallorganischen Verbindung der allgemeinen Formel XXI



(XXI)

in der R^1, R^2, A und B die oben angegebenen Bedeutungen besitzen und M die Bedeutung eines Metalls wie Lithium, Magnesium oder Titan besitzt, zur Reaktion bringt.

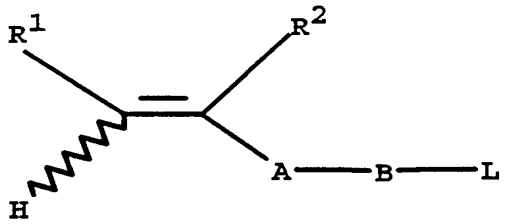
Verbindungen der allgemeinen Formel VIII werden nach bekannten Verfahren dadurch hergestellt, daß man eine Verbindung der Formel VI mit einem Phosphorylid der allgemeinen Formel XXII.



(XXII)

In der R^2, A, B und p die oben genannten Bedeutungen besitzen, R^9 Butyl, Phenyl oder p-Tolyl und Hal $^-$ Chlorid, Bromid oder Iodid bedeutet.

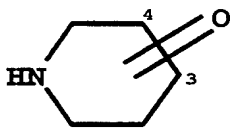
Verbindungen der allgemeinen Formel XI sind käuflich erwerblich und lassen sich in Spezialfällen durch Epoxydierung eines Olefins der allgemeinen Formel XXIII,



(XXIII)

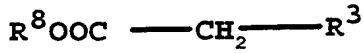
in der R^1, R^2, A, B und L die oben angegebenen Bedeutungen besitzen, herstellen.

Bei den Verbindungen der allgemeinen Formel XII handelt es sich in der Regel um käuflich erwerbliche Pipecolincarbonsäure-Derivate; in Spezialfällen lassen sich Verbindungen der Formel XII durch Umsetzung eines käuflich erwerblichen 3- oder 4-Piperidons der Formel XXIV,



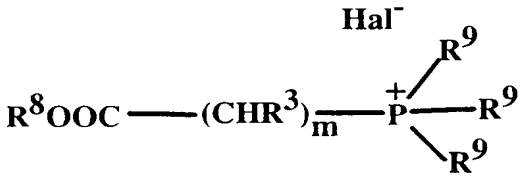
(XXIV)

mit einem käuflich erwerblichen Essigsäureester der allgemeinen Formel XXV,



(XXV)

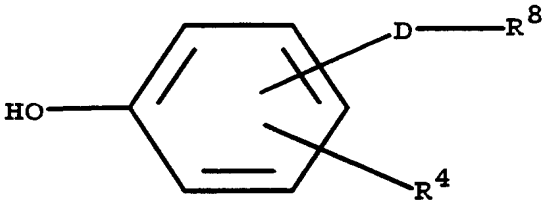
in der R^3 und R^8 die oben angegebenen Bedeutungen besitzen, oder mit einem Wittigreagenz der allgemeinen Formel XXVI,



(XXVI)

in der R^3, R^8, R^9, m und Hal^- die oben angegebenen Bedeutungen, herstellen.

Verbindungen der allgemeinen Formel XX sind zum Teil käuflich erwerblich und lassen sich in Spezialfällen nach bekannten Verfahren durch Kernhydrierung einer Arylcarbonsäure der allgemeinen Formel XXVII,

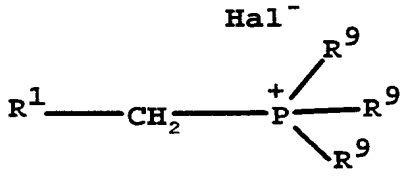


(XXVII)

in der R^4, R^8 und D die oben angegebenen Bedeutungen besitzen, erhalten.

Verbindungen der allgemeinen Formel XXI sind entweder käuflich erwerblich oder sie lassen sich in situ nach den allgemeinen Verfahren zur Herstellung metallorganischer Verbindungen synthetisieren.

Verbindungen der allgemeinen Formel X lassen sich nach bekannten Verfahren durch Umsetzung einer Verbindung IX mit einem Wittigreagenz der allgemeinen Formel XXVIII,



(XXVIII)

in der R^1, R^9 und Hal^- die oben angegebenen Bedeutungen besitzen, erhalten.

Wittigreagenzien der Formel XXII oder der Formel XXVI oder der Formel XXVIII sind teilweise käuflich erwerblich und lassen sich aus den entsprechenden käuflichen Halogenverbindungen und Triphosphinen herstellen.

Die Hydrolyse eines Ester der allgemeinen Formel II zu der entsprechenden Carbonsäure der allgemeinen Formel I führt man nach üblichen Verfahren durch, in dem man einen Carbonsäureester der allgemeinen Formel II in Wasser oder in einem Gemisch aus Wasser, Tetrahydrofuran, Dioxan, Methanol oder Ethanol vorzugsweise in einem Wasser/Tetrahydrofurangemisch mit einem Hydroxid wie Natrium-, Kalium-, oder Lithiumhydroxid, vorzugsweise Natrium- oder Lithiumhydroxid, oder mit einer Säure wie Salzsäure, Schwefelsäure oder Trifluoressigsäure, vorzugsweise Trifluoressigsäure und bei Temperaturen zwischen Raumtemperatur und 80°C, vorzugsweise bei Raumtemperatur, behandelt.

Die Umsetzung einer Verbindung der allgemeinen Formel XIII mit 1-Benzylpiperazin oder 4-Hydroxy- bzw. 4-Oxopiperidin (Schema 2) oder die Umsetzung einer Verbindung der Formel XI mit einer Verbindung der Formel XII oder einer Verbindung der Formel XI mit einem Amin der Formel XII erfolgt in der Regel in einem aprotischen Lösungsmittel wie Toluol, Tetrahydrofuran, Diethylether, Dimethylformamid oder Methylenchlorid, vorzugsweise Dimethylformamid oder Tetrahydrofuran unter Verwendung einer Base wie Kaliumhydrid, Natriumhydrid, Kaliumcarbonat oder Natriumhydrogencarbonat, vorzugsweise Natriumhydrid oder Kaliumcarbonat und bei Temperaturen zwischen Raumtemperaturen und 180°C, vorzugsweise bei 120°C oder Raumtemperatur.

Die Reaktion zwischen 3- oder 4-Piperidon der Formel XXIV und einem Ester der Formel XXV findet unter den Bedingungen der Aldolreaktion, in einem Lösungsmittel wie Methanol, Ethanol, Toluol, Tetrahydrofuran, Diethylether oder Dimethylformamid, vorzugsweise Tetrahydrofuran oder Dimethylformamid, unter Verwendung einer Base wie Natrium- oder Kaliummethylat oder -ethylat, Natriumhydrid, Kaliumhydrid, Lithiumdiisopropylamid, Kaliumhexamethyldisilazid, vorzugsweise Natriumhydrid oder Lithiumdiisopropylamid und bei Temperaturen zwischen -78°C und 90°C bevorzugt jedoch bei -78°C und Raumtemperatur statt.

Die Entfernung von Benzylschutzgruppen erfolgt bei Bedarf durch katalytische Hydrierung wie z.B. durch Palladium/Kohle/Wasserstoff.

Die Mitsunobureaktion zwischen einer Verbindung der Formel XVIII und Phthalimid wird nach Literaturverfahren durchgeführt (Mitsunobu O., Synthesis, Seite 1 (1981)).

Die reduktive Aminierung eines Ketons der Formel XVI mit Dibenzylamin oder einem Amin der Formel XXX erfolgt nach literaturbekannten Verfahren durch Umsetzung der Keton- und Aminkomponente in einem Lösungsmittel wie Methanol oder Ethanol in Gegenwart eines Reduktionsmittels wie Natriumcyanoborhydrid oder Natriumtriacetatoborhydrid unter Zugabe einer Brönsted.- oder Lewissäure wie Salzsäure, Essigsäure, Titantetrachlorid oder Titantetraisopropylat und bei einer Temperatur zwischen 0° und 100°C vorzugsweise bei Raumtemperatur, oder in Gegenwart eines Hydrierkatalysators wie Platindioxid und einer Wasserstoffatomosphäre (Borch R. F., Org. Synth. Coll. Vol. 6, 499(1988); Heinzelman R. V. Z. Chem. 8, 270 (1968); Mattson R. J., J. Org. Chem. 55, 2552 (1990); Barney C. L. Tetr. Letters 31, 5547 (1990); Hutchins R. O., J. Org. Chem. 46, 3571 (1981)).

Die Nitrosierung einer Verbindung der allgemeinen Formel XIV zu einer Verbindung der Formel XV führt man in der Regel mit Natriumnitrit oder Isoamylnitrit in Wasser oder Ethanol unter Zusatz einer Säure wie Salzsäure oder Essigsäure und bei einer Temperatur zwischen -20°C und 80°C, vorzugsweise bei Raumtemperatur, durch.

Die Reduktion einer Nitrosoverbindung der allgemeinen Formel XV erfolgt nach bekannten Verfahren dadurch, daß man eine Verbindung der Formel XV in einem Lösungsmittel wie Wasser, Essigsäure, Ethanol, Tetrahydrofuran oder Diethylether, vorzugsweise Essigsäure oder Tetrahydrofuran mit einem Reduktionsmittel wie elementares Zink, Lithiumaluminiumhydrid oder Natriumaluminiumhydrid, vorzugsweise elementares Zink oder Lithiumaluminiumhydrid und bei einer Temperatur zwischen Raumtemperatur und 120°C, bevorzugt jedoch bei 70°C umsetzt. Die Überführung einer Verbindung der allgemeinen Formel XV in einer Verbindung der Formel IV kann auch hydrogenolytisch

unter Verbindung eines Katalysators wie Palladium/Kohle stattfinden (Hatt. H. H., Org. Synth. Coll. Vol. 2, 211 (1943); Schüler F. W., J. Amer. Chem. Soc. 73, 4996 (1951).
Die Oxidation eines Alkohols der allgemeinen Formel XX zu einem Keton der allgemeinen Formel VI erfolgt nach bekannten Verfahren wie der Jones-Oxidation (Jones E. R. H., J. Chem. Soc. 36 (1946)), der Swern-Oxidation (Swern D., Tetrahedron 34, 1651 (1978), der Dess-Martin Oxidation (Dess D. B., Martin J. C., J. Org. Chem. 48, 4155 (1983) oder mit einem Brom-Urotropin-Komplex als Oxidationsmittel (Yavari I., J. Chem. Res. (S) 274 (1994).

Die Verwendeten Wittigreagenzien werden gegebenenfalls analog zu literaturbekannten Verfahren herstellt (Buddras J., Angew. Chem. 80, 535 (1968); Bestmann H. J. Angew. Chem. 77, 620, 651 (1965); Wittig G. Ber. Deutsch. Chem. Ges. 88, 1654 (1955)).

Die Wittigreaktion erfolgt nach bekannten Verfahren durch Rückflußerhitzen der Reaktanten in einem aprotischen Lösungsmittel wie Benzol, Toluol oder Xylol, vorzugsweise Toluol.

Die Phthalimidhydrolyse erfolgt in der Regel nach bekannten Verfahren durch Behandlung des Phthalimids mit Hydrazinhydrat oder halbkonzentrierter Mineralsäure wie Salzsäure oder Schwefelsäure, vorzugsweise mit Hydrazinhydrat oder Salzsäure bei Raumtemperatur.

Die Acylierung von Aminen führt man in der Regel in einem Lösungsmittel wie Methylenchlorid, Dimethylformamid oder Pyridin, vorzugsweise Methylenchlorid oder Pyridin unter Zusatz einer Hilfsbase wie Triethylamin oder 4-Dimethylaminopyridin und bei einer Temperatur zwischen -10°C und 50°C bevorzugt jedoch bei Raumtemperatur durch.

Die Ketalspaltung eines Ketals der allgemeinen Formel VIII wird nach Standardverfahren der organischen Chemie durchgeführt (ORGANIKUM; VEB Deutscher Verlag der Wissenschaften, Berlin 1977, Seite 486, 490).

Die katalytische Hydrierung von olefinischen Doppelbindungen wird analog zu literaturbekannten Verfahren durchgeführt (A. Nose, Chem. Pharm. Bull. 38, 2097 (1990); Tamura M. Bull. Chem. Soc. Jpn. 53, 561 (1980); Liu H.-J., Synth. Commun. 15, 965 (1985); Chido N., J. Chem. soc. Chem. Commun. 994 (1990); Büchi G., J. Amer. Chem. Soc. 89, 6745 (1967); Ernst I., Coll. Czech. Chem. Comm. 24, 3341 (1959); Johnson W. S., J. Amer. chem. Soc. 79, 1995 (1957); Muchowski J. M., Can. J. Chem. 47, 857 (1969)).

Die Epoxydierung eines Olefins der Formel VII oder der Formel X oder der Formel XXIII erfolgt nach literaturbekannten Verfahren durch ihre Umsetzung mit einer Persäure wie m-Chlorperbenzoesäure, Peressigsäure oder Trifluorperessigsäure, vorzugsweise m-Chlorperbenzoesäure in einem aprotischen Lösungsmittel wie Methylenchlorid und bei einer Temperatur zwischen -30°C und 50°C, vorzugsweise Raumtemperatur; weiterhin lassen sich die oben angeführten Olefine mittels der Sharpless-Epoxydierung in die entsprechenden Epoxyde überführen (Sharpless K.B., Org. Syntheses, Vol. 63, 66 (1985)).

Bei der im Schema 3 erwähnten metallorganischen Reaktion handelt es sich in der Regel um die Grignard-Reaktion, die nach literaturbekannten Verfahren durchgeführt wird. Gegebenenfalls kann jedoch das Magnesiumreagenz der Formel XXI in ein Lithium- oder Titanreagenz überführt werden, bevor es mit einer Carbonylverbindung der Formel VI umgesetzt wird (Reetz M.T., Chem. Ber. 118, 1421 (1985)).

Die Überführung eines Aminoalkohols der Formel III in ein Oxazolidinon der Formel II erfolgt nach literaturbekannten Verfahren durch Umsetzung eines Aminoalkohols der Formel III mit Diethylcarbonat (Evans D.A., Org. Syntheses, Vol. 68, 77 (1989)) oder Carbonyldiimidazol (Chadwick D.I., J. Chem. Soc. Perkin Trans. 481 (1984); Geffken D. Arch. Pharm. 313, 817 (1980)) oder Phosgen (Newman W.S., J. Am. Chem. Soc. 73, 4199 (1951)) oder Di-oder Triphosen (Hassner A., Synth. Commun. 23, 2839 (1993)), oder Chlorameisensäuremethyl-, -ethyl oder -benzylester (Kanoshinzo, J. Org. Chem. 53, 3865 (1988)) in einem Lösungsmittel wie Methylenchlorid, Dimethylformamid, Toluol, Dioxan, Tetrahydrofuran, Wasser oder Diethylether, vorzugsweise Dimethylformamid,

Methylenchlorid oder Tetrahydrofuran und bei einer Temperatur zwischen -50°C und 80°C, vorzugsweise bei Raumtemperatur.

Die katalytische Hydrierung einer Verbindung der Formel XXVII führt man in einem Lösungsmittel wie Methanol oder Ethanol unter Zusatz eines Katalysators wie Ruthe-niumoxid, Rhodiumoxid oder Palladium/Strontiumcarbonat, vorzugsweise Rhodiumoxid in einer Wasserstoffatmosphäre bei einem Druck von 1-200 bar, vorzugsweise bei 200 bar und einer Temperatur zwischen Raumtemperatur und 200°C durch (Rastin R.H., I. Chem. Soc. 1855 (1949).

Die Epoxidöffnung eines Epoxids der Formel V mit einem Amin der Formel IV findet in der Regel in einem Lösungsmittel wie Methanol, Ethanol, Dimethylformamid oder Toluol, vorzugsweise Ethanol oder Toluol und bei einer Temperatur zwischen 0°C und 120°C vorzugsweise 80°C statt.

Die Epoxidöffnung eines Epoxids der Formel V mit einem Metallazid erfolgt nach literaturbekannten Verfahren durch Umsetzung eines Epoxids der Formel V mit einem Metallazid wie Lithium-, Natrium-, Kalium-, Tributylzinn- oder Magnesiumazid, vorzugsweise Natriumazid, in einem Lösungsmittel wie Methanol, Ethanol, 1,4-Dioxan, Wasser, Dimethylformamid, Tetrahydrofuran, Acetonitril oder Hexamethylphosphortriamid, oder in Mischungen der genannten Lösungsmittel, bevorzugt jedoch in Methanol, Dimethylformamid oder 1,4-Dioxan-Wasser Gemischen und bei einer Reaktionstemperatur zwischen -10 °C und 120 °C vorzugsweise 80 °C (Vanderverf C.A., J.Am.Chem.Soc. 76, 1231 (1954); Saito S., Tetrahedron Lett. 30, 4153 (1989); Hudlicky T., J.Chem.Soc.Perkin Trans. I, 2907 (1991)). Die Umsetzung eines Epoxids der Formel V mit Trimethylsilylazid findet in der Regel in einem Lösungsmittel wie Methanol Tetrahydrofuran, Methylenchlorid, Chloroform, Dichlor-ethan oder Benzol, vorzugsweise Tetrahydrofuran oder Methylenchlorid, ohne weitere Zusätze oder unter Verwendung von Zusätzen wie Titantetraisopropylat, Aluminiumtriisopropylat, Dichlortitandiisopropylat oder Diethylaluminumfluorid, vorzugsweise Titantetraisopropylat oder Aluminiumtriisopropylat und bei einer Temperatur zwischen 0 °C und 100 °C bevorzugt jedoch bei Raumtemperatur statt (Emziane M., Synthesis, S. 541 (1988); Saito S.,

Tetrahedron Lett. 26, 5309 (1985); Blandy C., Tetrahedron Lett. 24, 4189 (1983); Jung M. E., J.Org.Chem., 56, 2614 (1991)).

Die Überführung eines Azids der Formel XXIX in ein Amin der Formel XXX erfolgt nach bekannten Verfahren: Suami T., Bull.Chem.Soc.Jpn., 51, 855 (1978); Boullanger P., Bull.Soc.Chim.Fr., S. 2149 (1973); Ackerman K., Can.J.Chem., 50, 3886 (1972); Hanessian S., Chem.Ind., S. 1296 (1965); Horner L., Liebigs Ann.Chem., 591, 117 (1955); Koziara A. Synthesis, S. 487 (1987); Vogel E., Ang. Chem.Int.Ed.Engl., 18, 962 (1979); Purwono B., Synlett, 3, 231 (1992).

Verbindungen der Formel I enthalten ein oder mehrere chirale Zentren und können daher in racemischer oder in optisch-aktiver Form vorliegen. Racemate können nach an sich bekannten Methoden mechanisch oder chemisch in die enantiomeren getrennt werden. Vorzugsweise werden aus dem racemischen Gemisch durch Umsetzen mit einer optisch-aktiven Säure wie die D- und L-Formen von Weinsäure, Diacetylweinsäure, Dibenzoylweinsäure, Mandelsäure, Äpfelsäure, Milchsäure oder die verschiedenen optisch-aktiven Camphersulfonsäuren wie β-Camphersulfonsäure Diastereomere gebildet.

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.

Als pharmakologisch verträgliche Salze werden vor allem Alkalisalze, Ammoniumsalze, Trifluoracetate oder Hydrochloride verwendet, die man üblicher Weise z.B. durch Titration der Verbindungen mit anorganischen oder organischen Basen oder Säuren wie z.B. Natrium- oder Kaliumhydrogencarbonat, Natronlauge, Kalilauge, wäßrigem Ammoniak oder Amine wie z.B. Trimethyl- oder Triethylamin, Trifluoressigsäure oder Salzsäure herstellt. Die Salze werden in der Regel durch Umfällen aus Wasser/Aceton gereinigt.

Die erfindungsgemäßen neuen Substanzen der Formel I und ihre Salze können in flüssiger oder fester Form enteral oder parenteral appliziert werden. Hierbei kommen alle übli-

chen Applikationsformen infrage, beispielsweise Tabletten, Kapseln, Dragees, Sirupe, Lösungen, Suspension 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), Gelantine, 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 10-1000 mg/Mensch, vorzugsweise bei 100-500 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 Pyridin- bzw. Pyridazinderivate:

1) 1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-piperidin-4-carbonsäure

2) 1-{3-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-propyl}-piperidin-4-carbonsäure

3) 1-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyl}-piperidin-4-carbonsäure

4) 1-{5-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentyl}-piperidin-4-carbonsäure

5) 1-[2-Oxo-5-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

6) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure

7) 1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-acetyl}-piperidin-4-carbonsäure

8) 1-{5-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentanoyl}-piperidin-4-carbonsäure

9) 1-[2-Oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-oxazolidin-5-ylmethy]-piperidin-4-carbonsäure

10) {1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-3-yl}-essigsäure

11) (1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-piperidin-3-yl}-essigsäure

12) {1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-3-yl}-essigsäure

13) (1-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyryl}-piperidin-3-yl)-essigsäure

14) (3-Hydroxy-1-{5-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentanoyl}-piperidin-3-yl)-essigsäure

15) (3-Hydroxy-1-{2-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-acetyl}-piperidin-3-yl)-essigsäure

16) {3-Hydroxy-1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-3-yl}-essigsäure

17) {3-Hydroxy-1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-3-yl}-essigsäure

18) (3-Hydroxy-1-{4-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyl}-piperidin-3-yl)-essigsäure

19) {1-[2-Oxo--4-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin4-yl}-essigsäure

20) {4-Hydroxy-1-[2-oxo-5-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-yl}-essigsäure

21) {1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-yl}-essigsäure

22) {1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-3-yl}-essigsäure

23) {3-Hydroxy-1-[5-methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-3-yl}-essigsäure

24) 1-[2-Oxo-5-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure

25) (1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-piperidin-4-yl)-essigsäure

26) (1-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyl}-piperidin-4-yl)-essigsäure

27) (4-Hydroxy-1-{2-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-piperidin-4-yl)-essigsäure

28) (4-Hydroxy-1-{5-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentyl}-piperidin-4-yl)-essigsäure

29) (1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-acetyl}-piperidin-4-yl)-essigsäure

30) (1-{5-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentanoyl}-piperidin-4-yl)-essigsäure

31) (4-hydroxy-1-{2-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-acetyl}-piperidin-4-yl)-essigsäure

32) (4-Hydroxy-1-{4-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyryl}-piperidin-4-yl)-essigsäure

33) {1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-yl}-essigsäure

34) {4-Hydroxy-1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-yl}-essigsäure

35) 1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-piperidin-3-carbonsäure

36) 1-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyl}-piperidin-3-carbonsäure

37) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-3-carbonsäure

38) 1-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyryl}-piperidin-3-carbonsäure

39) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-2-carbonsäure

40) 1-{5-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentyl}-piperidin-2-carbonsäure

41) 1-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyryl}-piperidin-2-carbonsäure

42) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-2-carbonsäure

43) 1-{2-[5-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-piperidin-2-carbonsäure

44) 1-{5-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentyl}-piperidin-2-carbonsäure

45) 1-{4-[5-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyryl}-piperidin-2-carbonsäure

46) 1-{5-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-pentanoyl}-piperidin-2-carbonsäure

47) 1-[2-Oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

48) 1-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

49) 1-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure

50) 1-[2-Oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure

51) 1-[2-Oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure

52) {1-[2-[Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl-]-piperidin-4-yl}-essigsäure

53) {4-Hydroxy-1-[2-oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-yl]-piperidin-4-yl}-essigsäure

54) 1-{3-[2-Oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-yl]-propyl}-piperidin-4-carbonsäure

55) 1-{3-[4-Methyl-2-oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-yl]-propionyl}-piperidin-4-carbonsäure

56) 1-[4-Methyl-2-oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

57) (Butan-1-sulfonylamino)-{1-[4-methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäure

58) (Butan-1-sulfonylamino)-(1-{3-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-propyl}-piperidin-4-yl}-essigsäure

59) (Butan-1-sulfonylamino)-{1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-yl}-essigsäure

60) 4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-cyclohexancarbonsäure

61) 4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-cyclohexancarbonsäure

62) 4-{3-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-propyl}-cyclohexancarbonsäure

63) 3-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5yl]-cyclohexancarbonsäure

64) 4-Hydroxy-4-{3-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-propyl}-cyclohexancarbonsäure

65) {4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-cyclohexyl}-essigsäure

66) (4-Hydroxy-4-{3-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-propyl}-cyclohexyl}-essigsäure

67) {1,4-Dihydroxy-4-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-cyclohexyl}-essigsäure

68) 3-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-ethyl}-cyclohexancarbonsäure

69) 2-{4-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl]-butyl}-cyclohexancarbonsäure

70) 4-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl}-cyclohexancarbonsäure

71) 4-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl]-cyclohexancarbonsäure

72) 4-[2-Oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-ylmethyl]-cyclohexancarbonsäure

73) (Butan-1-sulfonylamino)-{4-[4,5-dimethyl-2-oxo-3-(4-pyridazin-4-yl-piperazin-1-yl)-oxazolidin-5-ylmethyl]-1-hydroxy-cyclohexyl}-essigsäure

74) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-4-(3,4,5-trimethoxy-phenyl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure. Fp. 108 -114 °C

75) 1-[4-(3,4-Dimethoxy-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure. Fp.118 °C

76) 1-[4-(4-Cyano-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure. Fp. 100-105 °C

77) 1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure. Fp. 73-75 °C

78) (5S)-1-[5-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure. Fp. 223 °C (Zers.)

79) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-4-(3-trifluoromethyl-phenyl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure. Fp. 125-130 °C

80) 1-[4-(4-Chloro-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure. Fp. 110-115 °C

81) 1-[4-(4-Isopropyl-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

82) 1-[4-(4-tert.-Butyl-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

83) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

84) 1-{2-Oxo-3-[1-(2-piperidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

85) 1-{2-Oxo-3-[1-(2-phenylamino-pyrimidin-4-yl)-piperidin-4-yl]-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

86) 1-(2-Oxo-3-{1-[2-(pyrimidin-2-ylamino)-pyrimidin-4-yl]-piperidin-4-yl}-oxazolidin-5-ylmethyl)-piperidin-4-carbonsäure

87) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-hexahydro-benzooxazol-7a-ylmethyl}-piperidin-4-carbonsäure

88) 1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-hexahydro-cyclopentaoxazol-6a-ylmethyl}-piperidin-4-carbonsäure

89) 1-{3-[1-(2-Guanidino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

90) 1-{3-[1-(2-Acetimidoylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

91) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-4-ethyl-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

92) 1-[4-Ethyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

93) 1-[4-Butyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

94) 1-[2-Oxo-4-pentyl-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

95) 1-[4-Hexyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

96) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-4-(2-*p*-tolyl-ethyl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

97) 1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-4-butyl-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

Die nachfolgenden Beispiele zeigen einige der Verfahrensvarianten, die zur Synthese der erfindungsgemäßen Verbindungen verwendet werden können. Sie sollten jedoch nicht eine Einschränkung des Erfindungsgegenstandes darstellen. Die Struktur der Verbindungen wurde durch ^{1}H-, und gegebenenfalls durch ^{13}C-NMR-Spektroskopie sowie durch Massenspektrometrie gesichert. Die Reinheit der Substanzen wurde mittels C, H, N, sowie dünnschichtchromatographisch bestimmt.

Beispiel 1

1-[(5S)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

a) Die Lösung von 46 g (0.4 Mol) 4-Chlorpyridin und 123.5 g (0.86 Mol) 4-Piperidonethylenketal wird in 400 ml p-Xylol 48 h am Rückfluß erhitzt. Anschließend wird die Reaktionsmischung abgekühlt, der ausgefallene Niederschlag abfiltriert, die Mutterlauge zu Trockne eingeengt und der Rückstand an Kieselgel säulenchromatographisch (Essigsäureethylester/gesätt. ammonialkalisches Methanol 9/1) gereinigt. Man erhält so 79.7 g (90 %) 8-Pyridin-4-yl-1,4-dioxa-8-aza-spiro-[4.5]decan als weißes Pulver.m/e = 220; F_p = 65°C.

b) Die Lösung von 79.7 g des unter a) hergestellten Ketals in 2 l Tetrahydrofuran wird mit 1 l 6 n Salzsäure versetzt und die Reaktionsmischung 2 h bei Raumtemperatur gerührt. Anschließend wird das Tetrahydrofuran am Rotationsverdampfer im Vakuum abgezogen, die salzsaure Lösung mit halbkonzentrierter Ammoniumhydroxidlösung alkalisiert und viermal mit je 100 ml Methylenchlorid extrahiert. Nach dem Trocknen der vereinigten organischen Extrakten über Natriumsulfat und Abziehen des Lösungsmittels wird der Rückstand an Kieselgel säulenchromato-

graphisch gereinigt. Man erhält so 64.2 g (100 % Ausbeute) 2,3,5,6-Tetrahydro-[1.4']bipyridinyl-4-on als graues Pulver. m/e = 176; F_p = 102°C.

c) Die Lösung von 32 g des unter b) hergestellten Ketons und 19.9 ml Benzylamin in 400 ml Methylenchlorid wird unter Eiskühlung mit 50.4 g natriumtriacetatoborhydrid portionsweise versetzt. Anschließend tropft man 12 ml 100 %ige Essigsäure, läßt dann die Reaktionsmischung 4 h bei Raumtemperatur rühren und versetzt sie danach mit 100 ml Wasser. Nach der Phasentrennung wird die wäßrige Phase mit 2 n Natronlauge auf pH 12 alkalisch gestellt und fünfmal mit je 50 ml Methylenchlorid extrahiert. Nach dem Trocknen der vereinigten organischen Extrakten über Natriumsulfat und Abziehen des Lösungsmittels am Rotationsverdampfer wird das so erhaltene Benzyl-(3,4,5,6-tetrahydro-2H-[1.4']bipyridinyl-4-yl)-amin in 100 ml Methanol aufgenommen und die Lösung mit 3.5 g 10 %iger Palladium/Kohle versetzt. Nun hydriert man die methanolische Mischung bei Raumtemperatur solange, bis die Wasserstoffaufnahme beendet ist (30 h), filtriert dann den Katalysator ab und engt am Rotationsverdampfer ein. Man erhält so 22 g 3,4,5,6-Tetrahydro-2H-[1.4']bipyridinyl-4-ylamin als hellgelbes, zähes Oel, das allmählich kristallisiert. m/e = 177; ^{1}H-NMR (d^6-DMSO); δ = 8.10 ppm (d, 2H); 6.85 ppm (d, 2H); 3.80 ppm (d mit Feinaufspaltung, 2H); 2.85 ppm (t mit Feinaufspaltung, 2H); 2.70 ppm (m, 1H); 1.70 ppm (d mit Feinaufspaltung, 2H); 1.20 ppm (q mit Feinaufspaltung, 2H); F_p = 68°C.

d) Die Mischung von 5.7 g (2R)-Glycidyl-Tosylat (Fluka GmbH), 4 ml Piperidin-4-carbonsäureethylester und 3.5 g Kaliumcarbonat in 100 ml Acetonitril wird 2 h am Rückfluß erhitzt. Nach dem Abkühlen wird die Reaktionsmischung mit 50 ml Wasser versetzt und jeweils dreimal mit je 50 ml Methylenchlorid und je 50 ml Diethylether extrahiert. Nach dem Trocknen der vereinigten organischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels am Rotationsverdampfer wird der Rückstand an Kieselgel säulenchromatographisch (Essigsäureethylester/gesätt. methanolisches Ammoniak 95/5) gereinigt. Man erhält so 2.5 g (2S)-1-Oxiran-2-ylmethyl-piperidin-4-carbonsäure-ethylester.

^{1}H-NMR (d^6-DMSO): δ = 4.05 ppm (q, 2H); 3.00 (m, 1H); 2.95 (doppel-t, 1H); 2.85 (doppel-t, 1H); 2.70 (q, 1H); 2.62 (dd, 1H); 2.45 (dd, 1H); 2.30 (m, 1H); 2.15 (dd, 1H); 2.02 (m, 2H); 1.75 (breites d, 2H); 1.52 (Sextett, 2H); 1.15 (t, 3H).

e) Die Lösung von 0.43 g des unter c) hergestellten Amins und 0.173 g des unter d) hergestellten Oxirans in 10 ml Ethanol wird 48 h am Rückfluß erhitzt. Anschließend wird das Ethanol im Vakuum abgezogen und der Rückstand an Kieselgel säulenchromatographisch (Essigsäurethylester/gesätt. methanolisches Ammoniak 85/15) gereinigt. Das so erhaltene Produkt (325 mg) wird in 2 ml Dimethylformamid aufgenommen, die Lösung mit 200 mg Carbonyldiimidozol versetzt und die Reaktionsmischung 15 h bei Raumtemperatur gerührt. Anschließend wird die Reaktionsmischung mit 10 ml Wasser versetzt und dreimal mit je 10 ml Methylenchlorid geschüttelt. Nach dem Trocknen der vereinigten organischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels im Vakuum wird der Rückstand mittels präparativer HPLC (RP 18, Methanol/Puffer (pH = 7.5) 7/3) gereinigt. Man erhält so 235 mg 1-[(5S)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1.4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäureethylester.
m/e = 416; ^{1}H-NMR (d^6-DMSO): δ = 8.12 ppm (d, 2H); 6.82 (d, 2H); 4.60 (q, 1H); 4.05 (q, 2H); 3.99 (breites d, 2H); 3.75 (m, 1H); 3.50 (t, 1H); 3.15 (t, 1H); 2.90 (breites t, 2H); 2.75 (m, 2H); 2.50 (m, 2H); 2.25 (m, 1H); 2.10 (m, 2H); 1.80-1.40 (m, 8H); 1.12 (t, 3H).

f) Die Lösung von 230 mg des unter e) hergestellten Ethylesters in 2 ml Tetrahydrofuran und 1 ml Wasser wird mit 0.7 ml 1 n Natronlauge versetzt und 1 h bei Raumtemperatur gerührt. Anschließend wird das Tetrahydrofuran im Vakuum abgezogen und das Produkt mittels Ionenaustauscher (Dowex 50, H-Form) gereinigt. Man erhält so 120 mg der Titelverbindung als weißes Pulver. FAB = 388; ^{1}H-NMR (d^6-DMSO): δ = 8.15 ppm (d, 2H); 6.82 (d, 2H); 4.60 (m, 1H); 4.02 (breites d, 2H); 3.75 (m, 1H); 3.50 (t, 1H); 3.15 (dd, 1H); 2.95 (breites d, 2H); 2.80 (m, 2H); 2.52 (m, 2H); 2.10 (m, 3H); 1.80-1.40 (m, 8H).

Beispiel 2

1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1.4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

a) Die Mischung von 3.1 g Piperidin-4-carbonsäureethylester, 6.4 ml Epichlorhydrin und 0.1 g Tetrabutylammoniumbromid in 15 ml Toluol und 15 ml konzentrierter Natronlauge wird 4 h bei Raumtemperatur gerührt und anschließend mit 50 ml Wasser versetzt. Man trennt die organische Phase ab, schüttelt die wäßrige Phase dreimal mit je 20 ml Methylenchlorid, trocknet die vereinigten organischen Phasen über Natriumsulfat und entfernt das Lösungsmittel im Vakuum. Man erhält 2.1 g (rac)-1-Oxiran-2-ylmethylpiperidin-4-carbonsäureethylester.
m/e = 213.

b) Analog zum Beispiel 1e) erhält man aus 2.1 g Epoxid 2a), 2.6 g Amin 1c) und 0.4 g Carbonyldiimidazol 520 mg 1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1.4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäureethylester.
m/e = 416.

c) Analog zum Beispiel 1f) erhält man aus 520 mg Ethylester 2b) und 1.5 ml 1 n Natronlauge 190 mg der Titelverbindung. FAB: 388, ^{1}H-NMR (d^6-DMSO): identisch mit dem ^{1}H-NMR der Verbindung 1f).

Beispiel 3

{1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4]bipyridinyl-4yl)-oxazolodin-5-ylmethyl]-piperidin-4-yliden}-essigsäure

a) Analog zum Beispiel 2a) erhält man aus 1.43 g 4-Piperidonethylenketal, 3.1 ml Epichlorhydrin und 0.2 g Tetrabutylammoniumbromid 1.6 g 8-Oxiran-2-ylmethyl-1,4-dioxa-8-aza-spiro[4.5]decan als gelbes Oel.

^{1}H-NMR (d^6-DMSO): δ = 3.85 ppm (s, 4H); 3.0 (m, 1H); 2.70 (dt, 2H); 2.60 (d, 1H); 2.50 (m, 3H); 2.40 (m, 1H); 2.20 (dd, 1H); 1.60 (t, 4H).

b) Analog zum Beispiel 1e) erhält man aus 1.6 g Epoxid 3a), 1.9 g Amin 1c) und 0.4 g Carbonyldiimidazol 0.35 g 5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-2-on.
m/e = 402; ^{1}H-NMR (d^6-DMSO): δ = 8.15 ppm (d, 2H); 6.82 (d, 2H); 4.60 (m, 1H); 4.0 (breites d, 2H); 3.85 (s, 4H); 3.75 (m, 1H); 3.52 (t, 1H); 3.15 (t, 1H); 2.90 (breites t, 2H); 2.55 (m, 6H); 1.60 (m, 8H).

c) Analog zum Beispiel 1b) erhält man aus 1.2 g Ketal 3b) und 10 ml 6 n Salzsäure 1.1 g 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-yl-methyl]-piperidin-4-on als graues Pulver.
m/e = 358; ^{1}H-NMR ($CDCl_3$): δ = 8.20 ppm (d, 2H); 6.55 (d, 2H); 4.65 (m, 1H); 3.95 (m, 3H); 3.50 (t, 1H); 3.20 (t, 1H); 2.85 (m, 7H); 2.65 (dd, 1H); 2.45 (t, 4H); 1.80 (m, 2H); 1.65 (dq, 2H).

d) Die Mischung von 840 mg des Ketons 3c) und 820 mg Ethoxycarbonylethyliden-triphenylphosphoran (Aldrid GmbH & Co.) in 15 ml Toluol wird 24 h bei 100°C erhitzt. Anschließend wird das Toluol in Vakuum eingedampft und das Rohprodukt an Kieselgel gereinigt (Essigsäureethylester/gesätt. methanolisches Ammoniak 85/15). Man erhält so 820 mg {1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yliden}-essigsäureethylester.
m/e 428.

e) Analog zum Beispiel 1f) erhält man aus 210 mg Ethylester 3d) und 0.6 ml 1 n Natronlauge 48 mg der Titelverbindung als weißes Pulver. FAB: 400; ^{1}H-NMR (d^6-DMSO): δ = 8.15 ppm (d, 2H); 6.80 (d, 2H); 5.60 (s, 1H); 4.65 (m, 1H); 4.05 (breites d, 2H); 3.75 (m, 1H); 3.60 (t, 1H); 3.20 (t, 1H); 2.88 (m, 4H); 2.55 (m, 6H); 2.20 (m, 2H); 1.65 (m, 4H).

Beispiel 4

{1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäure

a) Die Lösung von 560 mg der Verbindung 3d) in 20 ml Methanol wird mit 50 mg Palladium/Kohle (10 %ig) versetzt und bei Raumtemperatur und Normaldruck solange hydriert, bis die Wasserstoffaufnahme beendet ist. Danach wird der Katalysator abfiltriert und die Lösung zu Trockne eingedampft. Man erhält so 400 mg {1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäureethylester als farbloses Oel.
m/e = 430.

b) Analog zum Beispiel 1f) erhält man aus 400 mg Ethylester 4a) und 1.1 ml 1 n Natronlauge 180 mg der Titelverbindung als hellgraues Pulver. FAB = 402;
^{1}H-NMR (d^6-DMSO): δ = 8.15 ppm (d, 2H); 6.80 (d, 2H); 4.60 (m, 1H); 4.05 (breites d, 2H); 3.75 (m, 1H); 3.50 (t, 1H); 3.12 (t, 1H); 2.85 (m, 4H); 2.48 (m, 2H); 2.0 (m, 4H); 1.65 (m, 7H); 1.12 (m, 2H).

Beispiel 5

{4-Hydroxy-1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäure

a) 0.5 ml Diisopropylamin werden unter Stickstoff bei -10°C mit 2.3 ml n-Butyllithium (1.6 M in n-Hexan) versetzt. Anschließend rührt man die Mischung noch 10 Min. bei -10°C, kühlt sie dann auf -78°C ab und gibt 10 ml trockenes Tetrahydrofuran hinzu. Zu der so hergestellten Lithiumdiisopropylamid-Lösung tropft man nun 0.45 ml Essigsäure-tert.-butylester in 2 ml trockenem Tetrahydrofuran, läßt dann die Reaktionsmischung 30 Min. bei -78°C rühren, versetzt sie mit einer Lösung von 1.1 g Keton 3c) in 10 ml trockenem Tetrahydrofuran, läßt 1 h bei -78°C rühren und

erwärmt anschließend langsam auf Raumtemperatur. Danach rührt man die Reaktionsmischung noch 15 h bei Raumtemperatur und versetzt sie dann mit 10 ml gesättigter Ammoniumchlorid-Lösung. Nach dreimaligen Extrahieren der wäßrigen Lösung mit je 10 ml Methylenchlorid, Trocknen der vereinigten organischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels am Rotationsdampfer wird das Rohprodukt mittels präparativer HPLC (Select B, 12 µ, Methanol/Puffer (pH 7.5) 6/4) gereinigt. Man erhält 0.85 g {4-Hydroxy-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäure-tert.-butyl-ester als gelbes Oel. m/e = 474.

b) Die Lösung von 100 mg tert.-Butylester 5a) in 2 ml Trifluoressigsäure wird 5 h bei Raumtemperatur gerührt. Anschließend wird die Reaktionsmischung zu Trockne eingedampft, der Rückstand in 3 ml Wasser aufgenommen und das Produkt mittels Ionenaustauscher (Dowex 50, H-Form) gereinigt. Man erhält 30 mg der Titelverbindung als weißes Pulver.

^{1}H-NMR (d^6-DMSO): δ = 8.15 ppm (d, 2H); 6.85 (d, 2H); 4.60 (m, 1H); 4.05 (breites d, 2H); 3.75 (m, 1H); 3.52 (t, 1H); 3.15 (t, 1H); 2.92 (t, 2H); 2.48 (m, 6H); 2.25 (s, 2H); 1.60 (m, 8H).

Beispiel 6

1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-3-carbonsäure

a) Analog zum Beispiel 1e) erhält man aus 2.7 g 1-Oxiran-2-ylmethyl-piperidin-3-carbonsäureethylester (hergestellt aus Epichlorhydrin und Piperidin-3-carbonsäureethylester analog dem Beispiel 2a)) 3.2 g Amin 1c) und 260 mg Carbonyldiimidazol 550 mg 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-3-carbonsäure-ethylester als Diastereomerengemisch. m/e = 416.

b) Analog zum Beispiel 1f) erhält man aus 550 mg Ethylester 6a) und 1.5 ml 1 n Natronlauge 300 mg der Titelverbindung als hellgraues Pulver.
m/e = 388; ^{1}H-NMR (d^6-DMSO): Diastereomerengemisch δ = 8.15 ppm (d, 2H); 6.85 (d, 2H); 4.60 (m, 2H); 4.02 (breites d, 2H); 3.72 (m, 1H); 3.50 (t, 1H); 3.15 (t, 1H); 2.90 (breites t, 3H); 2.65 (m, 1H); 2.50 (m, 2H); 2.30-1.95 (m, 3H); 1.80-1.50 (m, 6H); 1.45-1.20 (m, 2H).

Beispiel 7

1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

a) Analog zum Beispiel 1d) erhält man aus 20.3 g (rac)-trans-2-(p-Toluolsulfonyloxy--methyl)-3-methyloxiran (Evans R.D., Synthesis, S. 862 (1988)), 13.9 ml Piperidin-4-carbonsäureethylster und 13.8 g Kaliumcarbonat in 50 ml Dimethylformamid nach 12-stündigem Rühren bei Raumtemperatur 14.7 g 1-(3-Methyl-oxiranyl-methyl)-piperidin-4-carbonsäure-ethylester als gelbliches Öl.
^{1}H-NMR (d^6-DMSO): δ = 4.08 ppm (q, 2H); 2.99 (dt, 1H); 2.90-2.65 (m, 3H); 2.55 (dd, 1H); 2.32-2.12 (m, 2H); 2.10-1.95 (m, 2H); 1.90-1.62 (m, 4H); 1.21 (d, 3H); 1.18 (t, 3H).

b) Die Lösung von 2.5 g des unter 7a) hergestellten Epoxids, 1.0 g Natriumazid und 0.810 g Ammoniumchlorid in 25 ml einer Ethanol/Wasser-(80/20)-Mischung wird 24 h bei 50 °C erhitzt. Anschließend wird das Ethanol im Vakuum abgezogen, der Rückstand mit 10 ml Wasser verdünnt und die wäßrige Lösung dreimal mit je 15 ml Methylenchlorid extrahiert. Nach dem Trocknen der vereinigten or-ganischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels am Rotationsverdampfer wird das Rohprodukt an kieselgel chromatographiert (Essigsäureethylester/ Isohexan: 3/1). Man erhält so 1.4 g 1-(3-Azido-2-hydroxy-butyl)-piperidin-4-carbonsäure-ethylester.

^{1}H-NMR ($CDCl_3$): δ = 4.05 ppm (q, 2H); 3.48 (m, 1H); 2.40 (m, 1H); 2.77-2.57 (m, 2H); 2.48 (d, 1H); 2.35-2.08 (m, 4H); 2.02-1.55 (m, 5H); 1.20 (d und t, 5H).

c) Die Lösung von 1.4 g des unter 7b) hergestellten Azids in 20 ml Ethanol wird mit 0.5 g 10%iger Palladium/Kohle versetzt, und die Mischund 8 h bei Raumtemperatur hydriert. Anschließend wird der Katalysator abfiltriert und die Lösung am Rotationsverdampfer eingeengt. Man erhält so 1.1 g 1-(3-Amino-2-hydroxy-butyl)-piperidin-4-carbonsäure-ethylester.

d) Die Lösung von 1.0 g Amin 7c), 0.721 g Keton 1b) und 1.1 g Natriumtriacetatobor hydrid in 15 ml Methylenchlorid wird 15 h bei Raumtemperatur gerührt. Anschließend wird die Reaktionsmischung mit 10 ml Wasser versetzt und mit 1 N Salzsäure angesäuert. Nach der Phasentrennung wird die wäßrigsaure Phase noch einmal mit 10 ml Methylenchlorid extrahiert und dann mit 1 N Natronlauge alkalisiert. Nach dreimaligem Extrahieren der alkalischen Mischung mit je 15 ml Methylenchlorid und Trocknen der vereinigten organischen Phasen über Natriumsulfat wird das Lösungsmittel am Rotationverdampfer abgezogen. Das Rohprodukt wird dann mittels präp. HPLC (RP 18, Methanol/Puffer (pH=7.5) 70/30) gereinigt. Man erhält so 0.5 g 1-[2-Hydroxy-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-ylamino)-butyl]-piperidin-4-carbonsäure-ethylester.

^{1}H-NMR ($CDCl_3$): δ = 8.15 ppm (d, 2H); 6.60 (d, 2H); 4.05 (q, 2H); 3.78 (t, 1H); 3.72 (t, 1H); 3.58 (m, 1H); 2.97-2.70 (m, 5H); 2.40-2.25 (m, 4H), 2.06-1.60 (m, 7H); 1.38-1.10 (m, 3H); 2.20 (t, 3H); 0.98 (d, 3H).

e) Die Lösung von 0.5 g des Aminoalkohols 7d) und 243 mg Carbonyldiimidazol in 5 ml Dimethylformamid wird 24 h bei Raumtemperatur gerührt. Anschließend wird die Reaktionslösung zu Trockne eingedampft und der Rückstand mittels präp. HPLC (Merck, Select B, Methanol/Puffer (pH=7.5) 65/35) gereinigt. Man erhält so 0.26 g 1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazoli- din-5-ylmethyl]-piperidin-4-carbonsäure-ethylester. m/e=430.

f) Die Lösung von 0.26 g des Ethylesters 7e) und 0.72 ml 1N Natronlauge in 5 ml Methanol wird 1 h bei Raumtemperatur gerührt. Anschließend wird das Methanol im Vakuum abgezogen und das Produkt mittels Ionenaustauscher (Dowex 50, H-Form) gereinigt. Man erhält so 0.11 g der Titelverbindung als weißes Pulver.
Fp. > 220 °C. FAB = 402. ^{1}H-NMR (d^6-DMSO): δ = 8.15 ppm (d, 2H); 6.80 (d, 2H); 4.55 (q, 1H); 3.98 (m, 3H); 3.55 (m, 1H); 2.82 (m, 4H); 2.50 (m, 8 Linien, 1H); 2.0 (m, 4H); 1.75 (m, 6H); 1.50 (breites q, 2H); 1.09 (d, 3H).

Beispiel 8

1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

a) Zu einer Lösung von 16 ml 4-Piperidon-ethylenketal und 17.5 ml Triethylamin in 100 ml Ethanol tropft man unter Eiskühlung die Lösung von 18.5 g 2,4-Dichlorpyrimidin in 150 ml Ethanol zu. Anschließend rührt man die Reaktionsmischung noch 2.5 Stunden zieht dann das Ethanol im Vakuum ab, versetzt den Rückstand mit 100 ml Wasser und extrahiert die wäßrige Mischung dreimal mit je 50 ml Methylenchlorid. Nach dem Trocknen der vereinigten organischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels wird der feste Rückstand aus Essigsäureethylester/Isohexan umkristallisiert. Man erhält so 11 g 8-(2-Chloro-pyrimidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decan als weißes Pulver. Fp: 135-137 °C.

b) 6 g des 2-Chlorpyrimidins 8a) werden in 60 ml Methanol und 20 ml Tetrahydrofuran gelöst und nach Zugabe von 4.2 g Kaliumcarbonat und 1 g 10%iger Palladium/Kohle 6 Stunden lang bei Raumtemperatur und 44 mbar hydriert. Anschließend wird die Reaktionsmischung abfiltriert, das Filtrat zu Trockne eingedampft, der Rückstand in 20 ml Wasser aufgenommen und die wäßrige Mischung . dreimal mit je 20 ml Methylenchlorid extrahiert. Nach dem Trocknen der vereinigten organischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels erhält man 4.9 g 8-Pyrimidin-4-yl-1,4-dioxa-8-aza-spiro[4.5]decan als weißes Pulver. m/e: 221

c) Analog zum Beispiel 1b) erhält man aus 4.9 g Ketal 8b) und 60 ml 6n Salzsäure in 60 ml Tetrahydrofuran nach 55 Stunden Reaktionszeit 3.9 g 1-Pyrimidin-4-yl-piperidin-4-on als gelbes Pulfer. Fp: 75-80 °C

d) Aus 8 g Epoxid 2a), 3.8 g Natriumazid und 3.2 g Ammoniumchlorid in 100 ml Methanol/Wasser (8/1) erhält man analog dem Beispiel 7b) 8.5 g Rohprodukt, dessen säulenchromatographische Reinigung an Kieselgel (Essigsäureethylester/0.1% methanolisches Ammoniak) 7.4 g (77%) 1-(3-Azido-2-hydroxy-propyl)-piperidin-4-carbonsäure-ethylester als gelbes Öl liefert.

^{1}H-NMR (d^6-DMSO): δ = 5.01 ppm (breites s, 1H; OH); 4.05 (q, 2H); 3.80 (m, 1H); 3.20 (dddd, 2H); 2.85 (m, 2H); 2.30 (m, 3H); 2.05 (q, 2H); 1.88 (breites d, 2H); 1.55 (m, 2H); 1.12 (t, 3H).

e) Analog dem Beispiel 7c) erhält man bei der Hydrierung von 3.6 g Azid 8d) 2.9 g 1-(3-Amino-2-hydroxy-propyl)-piperidin-4-carbonsäure-ethylester als gelbes zähes Öl.

f) Analog dem Beispiel 7d) erhält man aus 2.5 g Amin 8e), 1.9 g Keton 8c) und 4.6 g Natriumtriacetatoborhydrid 1 g 1-[2-Hydroxy-3-(1-pyrimidin-4-yl-piperidin-4-ylamino)-propyl]-piperidin-4-carbonsäure-ethylester als hellgelbes Öl. ^{1}H-NMR (d^6-DMSO): δ = 8.49 ppm (s. 1H); 8.15 (d, 1H); 6.80 (d, 1H); 4.21 (breites d, 2H)); 4.05 (q, 2H); 3.61 (m, 1H); 3.02 (t, 2H); 2.80 (m, 1H); 2.65 (m, 2H); 2.45 (m, 1H); 2.24 (m, 3H); 2.00 (t, 3H); 1.88-1.68 (m, 4H); 1.57 (m, 2H); 1.25 (t, 3H); 1.19 (m, 3H).

g) Analog dem Beispiel 7e) liefert die Umsetzung von 1 g Aminoalkohol 8f) und 0.83 g 1.1'-Carbonyldiimidazol in 10 ml Dimethylformamid 1.2 g 1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure-ethylester als gelbes Öl. FAB (MH^+): 418.

h) Analog dem Beispiel 7f) liefert die Verseifung von 1.1 g Ethylester 8g) 0.61 g der Titelverbindung als weißes Pulver. Fp: 145 °C. FAB (MH^+): 418. ^{1}H-NMR (d^6-DMSO): δ = 8.22 ppm (s, 1H); 7.90 (d, 1H); 6.60 (d, 1H); 4.40 (m, 1H); 4.30 (m,

2H); 3.58 (m, 1H); 3.31 (t, 1H); 2.92 (m, 1H); 2.70 (t, 3H); 2.25 (m, 3H); 1.81 (m, 3H); 1.50 (m, 4H); 1.32 (m, 4H).

Beispiel 9

1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

a) Die Mischung von 8 g 8-(2-Chloro-pyrimidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decan 8a) und 7.2 ml Benzylamin wird 2 Sunden bei 150 °C erhitzt, dann abgekühlt, mit 20 ml Wasser versetzt und die wäßrige Lösung dreimal mit je 20 ml Methylenchlkorid extrahiert. Nach dem Trocknen der vereinigten organischen Phasen über Natriumsulfat und Abziehen des Lösungsmittels wird der Rückstand mit kaltem Isohexan gewaschen. Man erhält so 9.6 g Benzyl-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-pyrimidin-2-yl]-amin als gelbes Pulver. ^{1}H-NMR (d^6-DMSO): δ = 7.85 ppm (d, 1H); 7.40-7.18 (m, 5H); 7.15 (breites s, 1H, NH); 6.12 (d, 1H); 4.45 (d, 2H); 3.96 (s, 4H); 3.65 (m, 4H); 1.61 (m, 4H).

b) Analog zum Beispiel 1b) erhält man aus 9.6 g Ketal 9a) und 85 ml 6n Salzsäure in 80 ml Tetrahydrofuran nach 20 Stunden Reaktionszeit 10.29 g 1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-on als braunes Pulver. Fp: 98-102 °C.

c) Analog dem Beispiel 7d) erhält man aus 3.1 g Keton 9b), 2.5 g Amin 8e) und 4.6 g Natriumtriacetatoborhydrid 3.4 g 1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-ylamino]-2-hydroxy-propyl}-piperidin-4-carbonsäure-ethylester als gelbes Öl. m/e= 496. ^{1}H-NMR (d^6-DMSO): δ = 7.52 ppm (d, 1H); 7.10-6.95 (m, 5H); 6.80 (breites s, 1H, NH); 5.80 (d, 1H); 4.15 (d, 2H); 3.90 (m, 2H); 3.80 (q, 2H); 3.39 (m, 1H); 3.05 (breites s, 1H); 2.75-2.52 (m, 3H); 2.40 (m, 1H); 2.25 (m, 1H); 2.05 (m, 2H); 1.75 (m, 1H); 1.55 (m, 4H); 1.32 (m, 2H); 0.95 (t, 3H); 0.88 (m, 5H).

d) Analog dem Beispiel 7e) liefert die Umsetzung von 3.4 g Aminoalkohol 9c) und 2.2 g 1.1'-Carbonyldiimidazol in 20 ml Dimethylformamid 2.3 g 1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure-ethylester als gelbes Pulver. Fp: 122 °C.

e) Analog dem Beispiel 7f) liefert die Verseifung von 0.26 g Ethylester 9d) 0.21 g der Titelverbindung als weißes Pulver. Fp: 125-130 °C. FAB (MH^+): 495. ^{1}H-NMR (d^6-DMSO): δ = 7.90 ppm (d, 1H); 7.39 (d, 2H); 7.24 (m, 3H); 6.12 (d, 1H); 4.68 (q, 1H); 4.51 (d, 2H); 4.45 (m, 2H); 3.85 (t, 1H); 3.55 (t, 1H); 3.20 (t, 1H); 2.85 (m, 3H); 2.55 (m, 3H); 2.18 (m, 3H); 1.75 (m, 3H); 1.50 (m, 3H).

Beispiel 10

In analoger Weise zu Beispiel 9 wurden folgende Verbindungen hergestellt:

a) 1-[2-Oxo-4-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure; Fp. 150 °C (Zers.); m/e = 464

b) 1-[2-Oxo-4-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-carbonsäure; Fp. 77-80 °C; m/e = 478

c) 4-Hydroxy-4-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-cyclohexancarbonsäure; Fp > 250 °C; m/e = 403

d) 1-[4-(4-Methoxy-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-carbonyl]-piperidin-4-carbonsäure; Fp. 199 °C (Zers.); m/e = 508

Beispiel 11

1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-ylmethyl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

a) Eine Mischung aus 4.4 g (39 mmol) 4-Chlorpyridin und 4.4 g (39 mmol) 4-Aminomethyl-piperidin wird bei 150°C Ölbadtemperatur 1 h gerührt. Anschließend nimmt man die Schmelze in Wasser auf, wäscht mit Ether, stellt die wässrige Phase mit 10N Natronlauge alkalisch und extrahiert mit Dichlormethan. Nach dem Trocknen des Extrakts über Natriumsulfat und Abziehen des Lösungsmittels verbleiben 4.4 g (59 % d.Th.) 3,4,5,6-Tetrahydro-2*H*-[1,4']bipyridinyl-4-ylmethylamin als zähes Öl. m/e = 191; ^{1}H-NMR ($CDCl_3$): δ = 8.25 ppm (d, 2H); 6.70 (d, 2H); 3.90 (d mit Feinaufspaltung, 2H); 2.85 (t mit Feinaufspaltung, 2H); 2.60 (d, 2H); 1.80 (m, 4H); 1.55 (m, 1H); 1.25 (q mit Feinaufspaltung, 2H).

b) Analog zu Beispiel 1e) erhält man aus 2.8 g Epoxid 2a), 2.6 g Amin 11a) und 0.5 g Carbonyldiimidazol 1.0 g 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-ylmethyl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure-ethylester. m/e = 404; ^{1}H-NMR ($CDCl_3$): δ = 8.20 ppm (d, 2H); 6.65 (d, 2H); 4.65 (q, 1H); 4.10 (q, 2 H); 3.90 (breites d. 2H); 3.65 (m, 1H); 3.50 (s, 1H); 3.35 (t, 1H); 3.15 (d, 2H); 2.85 (m, 4H), 2.60 (d, 1H); 2.50 (m, 1H); 2.25 (m, 2H)1.80 (m, 8H); 1.25 (t+m, 5H).

c) Analog zum Beispiel 1f) erhält man aus 3.0 g Ethylester 11b) und 12 ml 1N Natronlauge 1.5 g der Titelverbindung als weißes Pulver vom Schmp. 94-96 °C. m/e = 402; ^{1}H-NMR (d_6-DMSO): δ = 8.10 ppm (d, 2H); 6.85 (d, 2H); 4.60 (m, 1H); 3.95 (breites d, 2H); 3.25 (dd, 1H); 3.05 (d, 2H); 2.85 (m, 4H); 2.15 (m, 3H); 1.75 (m, 8H); 1.15 (m, 4H).

Beispiel 12

1-{2-Oxo-3-[2-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-ethyl]-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

a) Analog zum Beispiel 11a) erhält man aus 5.7 g 4-Chlorpyridin und 12.8 g 4-(2-Amino-ethyl)piperidin (Sdp_{21} 100 - 104°C; hergestellt durch Hydrierung von 4-(2-Amino-ethyl)pyridin [J. Amer. Chem. Soc. 78, 4129 (1956)] über Ruthenium bei 150 °C und 150 bar Wasserstoffdruck) 5.2 g (51 % d.Th.) 2-(3,4,5,6-Tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)ethylamin. m/e = 205; ^{1}H-NMR ($CDCl_3$): δ = 8.20 ppm (d, 2H); 6.65 (d, 2H); 3.80 (breites d, 2H); 2.75 (m, 4H); 1.80 - 1.10 (m, 9H).

b) Analog zum Beispiel 1e) erhält man aus 1.9 g Epoxid 2a), 5.1 g Amin 12a) und 0.5 g Carbonyldiimidazol 0.8 g 1-{2-Oxo-3-[2-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-ethyl]-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure-ethylester. m/e = 444.

c) Analog zum Beispiel 1f) erhält man aus 0.7 g Ethylester 12b) und 5 ml 1N Natronlauge 0.4 g der Titelverbindung als amorphes Pulver. m/e = 416; ^{1}H-NMR ($CDCl_3$): δ = 8.15 ppm (d, 2H); 6.65 (d, 2H); 4.60 (m, 1H); 3.80 (breites d, 2H); 3.55 (t, 1H); 3.25 (m, 2H); 2.80 (m, 6H); 2.55 (br, 1H); 2.15 (m, 2H); 1.90 - 0.80 (m, 13H)

Beispiel 13

1-{2-Oxo-3-[1-(2-pyridin-4-yl-ethyl)-piperidin-4-yl]-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

a) Analog zum Beispiel 7b) erhält man aus 25.6 g Epoxid 2a) und 39 g Natriumazid 29 g (94 % d.Th.) 1-(3-Azido-2-hydroxy-propyl)piperidin-4-carbonsäure-ethylester als Öl. m/e = 256.

b) Analog zum Beispiel 7c) erhält man aus 29 g Azid 13a) durch katalytische Reduktion 21.1 g (81 % d.Th.) 1-(3-Amino-2-hydroxy-propyl)piperidin-4-carbonsäure-ethylester. m/e = 230; ^{1}H-NMR ($CDCl_3$): δ = 4.15 ppm (q, 2H); 3.65 (m, 1H); 2.95 (m, 1H); 2.80 (dd, 2H); 2.65 (dd, 1H); 2.30 (m, 7H), 2.05 - 1.65 (m, 4H); 1.25 (t, 3H).

c) Die Lösung von 16.2 ml (150 mmol) 4-Vinylpyridin in 5.7 ml Eisessig versetzt man mit 12.8 ml 4-Piperidon-ethylenketal und erwärmt 3 h auf 100 °C. Anschließend wird die Reaktionsmischung mit 2N Natronlauge alkalisch gestellt, 15 min bei Raumtemperatur gerührt und dann zum Abscheiden der Base mit 10N Natronlauge versetzt. Man extrahiert mit Dichlormethan, trocknet über Natriumsulfat, dampft im Vakuum ein und chromatographiert an Kieselgel. Mit Isohexan/Ethylacetat 3:1 eluiert man 16.3 g (66 % d.Th.) 8-(2-Pyridin-4-yl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decan. ^{1}H-NMR ($CDCl_3$): δ = 8.50 ppm (d, 2H); 7.15 (d, 2H); 3.95 (s, 4H); 2.75 (m, 2H); 2.55 (m, 6H); 1.75 (dd, 4H).

d) Analog zum Beispiel 1b) erhält man aus 12.4 g Ketal 13c) 10.2 g (100 % d.Th.) 1-(2-Pyridin-4-yl-ethyl)piperidin-4-on als Öl. ^{1}H-NMR ($CDCl_3$): δ = 8.50 ppm (d, 2H); 7.15 (d, 2H); 2.75 (m, 8H); 2.45 (t, 4H).

e) Analog zum Beispiel 7d) erhält man aus 2.1 g Amin 13b) und 1.9 g Keton 13d) 0.9 g 1-{2-Hydroxy-3-[1-(2-pyridin-4-yl-ethyl)-piperidin-4-ylamino]propyl}-piperidin-4-carbonsäure-ethylester als Öl. ^{1}H-NMR ($CDCl_3$): δ = 8.50 ppm (d, 2H); 7.15 (d, 2H); 4.10 (q, 2H); 3.80 (m, 1H); 2.90 (m, 4H); 2.75 (m, 4H); 2.55 (m, 4H); 2.30 (m, 4H); 2.05 (m, 2H); 1.85 (br,d, 4H); 1.75 (m, 2H); 1.40 (m, 2H); 1.25 (t, 3H).

f) Analog zum Beispiel 7e) erhält man aus 2.6 g des Aminoalkohols 13e) und 1.3 g Carbonyldiimidazol 1.7 g 1-{2-Oxo-3-[1-(2-pyridin-4-yl-ethyl)-piperidin-4-yl]-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure-ethylester als Öl. m/e = 444; ^{1}H-NMR ($CDCl_3$): δ = 8.50 ppm (d, 2H); 7.15 (d, 2H); 4.60 (m, 1H); 4.15 (q, 2H); 3.70 (m, 1H); 3.55 (t, 1H); 3.30 (t, 1H); 3.05 (br, d, 2H); 2.80 (m, 4H); 2.60 (m, 4H); 2.20 (m, 5H); 1.80 (m, 8H); 1.25 (t, 3H).

g) Analog zum Beispiel 1f) erhält man aus 1.7 g Ethylester 13f) und 5.2 ml 1N Natronlauge 1.2 g (75 % d.Th.) der Titelverbindung als amorphes Pulver. m/e = 416; ^{1}H-NMR (d_6-DMSO): δ = 8.20 ppm (d, 2H); 7.05 (d, 2H); 4.40 (br, t, 1H); 3.30 (m, 2H); 2.95 (t, 1H); 2.75 (br, d, 2H); 2.55 (m, 4H); 2.25 (m, 4H); 1.80 (m, 5H); 1.55 (m, 2H); 1.35 (m, 6H).

Beispiel 14 **Pharmakologische Daten**

Assay

Mikrotiterplatten wurden über Nacht mit 2 µg/ml isoliertem aktiviertem GpIIb/IIIa-Rezeptor beschichtet. Nachdem der ungebundene Rezeptor durch einige Waschschritte entfernt wurde, wurde die Oberfläche der Platte mit 1 % Kasein blockiert und nochmals gewaschen. Die Testsubstanz wurde in den notwendigen Konzentrationen dazugegebenen, anschließend wurden die Platten für 10 Minuten unter Schütteln in einem Linearschüttler inkubiert. Der natürliche Ligand des gpIIb/IIIa-Rezeptors, Fibronogen, wurde dazugegeben. Nach 1stündigem Inkubieren wurde das ungebundene Fibrinogen durch mehrere Waschschritte entfernt, und das gebundene Fibronogen wurde bestimmt, indem die optische Dichteänderung bei 405 nm durch einen Peroxidase-konjugierten monoklonaler Antikörper in einem ELISA-Ableser bestimmt wurde. Inhibierung der Fibrinogen-GpIIb/IIIa-Wechselwirkung führt zu niedrigen optischen Dichten. Der IC_{50}-Wert wurde anhand einer Konzentration-Effekt-Kurve bestimmt.

Literatur:

Der GpIIb/IIIa-Fibrinogen-ELISA ist eine Modifikation des Assays, der in folgenden Referenzen beschrieben ist:

Nachman, R.L. & Leung, L.L.K. (1982): Complex formation of platelet membrane glycoproteins IIb and IIIa with fibrinogen. J. Clin. Invest. **69**:263-269.

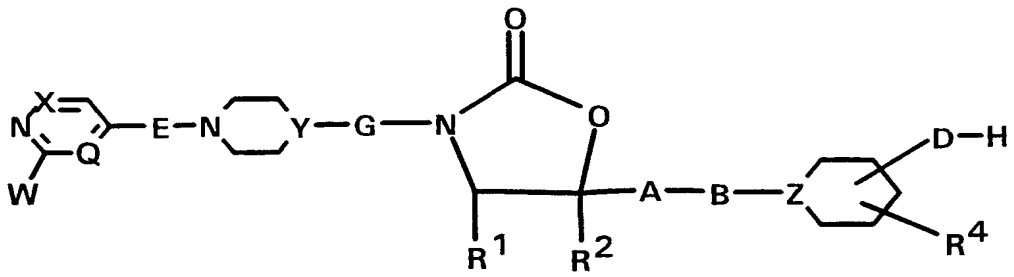
Wright, P.S. et al. (1993): An echistatin C-terminal peptide activated GpIIbIIIa binding to fibrinogen, fibronectin, vitronectin and collagen type I and type IV. Biochem. J. **293**:263-267.

Tabelle:

Beispiel	IC_{50} (µMol/l)	Bezeichnung
1	< 0.30	1-[(5S)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure
2	< 0.30	1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1.4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure
3	1.40	{1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4]bipyridinyl-4yl)-oxazolodin-5-ylmethyl]-piperidin-4-yliden}-essigsäure
5	1.00	{4-Hydroxy-1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bi-pyri-dinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäure
7	< 0.30	1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyri-dinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure
8	0.30	1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure
9	0.070	1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure
10 a)	0.30	1-[2-Oxo-4-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyri-dinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure
10 c)	< 0.30	4-Hydroxy-4-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']-bi-pyridinyl-4-yl)-oxazolidin-5-ylmethyl]-cyclohexancarbon-csäure
Nr. 78	0.60	(5S)-1-[5-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazoli-din-5-ylmethyl]-piperidin-4-carbonsäure
Nr. 79	1.30	1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-4-(3-trifluoromethyl-phenyl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure
Nr. 80	0.50	1-[4-(4-Chloro-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

Patentansprüche

1. Verbindungen der allgemeinen Formel I,



(I)

in der

X, Y und Q unabhängig voneinander Stickstoff oder CH bedeuten,

W Wasserstoff oder NR^0R^{00} bedeutet

Z Stickstoff, CH oder C-OH bedeutet,

A, E und G unabhängig von einander den Valenzstrich oder eine Alkylenkette $-(CH_2)_n-$ bedeuten,

B Valenzstrich und für den Fall, daß Z gleich N ist, auch die Carbonylgruppe bedeutet,

D eine Seitenkette der Form $-(CHR^3)_m-COO-$ oder $=CR^3-COO-$ bedeutet,

n = 1-5 bedeutet,

m = 0,1 bedeutet,

R^1, R^2 unabhängig voneinander Wasserstoff, niederes Alkyl oder Aryl bedeuten, oder zusammen einen carbocyclischen fünf- oder sechsgliedrigen Ring bilden,

R^3 Wasserstoff oder eine Gruppe $-OR^5$ oder $-NR^6R^7$ bedeutet,

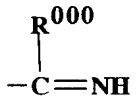
R^4 Wasserstoff oder eine Gruppe $-OR^5$ bedeutet,

R^5 Wasserstoff, niederes Alkyl, Aryl oder Arylalkyl bedeutet,

R^6 Wasserstoff, niederes Alkyl oder Arylalkyl bedeutet,

R^7 Wasserstoff, niederes Alkyl, Arylalkyl, Acyl, Alkylsulfonyl oder Arylsulfonyl bedeutet,

R^0, R^{00} unabhängig voneinander Wasserstoff, niederes Alkyl, Aryl, Arylalkyl, Hetaryl, Acyl oder einen gegebenenfalls substituierten carbocyclischen oder heterocyclischen Ring bedeuten, oder zusammen mit dem Stickstoff an dem sie gebunden sind, einen gegebenenfalls substituierten fünf- oder sechsgliedrigen Ring bilden, der noch 1 bis 3 weitere Heteroatome enthalten kann, oder eine Gruppe



bedeuten,

R^{000} Wasserstoff, niederes Alkyl, Arylalkyl oder eine Gruppe NHR^{0000} bedeutet,

R^{0000} Wasserstoff, niederes Alkyl, Arylalkyl, Acyl, Alkylsulfonyl oder Arylsulfonyl bedeutet,

sowie deren Konformationsisomere und deren pharmakologisch unbedenklichen Salze.

2. Verbindungen der allgemeinen Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß n den Wert 1, 2 oder 3 annimmt.

3. Die Verbindungen der Formel I gemäß Anspruch 1 oder 2:

1-[(5S)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1.4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

{1-[(rac)-2-Oxo-3-(3,4,5,6-tetrahydro-2H-[1,4]bipyridinyl-4yl)-oxazolodin-5-ylmethyl]-piperidin-4-yliden}-essigsäure

{4-Hydroxy-1-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyri-dinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-yl}-essigsäure

1-[4-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-carbonsäure

1-[2-Oxo-4-phenyl-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

4-Hydroxy-4-[2-oxo-3-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-cyclohexancarbonsäure

(5S)-1-[5-Methyl-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazoli-din-5-ylmethyl]-piperidin-4-carbonsäure

1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-4-(3-trifluoromethyl-phenyl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

1-[4-(4-Chloro-phenyl)-2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-oxazolidin-5-ylmethyl]-piperidin-4-carbonsäure

sowie deren Konformationsisomere und deren pharmakologische unbedenkliche Salze.

4. Pharmazeutische Zusammensetzung, enthaltend mindestens eine Verbindung gemäß Formel I nach einem der Ansprüche 1-3 neben üblichen Träger- und Hilfsstoffen.

5. Verwendung von Substanzen nach einem der Ansprüche 1-3 zur Herstellung von Arzneimitteln zur Behandlung von Krankheiten, die auf eine Blutplättchenaggregation zurückzuführen sind.

INTERNATIONAL SEARCH REPORT

I. .ational Application No
PCT/EP 96/02939

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/14 A61K31/42 A61K31/445 A61K31/44 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 623 615 (MERCK PATENT GMBH) 9 November 1994 cited in the application see claims ---	1-5
A	EP,A,0 537 980 (GLAXO GROUP LTD) 21 April 1993 cited in the application see claims ---	1-5
A	EP,A,0 635 505 (MERCK PATENT GMBH) 25 January 1995 see claims ---	1-5
A	WO,A,93 14077 (GLAXO GROUP LTD) 22 July 1993 cited in the application see claims --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 1996	25. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

I. ational Application No
PCT/EP 96/02939

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 645 376 (MERCK PATENT GMBH) 29 March 1995 see claims	1-5

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

L .ational Application No
PCT/EP 96/02939

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0623615	09-11-94	DE-A-	4405633	03-11-94
		AU-A-	6064394	03-11-94
		CA-A-	2122571	02-11-94
		CN-A-	1097421	18-01-95
		CZ-A-	9401019	16-11-94
		HU-A-	70541	30-10-95
		JP-A-	7002847	06-01-95
		NO-A-	941592	02-11-94
		SK-A-	48494	08-02-95
		US-A-	5532255	02-07-96
		ZA-A-	9402973	18-01-95
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		CN-A-	1073433	23-06-93
		WO-A-	9308181	29-04-93
		EP-A-	0609282	10-08-94
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		HU-A-	71110	28-11-95
		JP-A-	7070117	14-03-95
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/02939

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0645376		CN-A-	1106806	16-08-95
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		HU-A-	71233	28-11-95
		JP-A-	7179441	18-07-95
		NO-A-	943523	24-03-95
		PL-A-	305144	03-04-95
		SK-A-	112194	10-05-95
		US-A-	5561148	01-10-96
		ZA-A-	9407405	15-05-95

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 96/02939

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C07D413/14 A61K31/42 A61K31/445 A61K31/44 A61K31/505

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C07D

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP,A,0 623 615 (MERCK PATENT GMBH) 9.November 1994 in der Anmeldung erwähnt siehe Ansprüche ---	1-5
A	EP,A,0 537 980 (GLAXO GROUP LTD) 21.April 1993 in der Anmeldung erwähnt siehe Ansprüche ---	1-5
A	EP,A,0 635 505 (MERCK PATENT GMBH) 25.Januar 1995 siehe Ansprüche ---	1-5
A	WO,A,93 14077 (GLAXO GROUP LTD) 22.Juli 1993 in der Anmeldung erwähnt siehe Ansprüche ---	1-5

-/--

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
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"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
21.Oktober 1996	25. 10. 96
Name und Postanschrift der Internationale Recherchenbehörde Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Bevollmächtigter Bediensteter Henry, J

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 96/02939

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP,A,0 645 376 (MERCK PATENT GMBH) 29.März 1995 siehe Ansprüche -----	1-5

1

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentl.. ..ngen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 96/02939

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A-0623615	09-11-94	DE-A-	4405633	03-11-94
		AU-A-	6064394	03-11-94
		CA-A-	2122571	02-11-94
		CN-A-	1097421	18-01-95
		CZ-A-	9401019	16-11-94
		HU-A-	70541	30-10-95
		JP-A-	7002847	06-01-95
		NO-A-	941592	02-11-94
		SK-A-	48494	08-02-95
		US-A-	5532255	02-07-96
		ZA-A-	9402973	18-01-95
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		CN-A-	1073433	23-06-93
		WO-A-	9308181	29-04-93
		EP-A-	0609282	10-08-94
		JP-T-	7500327	12-01-95
		ZA-A-	9207955	13-08-93
EP-A-0635505	25-01-95	DE-A-	4324393	26-01-95
		AU-A-	6753694	02-02-95
		CA-A-	2128380	22-01-95
		CN-A-	1106008	02-08-95
		CZ-A-	9401738	17-05-95
		HU-A-	71110	28-11-95
		JP-A-	7070117	14-03-95
		NO-A-	942715	23-01-95
		PL-A-	304349	23-01-95
		SK-A-	85294	08-03-95
		US-A-	5561145	01-10-96
		ZA-A-	9405340	01-03-95
WO-A-9314077	22-07-93	AU-A-	3351293	03-08-93
		EP-A-	0623120	09-11-94
		JP-T-	7503459	13-04-95
		ZA-A-	9300377	29-11-93
EP-A-0645376	29-03-95	DE-A-	4332384	30-03-95
		AU-A-	7305094	06-04-95
		CA-A-	2132579	24-03-95

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffent.. ..ngen, die zur selben Patentfamilie gehören

I. ..ationales Aktenzeichen
PCT/EP 96/02939

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A-0645376		CN-A-	1106806	16-08-95
		CZ-A-	9402247	12-07-95
		HU-A-	71233	28-11-95
		JP-A-	7179441	18-07-95
		NO-A-	943523	24-03-95
		PL-A-	305144	03-04-95
		SK-A-	112194	10-05-95
		US-A-	5561148	01-10-96
		ZA-A-	9407405	15-05-95

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 413/10, A61K 31/42, C07D 417/14 | A1

(11) International Publication Number: **WO 97/09328**

(43) International Publication Date: 13 March 1997 (13.03.97)

(21) International Application Number: PCT/US96/12766

(22) International Filing Date: 13 August 1996 (13.08.96)

(30) Priority Data:
60/003,149 1 September 1995 (01.09.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 60/003,149 (CIP)
Filed on 1 September 1995 (01.09.95)

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

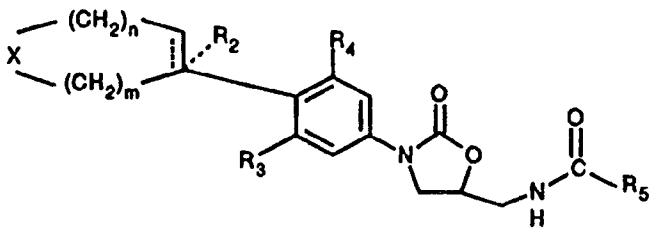
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HUTCHINSON, Douglas, K. [US/US]; 5641 Whitmore Drive, Kalamazoo, MI 49001 (US). ENNIS, Michael, D. [US/US]; 2416 Deep Forest Court, Portage, MI 49002 (US). HOFFMAN, Robert, L. [US/US]; 1522 Evanston Avenue, Kalamazoo, MI 49008 (US). THOMAS, Richard, C. [US/US]; 2166 Wild Cherry Lane, Kalamazoo, MI 49009 (US). POEL, Toni-Jo [US/US]; 304 Anderson, Wayland, MI 49348 (US). BARBACHYN, Michael, Robert [US/US]; 1216 Miles Avenue, Kalamazoo, MI 49001 (US). BRICKNER, Steven, J. [US/US]; 9 Fargo Drive, Ledyard, CT 06339 (US). ANDERSON, David, J. [GB/US]; 3809 Middlebury, Kalamazoo, MI 49006 (US).

(74) Agent: YANG, Lucy, X.; Pharmacia & Upjohn Company, Intellectual Property Law, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, 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: PHENYLOXAZOLIDINONES HAVING A C-C BOND TO 4-8 MEMBERED HETEROCYCLIC RINGS



(I)

(57) Abstract

A compound of formula (I), or pharmaceutical acceptable salts thereof wherein X is NR_1, $S(O)_g$, or O; R_1 is H, C_{1-6} alkyl optionally substituted with one or more OH, CN, or halo, or R_1 is $-(CH_2)_h$-aryl, $-COR_{1-1}$, $-COOR_{1-2}$, $-CO-(CH_2)_h-COR_{1-1}$, C_{1-6} alkyl sulfonyl,$-SO_2-(CH_2)_h$-aryl, or $-(CO)_i$-Het; R_2 is H, C_{1-6} alkyl, $-(CH_2)_h$-aryl, or halo; R_3 and R_4 are the same or different and are H or halo; R_5 is H, C_{1-12} alkyl optionally substituted with one or more halo, C_{3-12} cycloalkyl, C_{1-6} alkoxy. The compounds are useful antimicrobial agents.

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PHENYLOXAZOLIDINONES HAVING A C-C BOND TO 4-8 MEMBERED HETEROCYCLIC RINGS

BACKGROUND OF THE INVENTION

The present invention relates to new and useful N-phenyloxazolidinone compounds and their preparations, and more particularly to N-phenyloxazolidinone compounds in which the phenyloxazolidinone moiety is linked to a variety of saturated, or partially saturated, 4-8 membered heterocycles containing oxygen, nitrogen, and sulfur through a carbon-carbon bond.

The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as 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

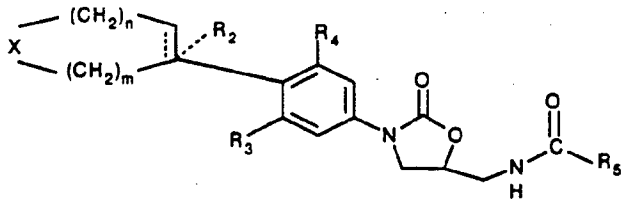
A series of Delalande patent applications (Derwent Abstracts 61219Y/35, 67436R-B, 84475A/47) disclose a saturated nitrogen heterocycle linked through the nitrogen atom to a phenyloxazolidinone moiety.

French Patent (FR2500450 A1 820827) discloses cyclohexenone attached at the 3-position to a phenyloxazolidinone.

Other references disclose fully aromatic heterocycles attached to a phenyloxazolidinone, including European Patent Publication 0352 781 A2, US Patent 5,130,316, US Patent 5,254,577, US Patent 4,948,801, and WO 9309103-A1, whereas in our present invention the heterocycle is saturated or partially saturated.

SUMMARY OF THE INVENTION

The present invention provides new compounds of the Formula (I)



(I)

or pharmaceutical acceptable salts thereof wherein:

X is

NR_1, $S(O)_g$, or O;

R_1 is

a) H,

b) C_{1-6} alkyl, optionally substituted with one or more OH, CN, or halo,

c) $-(CH_2)_h$-aryl,

d) $-COR_{1-1}$,

e) $-COOR_{1-2}$,

f) $-CO-(CH_2)_h-COR_{1-1}$,

g) $-SO_2-C_{1-6}$ alkyl,

h) $-SO_2-(CH_2)_h$-aryl, or

i) $-(CO)_i$-Het;

R_{1-1} is

a) H,

b) C_{1-6} alkyl, optionally substituted with one or more OH, CN, or halo,

c) $-(CH_2)_h$-aryl, or

d) $-(CH_2)_h-OR_{1-3}$;

R_{1-2} is

a) C_{1-6} alkyl, optionally substituted with one or more OH, CN, or halo,

b) $-(CH_2)_h$-aryl, or

c) $-(CH_2)_h-OR_{1-3}$;

R_{1-3} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_h$-aryl, or

d) $-CO(C_{1-6}$ alkyl);

R_2 is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_h$-aryl, or

d) halo;

R_3 and R_4 are the same or different and are

a) H, or

b) halo;

R_5 is

a) H,

b) C_{1-12} alkyl, optionally substituted with one or more halo,

c) C_{3-12} cycloalkyl,

d) C_{1-6} alkoxy;

g is 0, 1, or 2;

h is 1, 2, 3, or 4;

i is 0 or 1;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, 3, 4, or 5;

and with the provisio that m and n taken together are 1, 2, 3, 4, or 5.

More particularly, the present invention provides compounds of formula (I) wherein R_1 is H, fluoroethyl, cyanomethyl, methyl sulfonyl, formyl, hydroxyacetyl, acetyl, methoxyacetyl, benzyloxyacetyl, acetoxyacetyl, dichloroacetyl, methoxy carbonyl, tert-butoxy carbonyl, benzyloxy carbonyl, 3-hydroxypropionyl, 3-methoxypropionyl, 4-oxopentanoyl, 2-indole carbonyl, 5-isoxazole carbonyl, 5-nitro-2-thiazoyl, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl.

R_2 is H, F, or CH_3;

R_3 and R_4 are the same or different and are H or F; and

R_5 is methyl or methyl substituted with one or more F or Cl.

The present invention also provides a method for treating microbial infections in patients by administering to a patient in need thereof an effective amount of a compound of Formula (I). The compound can be administered orally, parenterally or topically in a pharmaceutical composition. Preferably, the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, the term "C_{1-6} alkyl" and the term "C_{1-12} alkyl" refer to any straight or branched alkyl group having one to six or one to twelve carbons respectively such as, for example, methyl, ethyl, n-propyl,

isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, n-octyl and the like.

The term "C_{1-6} alkyl sulfonyl" refers to any straight or branched alkyl group having one to six carbons attached to -SO_2 forming such groups as, for example, methyl sulfonyl, ethyl sulfonyl, isopropyl sulfonyl and the like.

The term "C_{3-12} cycloalkyl" refers to three to twelve carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "C_{1-4} alkoxy" and the term "C_{1-6} alkoxy" refer to any straight or branched alkyl group having one to four or one to six carbons , respectively, attached to an oxygen forming such groups as, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, isobutyloxy, sec-butyloxy, t-butyloxy, n-pentyloxy, isopentyloxy, n-hexyloxy, iso-hexyloxy and the like.

The term halo refers to fluoro, chloro, bromo, or iodo.

The term "aryl" refers to a phenyl, pyridyl or napthyl moiety which can be optionally substituted with one or more F, Cl, Br, I, CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} thioalkyl.

The term "Het" refers to 5 to 10 membered heterocyclic rings containing one or more oxygen, nitrogen, and sulfur forming such groups as, for example, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxathiole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 7-oxo-2-isoindolyl,1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-

dithiazolone. Each of these moieties may be substituted as appropriate.

The term "pharmaceutically acceptable salts" refers to salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citrate, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

In the structural representation of Formula (I) the dotted line in the heterocyclic ring means that this bond can be either single or double. In the case where the dotted line is a double bond, the R_2 group will not be present.

In a preferred embodiment of the N-phenyloxazolidinone compounds of the present invention, the X group is preferably NR_1, SO_2, or oxygen.

The R_1 substituent on the nitrogen atom can be introduced by synthetic methods known to those skilled in the art from commercially available reagents.

The preferred R_1 substituent is H, fluoroethyl, cyanomethyl, methyl sulfonyl, formyl, hydroxyacetyl, acetyl, methoxyacetyl, benzyloxyacetyl, acetoxyacetyl, dichloroacetyl, methoxy carbonyl, tert-butoxy carbonyl, benzyloxy carbonyl, 3-hydroxypropionyl, 3-methoxypropionyl, 4-oxopentanoyl, 2-indolecarbonyl, 5-isoxazole carbonyl, 5-nitro-2-thiazolyl, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl. The most preferred R_1 substituent is formyl, methoxy carbonyl, or hydroxyacetyl.

Where heterocyclic rings are the saturated derivatives, the preferred R_2 substituent is hydrogen, fluoro, or methyl.

The preferred R_3 and R_4 substituents are independently hydrogen or fluoro.

The preferred R_5 substituent is methyl.

The most preferred compounds in this series would be prepared as the optically pure enantiomers having the (S)-configuration according to the Cahn-Ingold-Prelog notation at C5 of the oxazolidinone ring. Optically pure material could be prepared by one of a number of asymmetric syntheses. For example, treatment of intermediate compound **12** in CHART B with an appropriate base, followed by addition of (R)-glycidyl butyrate would afford the corresponding oxazolidinone in optically pure form with the requisite (S)- configuration at the 5-position of the oxazolidinone ring. Although the (S)-enantiomer of this series of compounds is preferred since it is pharmacologically active as an antibacterial agent, the racemic modification is also useful in the same manner as the pure (S)-enantiomer; the difference being that twice as much racemic material is required to elicit the same antibacterial effect.

CHART A illustrates methods for preparing compounds of Formula (I)

having a heterocycle containing nitrogen. As shown in CHART A, the key intermediate **1** can be used to make derivatives by reactions known to those skilled in the art. For example, acylation affords **2** and **3**, the subsequent deprotection of **2** provides **2'**, alkylation affords **5** (the substituents including hydroxy, nitro, halo, aryl, and sulfonyl; structure **5** also encompasses products having a heteroatomic nucleus), sulfonylation affords **6**, and alkoxyacylation affords **4**.

A method for preparing compounds of intermediate **1** having a 4-membered heterocycle containing nitrogen in highly enantiomerically enriched form is depicted in CHART B. The first step involves treatment of structure **7** with ethyl cyanoacetate in the presence of an appropriate base, such as sodium hydride or potassium carbonate, at a temperature in the range of -10°C to 100°C. The subsequent alkylation using alkyl halides or tosylates affords nitrile derivative **8**. The nitrile derivative **8** is then reduced by catalytic hydrogenation in the presence of an appropriate catalyst, such as palladium on carbon, W-2 Raney nickel or platinum on sulfide carbon, in an appropriate solvent, such as ethyl acetate, THF, methanol or combinations thereof, to give amino-aniline **9**, which upon treatment with an appropriate base, preferably methyl or ethyl Grignard, affords the lactam **10**. Reduction of **10** by using an appropriate reducing agent, such as LAH or borane, gives the azetidine **11**, which reacted with benzyl chloroformate, at a temperature in the range of -10°C to 10°C, affords the corresponding benzyl carbamate derivatives **12**. The treatment of **12** with n-butyllithium in an appropriate solvent such as THF, at a temperature in the range of -78°C to -40°C, followed by addition of commercially available (R)-glycidyl butyrate dropwise would afford the corresponding oxazolidinone **13** in enantiomerically enriched form at the 5-position of the oxazolidinone ring. As shown in CHART B, compound **13** can be converted to the corresponding alkyl or aryl sulfonate **14** by treatment with alkyl or aryl sulfonyl chloride in the presence of triethylamine or pyridine (wherein R' is C_{1-4} alkyl or (un)substituted phenyl). The resultant sulfonate **14** is then treated with an alkali metal azide such as sodium or potassium azide, in an aprotic dipolar solvent such as DMF or N-methylpyrrolidinone (NMP), with an optional catalyst such as 18-crown-6, at a temperature in the range of 50°C to 90°C to afford azide derivatives. The azide derivatives can be reduced to the corresponding amine **15** by hydrogenation in the presence of a palladium, platinum or nickel catalyst, in an appropriate solvent such as ethyl acetate, THF, or methanol. Alternatively, amine **15** can be prepared by treating **14** with an appropriate solvent such as methanol and/or THF which is

saturated with ammonia and heating the mixture to 100°C in a sealed tube. The reaction occurs over hours, e.g., 40 - 70 hours. Amine **15** is then acylated with an acid chloride or anhydride in the presence of a base such as pyridine or triethylamine at temperatures ranging from -40°C to 40°C to provide the N-acyl oxazolidinone **16**. Finally, catalytic hydrogenation of **16** in the presence of a noble metal catalyst, such as palladium on carbon or palladium hydroxide on carbon affords the azetidine **17**. The azetidine **17** can be used to prepare derivative compounds demonstrated in CHART A.

The following compounds of Formula (I) having a 4-membered heterocycle containing nitrogen, for example, are prepared directly by the methods described in CHART A and CHART B:

(S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-(3-methyl)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(methoxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(dichloroacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(3-methoxypropionyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(3-hydroxypropionyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(4-oxopentanoyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-acetyl-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(2-fluoroethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(cyanomethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(5-nitro-2-thiazolyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-

oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(methanesulfonyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(benzyloxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide.

A second method for preparing compounds of intermediate **1** having a 4-membered heterocycle containing nitrogen, wherein R_2 is H, in highly enantiomerically enriched form is depicted in CHART C. The first step involves reaction of structure **18** with a protected aniline **19** in the presence of an appropriate base, such as *sec*-butyllithium, in an appropriate solvent, such as THF, at a temperature range of -40°C to -78°C to afford compounds **20**. Reaction of **20** with benzyl chloroformate at 0°C to 25°C gives compound **21** which reacts further at 25°C to 100°C to give compound **22**. Treatment of **22** with excess triethylsilane and trifluoroacetic acid in a suitable solvent such as methylene chloride, at a temperature range of 10°C to 40°C gives compound **23**. The remaining synthetic steps which lead to structure **17** are similar to the procedures outlined in CHART B.

The following compounds of Formula (I) having a 4-membered heterocycle containing nitrogen, for example, are prepared directly by the methods described in CHART A and CHART C:

(S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

CHART D depicts a method for preparing compounds of intermediate **1** having a 5-membered heterocycle containing nitrogen. As shown in CHART D, the first step involves the coupling of vinyltributyltin **24** (commercially available) and compound **25**. The compound **25** can be prepared according to the procedures described in PCT/US92/08267 and PCT/US93/09589. The coupling occurs in the presence of palladium catalyst to afford compound **26**. The reaction is carried out at

a high temperature for several hours, e.g., reflux for 5-8 hours. The compound **26** is then treated with a solution of N-benzyl-N-(methoxymethyl)trimethylsilyl-methylamine (prepared according to the literature from commercially available material) and trifluoroacetic acid in an appropriate solvent to provide **27**. The reaction occurs over several hours, e.g., 8-17 hours. The N-benzyl group of **27** is then removed by catalytic hydrogenation in the presence of a noble metal catalyst, such as palladium on carbon or palladium hydroxide on carbon to afford **28**. The compound **28** can be used to prepare the derivative compounds demonstrated in CHART A. Following a similar procedure and making non-critical variations but substituting different vinyl tributylstannyl derivatives for structure **24**, a variety of other heterocyclic derivatives of compound **26** can be obtained as illustrated in EXAMPLE 80.

Alternatively, another method for preparing compounds of intermediate **1** having a 5-membered heterocycle containing nitrogen is depicted in CHART E. As shown in CHART E, nucleophilic aromatic substitution of **7** with dimethylmalonate (commercial available) affords the adduct **29**. The reaction occurs in an appropriate solvent such as THF, at a temperature in the range of -100°C to 60°C. The compound **29** is readily alkylated by a reaction known to those skilled in the art to provide nitrile **30**. Catalytic reduction of **30** in the presence of a palladium, platinum or nickel catalyst, in an appropriate solvent such as methanol converts both nitro and nitrile to amines with concommittant intramolecular cyclization to afford the lactam **31**. The lactam **31** is then decarboxylated to provide **32**, which upon reduction with an appropriate reducing agent such as lithium aluminum hydride or borane, in an appropriate solvent such as THF or ether, affords compound **33**. The remaining synthetic steps which lead to structure **34** are similar to the procedures outlined in CHART B.

The following compounds of Formula (I) having a 5-membered heterocycle containing nitrogen, for example, are prepared directly by the methods described in CHART A, CHART D and CHART E:

(S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2 fluorophenyl]-1-pyrrolidinecarboxylic acid methyl ester.

Following the general procedure depicted in CHART D for the preparation of compound **26** and making non-critical variations but substituting 6-(tributylstannyl)-3,4-dihydro-2H-dihydropyran for structure **24**, the following compound is prepared:

(*S*)-N-[[3-[3-Fluoro-4-(3,4-dihydro-2H-pyran-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A method for preparing compounds of formula (I) having a 5-membered heterocycle containing a sulfur atom, oxygen atom, sulfone group or sulfoxide group in highly enantiomerically enriched form wherein R_3 or R_4 is halo is depicted in CHART F. As shown in CHART F, structure **35** (wherein X is O or S) is reacted with a protected aniline **19** in the presence of an appropriate base, such as *sec*-butyllithium, in an appropriate solvent, such as THF, at a temperature range of -40°C to -78°C to afford compounds **36**. Reaction of **36** with benzyl chloroformate at 0°C to 25°C gives compound **37**. The subsequent elimination reaction known to those skilled in the art affords regiosiomers **38** and **39** as a mixture. Following the general procedure outlined in CHART B provides compounds **40** and **41** as a mixture. In the case where X is S, the sulfur group can be oxidized by an appropriate oxidizer such as N-methylmorpholine N-oxide and osmium tetroxide in an appropriate solvent such as mixtures of water and acetone, or by $NaIO_4$ in an appropriate solvent such as mixtures of water and methanol, to provide the corresponding sulfones and sulfoxides, respectively. When it is desirable, the double bond in the heterocycle ring may be reduced by catalytic hydrogenation in the presence of an appropriate catalyst and a suitable solvent. Furthermore, in the case where X is O, SO, or SO_2, the regioisomeric mixture of **40** and **41** can be separated by chromatography as illustrated in EXAMPLEs 68 and 69.

The following compounds of Formula (I) having a 5-membered heterocycle containing a sulfur atom, oxygen atom, sulfone group or sulfoxide group, for example, are prepared directly by the method of CHART F:

(S)-(-)-N-[[3-[3-Fluoro-4-(dihydrothien-3-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1-oxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-(4,5-dihydro-1-oxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide.

A method for preparing compounds having a 6-membered heterocycle containing a nitrogen atom, sulfur atom, oxygen atom, sulfone group or sulfoxide group wherein R_3 and R_4 are hydrogen is depicted in CHART G. As shown in CHART G, the first step involves the condensation of structures **42** and **43** (wherein X is O, S, or N) to afford compound **44**. In the case where X is a nitrogen atom, the amino group should be protected with an appropriate protecting group such as carbobenzyloxy (CBz). The protecting group is optionally removed after the synthesis to give compounds **46** or **47** (wherein X is NH), which can be used to prepare the derivative compounds demonstrated in CHART A. The reaction of **42** with **43** occurs in an appropriate solvent such as THF, at an appropriate temperature such as -78°C to -40°C, in the presence of a lithium base such as n-butyllithium. The subsequent elimination reaction known to those skilled in the art provides compound **45**. The remaining synthetic steps which lead to the compound **46** are similar to the procedures outlined in CHART B. When it is desirable, the double bond in the heterocyclic ring may be reduced to give **47** by catalytic hydrogenation; and when X is a sulfur atom, the sulfur group can be oxidized to afford the corresponding sulfones and sulfoxides as described above for CHART F.

CHART H depicts a method for preparing compounds having a 6-membered heterocycle wherein substitutes R_3 and/or R_4 are halo. As shown in CHART H, structure **48** (X is O, S, or NR wherein R is an appropriate protecting group) is reacted with a protected aniline **19** in the presence of an appropriate base, such as sec-butyllithium in an appropriate solvent such as THF at a temperature in the range of -40°C to -78°C, followed by the addition of zinc chloride and an appropriate catalyst such as tetrakis(triphenylphosphine) palladium with further reaction at reflux to afford compound **49**. Optionally, in the case where X is nitrogen, structure **49** can be reduced to the saturated derivatives at this point and carried on, or structure **49** can be acylated by the reaction known to those skilled in the art to provide structure **50**. The remaining synthetic steps which lead to compound **51** are similar to the procedures outlined in CHART B. In the case where X is a sulfur atom, the sulfur group of structure **51** can be oxidized to afford the corresponding sulfones and sulfoxides as described above. In addition, where X is O, NR, or SO_2, structure **51** may be reduced to saturated derivatives by catalytic hydrogenation in the presence of an appropriate catalyst and a suitable solvent to provide the saturated derivative **52**. As stated above, in the case where X is a nitrogen atom,

the amino group is protected during the preparation with an appropriate protecting group. In this case, the preferred protecting group is 1,1-dimethylethyl carbamate (BOC). The protecting group is removed after the synthesis, and the resultant compound can used to prepare the derivative compounds demonstrated in CHART A.

The following compounds of Formula (I) having a 6-membered heterocycle containing a nitrogen atom, sulfur atom, oxygen atom, sulfone group or sulfoxide group, for example, are prepared directly by the methods of CHART A, CHART G, and CHART H:

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid phenylmethyl ester;

(S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Indole-2-carbonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Isoxazole-5-carbonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Methylsulfonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid methyl ester;

(S)-(-)-N-[[3-[4-[1-(Cyanomethyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(2-Fluoroethyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[[(2,2-Dichloroacetyl)amino]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-(hydroxyacetyl)-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide;

(S)-(-)-N-[[3-[4-(Tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

CHART I depicts a method for preparing compounds of intermediate **1** which have a partially saturated 6-membered heterocycle containing nitrogen in highly enantiomerically enriched form. As shown in CHART I, the first step involves the coupling of structure **53** and structure **54** to provide compounds **55** and **56**. The triflate group of structure **53** may be at either side of the double bond, wherein both are readily prepared from the corresponding commercially available ketones. The structure **54** may be prepared according to the procedures described in PCT/US92/08267 and PCT/US93/09589. The reaction occurs over a few days, e.g. 1-5 days in the presence of an appropriate catalyst such as tris(dibenzylideneacetone)dipalladium(0). The amino protecting group of **55** is removed by treatment with iodotimethylsilane and that of **56** is removed by treatment with either trifluoroacetic acid or iodotrimethylsilane to give the corresponding compounds **57** and **58**. Compounds **57** and **58** can be used to prepare the derivative compounds demonstrated in CHART A.

Following the general procedure as described above, and making non-critical variations but substituting 7- or 8-membered rings for the 6-membered ring of structure **53**, compounds that have a 7- or 8-membered heterocycle containing nitrogen in highly enantiomerically enriched form can be prepared. Their preparations are illustrated in further detail in EXAMPLEs 75 to 79.

The following compounds of Formula (I) for example, are prepared directly by the methods of CHART A and CHART I:

(S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-3,6-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester;

(S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester;

(S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-3-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[4-[1-(Hydroxyacetyl)-5,6-dihydro-2H-pyridin-3-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)hexahydro-1H-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A second method for preparing compounds of intermediate **1** which have a partially saturated 6-membered heterocycle containing nitrogen in highly enantiomerically enriched form is depicted in CHART J. As shown in CHART J, structure **59** is reacted with a protected aniline **19** to afford structure **60**. The subsequent acylation reaction provides structure **61** which is treated with an appropriate acid to give a mixture of **62** and **63**. The regioisomers can be separated by chromatography as described in EXAMPLEs 72 and 73 and carried on. The protecting groups then are removed by treatement with iodotrimethylsilane to give the desired compounds **64** and **57**, which can be used to prepare the derivative compounds demonstrated in CHART A. Use of the 4-keto isomer of structure **59**

provides an alternate route to the 4-isomer, structure **58**. Alternatively, the hydroxy group of structure **61** or its 4-isomer may be replaced by a fluoro atom using an appropriate agent such as diethylaminosulfur trifluoride in an appropriate solvent such as methylene chloride. The elimination step shown for structure **61** is not conducted in this situation. This replacement reaction is further detailed in EXAMPLE 74.

The following compounds of Formula (I) for example, are prepared directly by the methods of CHART A and CHART J.

(S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,4-dihydro-2H-pyridin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,4-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(S)-(-)-N-[[3-[4-[1-Formyl-4-fluoro-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

These compounds are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration.

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., 2-4 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) or 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 are compared against well-known antimicrobials vancomycin and U-100592 as controls. See "Upjohn Oxazolidinone Antibacterial Agent", posters presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. The data are shown in Table 1 and Table 2.

TABLE 1

EXAMPLE No.	ED_{50}(mg/kg)	Vancomycin ED_{50}(mg/kg)
3	5.00	3.00
4	>20.00	3.10
5	3.60	1.30
6	>20.00	5.00
10	20.00	2.00
11	>20.00	2.90
12	20.00	2.00
13	>10.00	1.50
16	17.00	3.60
19	6.80	1.80
21	>20.00	1.80
22	2.30	2.40
23	>20.00	1.60

24	>20.00	1.90
28	15.30	1.90
29	5.00	1.90
33	10.60	1.60
34	6.30	1.60
37	8.70	1.80
39	3.00	1.80
40	1.00	1.80
44	5.00	0.90
47	7.10	1.90

TABLE 2

EXAMPLE No.	ED_{50}(mg/kg)	U-100.592 ED_{50}(mg/kg)
45	2.80	2.10
46	7.90	2.30
48	17.50	2.10
49	2.40	2.10
50	2.20	2.90
51	2.80	5.20
52	4.00	2.30
53	>20.00	2.30
54	6.60	2.90
55	2.30	2.50
56	4.40	2.70

57	6.20	2.70
59	4.2	4.40
60	3.1	4.40
61	6.10	2.70
62	12.0	2.40
63	4.90	4.60
64	4.60	2.90
67	13.3	6.0
68(a)	3.50	3.50
69(a)	10.0	7.80
71	13.4	4.40
74	10.3	4.40
76	>20	3.50
78	6.0	3.20
83	7.50	4.10
84	6.50	4.10

In order to more fully illustrate the nature of the invention and the manner of practicing the same, the following experimental examples are presented.

EXAMPLE 1 (S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-(3-methyl)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl-acetamide

Step 1: Ethyl 1-cyano-1-(4-nitro-2-fluorophenyl)propionate

A flame-dried 3-neck 1-L round bottom flask equipped with a magnetic spinbar and addition funnel was charged with 6.40 g sodium hydride (0.160 mol, 60% oil dispersion) followed by washing with pentane (3 x 40 mL) and drying under house vacuum. The hydride was suspended in 100 mL tetrahydrofuran, cooled to 0°C, and treated with a solution of ethyl cyanoacetate (8.6 mL, 0.080 mol) in 150 mL THF over 15 minutes with gas evolution. The resulting milky solution of enolate was stirred five minutes then treated with a solution of 3,4-difluoronitrobenzene (I)

(8.8 mL, 0.080 mol) in 150 mL THF with immediate orange coloration. The cooling bath was removed and the reaction mixture was warmed to 50°C for 18 hours. The now red suspension was cooled to room temperature and successively treated with 100 g iodomethane (0.72 mol), 33 g potassium carbonate (0.24 mol), and 100 mL acetone. The visually unchanged solution was warmed to 60°C for an additional 16 hours. The now tan suspension was cooled to room temperature, filtered through a pad of CELITE, and the filtrate was concentrated *in vacuo*. The resulting residue was diluted with 500 mL water and extracted twice with ethyl acetate (500 mL). The combined organics were washed once with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to give 21.39 g of a brown oil. This crude material was purified by LC on 850 g (230-400) silica gel eluting with 20% ethyl acetate/hexanes to afford 18.14 g (100%) of the title compound as a yellow oil that spontaneously crystallized. mp 56.0-57.0°C; R_f 0.34 (20% ethyl acetate/hexanes); IR (neat) 1752, 1534, 1423, 1355, 1248, 1239, 1213, 1099, 811, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (m, 1H, aromatic), 8.03 (dd, 1H, J=2.3 Hz, J=10.4 Hz, aromatic), 7.80 (dd, 1H, J=7.6 Hz, J=8.6 Hz, aromatic), 4.33 (m, 2H, O-CH_2), 2.04 (s, 3H, CH_3), 1.28 (t, 3H, J=7.2 Hz, O-CH_2-$\underline{CH_3}$). HRMS Calcd for $C_{12}H_{11}N_2O_4F_1 + H_1$: 267.0781. Found: 267.0799.

Step 2: Ethyl 1-aminomethyl-1-(4-amino-2-fluorophenyl)propionate

A solution of ethyl 1-cyano-1-(4-nitro-2-fluorophenyl)propionate (17.9 g, 67.3 mmol) in absolute ethanol (500 mL) was treated with Raney-Nickel (30.9 g of a 50% slurry in water) and subjected to hydrogenation in a Parr apparatus for 17 hours (25-30 psi H_2, room temperature). The reaction mixture was then filtered through Celite (repeated EtOH washings) and concentrated in vacuo (heat gun, Hi-vac) to give the title compound as a golden syrup (15.6 g, 97%). This material could be purified by chromatography on silica gel using 15% methanol/ethyl acetate but was typically carried on to the next step without further purification: R_f 0.32 (15% MeOH/EtOAc); ^1H NMR ($CDCl_3$) δ 7.00 (t, J=8.5, 1H, aromatic), 6.45 (dd, J=8.2, 2.3, 1H, aromatic), 6.36 (dd, J=13.1, 2.4, aromatic), 4.18 (q, J=7.0, 3H, -$CH_2\underline{CH_3}$), 3.76 (br s, 2H, NH_2), 3.06 (dd, J=18.2, 13.8, 2H, CH_2N), 1.52 (s, 3H, CCH_3), 1.21 (t, J=7.1, 2H, -$\underline{CH_2}CH_3$); IR (liquid) 1722, 1634, 1513, 1445, 1305, 1283, 1243, 1172, 1132, 845 cm^{-1}; HRMS: Calcd ($C_{12}H_{17}F_1N_2O_2$) 240.1274; Found 240.1293.

Step 3: 3-Methyl-3-(4-amino-2-fluorophenyl)-azetidinone

A solution of ethyl 1-aminomethyl-1-(4-amino-2-fluorophenyl)propionate (2.1 g, 8.7 mmol) in THF (50 mL) was added slowly via syringe to a cold (0°C) solution of methyl magnesium bromide (15 mL of a 3 M solution in ether, 45 mmol, diluted

with 100 mL THF). When addition was complete, the syringe was rinsed with additional THF (2 x 12 mL). The cooling bath was removed and the beige solution was allowed to stir at room temperature for three hours, at which point it was poured into saturated ammonium chloride (aq, ca. 500 mL) and volatiles were removed in vacuo. The resulting aqueous phase was extracted three times with *t*-butyl methyl ether and the combined organics were washed once with water, once with brine, dried over $MgSO_4$, filtered, and concentrated to give 1.4 g of a yellow syrup. Extraction of the aqueous phase with ethyl acetate provided and additional 190 mg crude product. The crude products thus obtained were combined and chromatographed on silica gel using 50% ethyl acetate/hexane to give the title compound (1.0 g, 60%) as a pale yellow solid, mp 125-127 °C: R_f 0.21 (50% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.46 (t, J=8.3, 1H, aromatic), 6.43-6.35 (m, 2H, aromatics), 5.77 (br s, 1H, NH), 3.75 (br s, 2H, NH_2), 3.54 (dd, J=5.5, 2.4, 1H, CH_2), 3.45 (d, J=5.5, 1H, CH_2), 1.64 (s, 3H, CH_3); IR (mull) 3439, 3342, 3236, 1738, 1635, 1516, 1441, 1210, 1146, 631 cm^{-1}; Anal. calcd for $C_{10}H_{11}F_1N_2O_2$; C, 61.84, H, 5.71, N, 14.43. Found: C, 62.13, H, 5.81, N, 14.36.

Step 4: 3-(4-Amino-2-fluorophenyl)-3-methylazetidine

A flame-dried 3-neck 2-L round bottom flask equipped with mechanical stirrer, reflux condenser, and addition funnel was charged with 300 mL tetrahydrofuran and 350 mL 1M lithium aluminumhydride (0.35 mol) followed by cooling to 0°C. This solution was treated with a solution of 9.85 g 3-Methyl-3-(4-amino-2-fluorophenyl)-2-azetidinone (0.051 mol) in 210 mL THF with gas evolution and a yellow coloration. The cooling bath was removed and the reaction was heated to reflux with the rapid formation of a white precipitate. After 20 hours, the visually unchanged reaction mixture was cooled to room temperature and quenched by the successive addition of 13 mL water, 12 mL 5M sodium hydroxide, and 47 mL water. The resulting thick gelatinous suspension was diluted with one L ethyl acetate, filtered through a pad of CELITE, concentrated, and high vacuum dried to afford 9.82 g of the title compound as a light orange syrup. ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (t, 1H, J=8.5 Hz, aromatic), 6.37 (m, 2H, aromatic), 4.06 (d, 2H, J=8.2 Hz, N-CH_{2a}s), 3.81 (bs, 3H, NHs), 3.58 (d, 2H, J=8.2 Hz, N-CH_{2b}s), 1.65 (s, 3H, CH_3).

Step 5: N-Carbobenzyloxy-3-(N-carbobenzyloxy-3-fluoroanilin-4-yl)-3-methylazetidine

A 500 mL round bottom flask equipped with a magnetic spinbar and addition funnel was charged with 85 mL water, 38.4 g sodium bicarbonate (0.46

mol) and a solution of 9.82 g 3-(4-amino-2-fluorophenyl)-3-methylazetidine (0.051 mol theory) in 165 mL acetone. The resulting orange suspension was cooled to 0°C and treated with 43 mL benzylchloroformate (0.30 mol) with gas evolution and the reaction turning a light yellow color. The cooling bath was removed and the reaction mixture was stirred at room temperature for 65 hours. TLC indicates incomplete consumption of the starting aminoaniline and an additional 12.8 g sodium bicarbonate (0.15 mol) and 14 mL benzylchloroformate (0.10 mol) was added with additional gas evolution. After two hours, the reaction mixture was diluted with 350 mL saturated sodium bicarbonate and extracted three times with ethyl acetate (300 mL). The combined organics were washed once with water (200 mL), once with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to give 29.86 g of a light yellow oil. This crude material was purified by LC on 850 g (230-400) silica gel eluting with 25% ethyl acetate/hexanes to afford 11.67 g (51%) of the title compound as a light yellow solid. R_f 0.18 (25% ethyl acetate/hexanes); IR (neat) 1735, 1707, 1693, 1600, 1534, 1455, 1424, 1414, 1221, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 11H, aromatic), 6.96 (m, 3H, aromatic & NH), 5.19 (s, 2H, Ph-CH_2), 5.09 (s, 2H, Ph-CH_2), 4.30 (d, 2H, J=8.2 Hz, N-CH_{2a}s), 4.00 (d, 2H, J=8.4 Hz, N-CH_{2b}s), 1.59 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 160.4 (d, J_{CF}=245 Hz), 156.6, 153.0, 138.1 (d, J_{CF}=11 Hz), 136.5, 135.7, 128.6, 128.4, 128.2, 127.9, 127.8, 127.5, 127.0, 126.9, 113.9, 106.6 (d, J_{CF}=27 Hz), 67.1, 66.6, 60.8, 60.2, 36.1, 28.2; Anal. Calcd for $C_{26}H_{25}N_2O_4F_1$: C, 69.63; H, 5.62; N, 6.25. Found: C, 69.37; H, 5.69; N, 5.87.

Step 6: (R)-(-)-N-Carbobenzyloxy-3-methyl-3-[2-fluoro-4-[5-hydroxymethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine

A 500 mL round bottom flask containing 11.48 g N-carbobenzyloxy-3-(N-carbobenzyloxy-3-fluoroanilin-4-yl-3-methylazetidine (25.6 mmol) was equipped with a magnetic spinbar, charged with 100 mL tetrahydrofuran (freshly distilled), and cooled to -78°C. This light yellow homogenous solution was treated with 16.6 mL n-butyllithium (26.6 mmol) with a slight darkening in color. The carbamate ion was stirred 30 minutes at this reduced temperature followed by treatment with 3.8 mL R-glycidylbutyrate (26.6 mmol) with no observable change. The cooling bath was removed and the reaction was warmed to room temperature for 16 hours. The now orange opaque solution was diluted with 200 mL saturated ammonium chloride and extracted twice with ethyl acetate (250 mL). The combined organics were washed once with saturated sodium bicarbonate (200 mL), once with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to give 15.72 g of the title

compound as an orange oil. This crude material was purified by LC on 530 g (230-400) silica gel eluting with 80% ethyl acetate/hexanes to afford 6.79 g (64%) of a light yellow amorphous solid. R_f 0.28 (80% ethyl acetate/hexanes); $[\alpha]_D$ -35°(c 0.8967, methanol); IR (neat) 1754, 1708, 1516, 1454, 1429, 1415, 1358, 1228, 1194, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, 1H, J=2.2 Hz, J=13.0 Hz, aromatic), 7.33 (m, 5H, aromatic), 7.19 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.03 (t, 1H, J=8.7 Hz, aromatic), 5.09 (s, 2H, Ph-CH_2), 4.73 (m, 1H, methine), 4.30 (d, 2H, J=8.2 Hz, Ph-C-CH_{2a}s), 3.97 (m, 5H, Ph-C-CH_{2b}s, Ph-N-CH_2s, HO-CH_{2a}), 3.73 (m, 1H, HO-CH_{2b}), 2.80 (t, 1H, J=6.3 Hz, HO), 1.60 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 160.2 (d, J_{CF}=246 Hz), 156.5, 154.2, 138.0 (d, J_{CF}=11 Hz), 136.3, 128.2, 128.1, 127.8, 127.7, 126.9 (d, J_{CF}=7 Hz), 113.1 (d, J_{CF}=3Hz), 106.2 (J_{CF}=27 Hz), 72.6, 66.5, 62.4, 60.1, 46.0, 35.9, 28.0; Melt solvate = 3.8% ethyl acetate; Anal. Calcd for $C_{22}H_{23}N_2O_5F_1$ plus 3.8% ethyl acetate: C, 63.41; H, 5.73; N, 6.50. Found: C, 63.15; H, 5.52; N, 6.58. HRMS Calcd for $C_{22}H_{23}N_2O_5F_1$: 415.1169. Found: 415.1674.

Step 7: (R)-(-)-N-Carbobenzyloxy-3-methyl-3-[2-fluoro-4-[5-hydroxymethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine methone sulfuride ester

A 500 mL round bottom flask containing 6.55 g (R)-(-)-N-carbobenzyloxy-3-methyl-3-[2-fluoro-4-[5-hydroxymethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine (15.3 mmol) was equipped with a magnetic spinbar, charged with 150 mL dichloromethane, and cooled to 0°C. This light yellow homogenous solution was treated successively with 3.2 mL triethylamine (23.0 mmol) and 1.4 mL methanesulfonyl chloride (18.4 mmol) with no observable change. The cooling bath was removed and the reaction mixture was warmed to room temperature for one hour. The visually unchanged solution was diluted with 100 mL 0.5 N hydrochloric acid, shaken, layers separated and the acidic layer extracted once with dichloromethane (100 mL). The combined organics were washed once with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated to give 7.68 g (100%) of the title compound as a light yellow amorphous solid. R_f 0.40 (80% ethyl acetate/hexanes); IR (mull) 1758, 1703, 1516, 1418, 1358, 1337, 1230, 1176, 1075, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, 1H, J=2.2 Hz, J=12.8 Hz, aromatic), 7.33 (m, 5H, aromatic), 7.17 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.06 (t, 1H, J=8.5 Hz, aromatic), 5.10 (s, 2H, Ph-CH_2), 4.92 (m, 1H, methine), 4.50 (dd, 1H, J=3.6 Hz, J=11.7 Hz, MsO-CH_{2a}), 4.42 (dd, 1H, J=4.1 Hz, J=11.7 Hz, MsO-CH_{2b}), 4.31 (d, 2H, J=8.1 Hz, Ph-C-CH_{2a}s), 4.13 (t, 1H, J=9.2 Hz, Ph-N-CH_{2a}), 4.00 (d, 1H, J=8.5 Hz, Ph-C-CH_{2b}s), 3.94 (dd, 1H, J=6.2 Hz, J=9.2 Hz, Ph-N-CH_{2b}), 3.10

(s, 3H, S-CH_3), 1.62 (s, 3H, C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 160.3 (d, J_{CF}=247 Hz), 156.5, 153.3, 137.6 (d, J_{CF}=11 Hz), 136.4, 129.0, 128.8, 128.3, 127.9, 127.8, 127.3, 127.2 (d, J_{CF}=6 Hz), 113.3 (d, J_{CF}=3 Hz), 106.5 (d, J_{CF}=28 Hz), 69.4, 67.8, 66.6, 60.4, 46.2, 37.7, 36.1, 28.1; Anal. Calcd for $C_{23}H_5N_2O_7F_1S_1$: C, 56.09; H, 5.12; N, 5.69. Found: C, 55.76; H, 5.17; N, 5.61.

Step 8: (R)-(-)-N-Carbobenzyloxy-3-methyl-3-[2-fluoro-4-[5-aminomethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine

Two oven-dried 100 mL sealable tubes equipped with magnetic spinbars were equally charged with a solution of 7.50 g (R)-(-)-N-carbobenzyloxy-3-methyl-3-[2-fluoro-4-[5-hydroxymethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine methone sulfuride ester (15.2 mmol) in 75 mL methanol and 75 mL tetrahydrofuran (freshly distilled). These light yellow homogenous solutions were saturated with gaseous ammonia over ten minutes becoming almost colorless, sealed with teflon screwcaps, and heated to 100°C for 64 hours. The reaction mixtures were combined and concentrated to afford the title compound as a crude yellow foam.

Step 9: (S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-(3-methyl)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

The title compound was prepared as follows: (R)-(-)-N-carbobenzyloxy-3-methyl-3-[2-fluoro-4-[5-aminomethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine was diluted with 220 mL dichloromethane, cooled to 0°C, and successively treated with 3.7 mL pyridine (46 mmol) and 1.8 mL acetic anhydride (19 mmol) with no observable change. The cooling bath was removed and the reaction mixture was warmed to room temperature for 16 hours. The visually unchanged solution was concentrated to a yellow foam, rediluted with 50 mL dichloromethane, and filtered to remove the remaining insoluble precipitate. The filtrate was purified by LC on 340 g (230-400) silica gel eluting with 2.5% methanol/ethyl acetate to afford 5.85 g (84%) of (S)-N-[[3-[3-fluoro-4-[1-(carbobenzyloxy)-(3-methyl)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide as a colorless glass. R_f 0.24 (2.5% methanol/ethyl acetate); $[\alpha]_D$ -19°(c 0.9971, methanol); IR (mull) 1754, 1706, 1676, 1516, 1430, 1415, 1357, 1227, 1194, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, 1H, J=2.1 Hz, J=12.9 Hz, aromatic), 7.33 (m, 5H, aromatic), 7.13 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.04 (t, 1H, J=8.5 Hz, aromatic), 6.56 (bt, 1H, J=6.2 Hz, NH), 5.10 (s, 2H, Ph-CH_2), 4.79 (m, 1H, methine), 4.30 (d, 2H, J=8.2 Hz, Ph-C-CH_{2a}s), 4.01 (m, 3H, Ph-C-CH_{2b}s, Ph-N-CH_{2a}), 3.78 (dd, 1H, J=6.7 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.64 (m, 2H, NH-CH_2s), 2.02 (s, 3H, O=C-CH_3), 1.60, (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 160.3 (d, J_{CF}=246 Hz), 156.6, 154.2, 137.9

(d, J_{CF}=11 Hz), 136.5, 128.9 (d, J_{CF}=14 Hz), 128.4, 127.9, 127.2 (d, J_{CF}=7 Hz), 113.2 (d, J_{CF}=2 Hz), 106.4 (d, J_{CF}=28 Hz), 72.0, 66.6, 60.7, 60.3, 47.3, 41.7, 36.1, 28.1, 22.9; Anal. Calcd for $C_{24}H_{26}N_3O_5F_1$: C, 63.29; H, 5.75; N, 9.23. Found: C, 62.98; H, 5.96; N, 8.98.

EXAMPLE 2 (S)-N-[[3-[3-Fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

A 500 mL Parr flask was charged with a solution of 5.83 g (S)-N-[[3-[3-fluoro-4-[1-(carbobenzyloxy)-(3-methyl)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (12.8 mmol) in 100 mL methanol and 1.17 g 10% palladium on carbon. The black suspension was placed under 40 psi hydrogen with shaking for four hours with the pressure remaining constant at 28 psi. The Parr was removed from the hydrogenator, the reaction mixture was filtered through a pad of CELITE, and concentrated to afford 4.05 g (99%) of an off-white amorphous solid. A 1.00 g portion of this material was purified by LC on 100 g (230-400) silica gel eluting with 2: 17: 83 NH_4OH/methanol/dichloromethane to afford 776 mg of the title compound as a colorless glass. R_f 0.26 (2: 17: 83 NH_4OH/methanol/dichloromethane); $[\alpha]_D$ -23°(c 0.9015, methanol); IR (mull) 1752, 1662, 1630, 1554, 1515, 1483, 1435, 1412, 1227, 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, 1H, J=2.2 Hz, J=12.8 Hz, aromatic), 7.12 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 6.99 (t, 1H, J=8.6 Hz, aromatic), 6.33 (bt, 1H, J=6 Hz, O=C-NH), 4.78 (m, 1H, methine), 4.04 (m, 3H, Ph-C-CH_{2a}s, Ph-N-CH_{2a}), 3.78 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.66 (m, 2H, NH-CH_2s), 3.56 (d, 2H, J=7.8 Hz, Ph-C-CH_{2b}s), 2.40 (bs, 1H, NH), 2.02 (s, 3H, O=C-CH_3), 1.67 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 160.0 (d, J_{CF}=246 Hz), 154.2, 137.3 (d, J_{CF}=11 Hz), 130.8 (d, J_{CF}=15 Hz), 126.9 (d, J_{CF}=7 Hz), 113.2, 106.3 (d, J_{CF}=27 Hz), 71.9, 58.0, 47.3, 41.7, 40.5, 27.3, 22.9; K.F. Water = 0.89%; Anal. Calcd for $C_{16}H_{20}N_3O_3F_1$ with 0.89% water: C, 59.27; H, 6.32; N, 12.96. Found: C, 59.07; H, 6.45; N, 12.89. HRMS Calcd for $C_{16}H_{20}N_3O_3+H_1$: 322.1567. Found: 322.1569.

EXAMPLE 3 (S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 25 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 8 mL dichloromethane, and cooled to

0°C. The colorless but slightly opaque solution was treated with 0.16 mL triethylamine (1.1 mmol) and 70 µL methylchloroformate (0.90 mmol) with the reaction mixture becoming clear. The cooling bath was removed and the reaction mixture was warmed to room temperature over two hours. The visually unchanged solution was diluted with 30 mL dichloromethane, washed once with water (20 mL), once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 267 mg of a white foam. This crude material was purified by LC on 18 g (230-400) silica gel eluting with 5% methanol/dichloromethane to afford 219 mg (77%) of the title compound as a white foam. R_f 0.30 (5% methanol/dichloromethane); $[\alpha]_D$ - 21°(c 1.0194, methanol); IR (mull) 1755, 1706, 1676, 1631, 1517, 1394, 1227, 1208, 1195, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, 1H, J=2.2 Hz, J=12.9 Hz, aromatic), 7.14 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.05 (t, 1H, J=8.6 Hz, aromatic), 6.35 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.28 (d, 2H, J=8.2 Hz, CO_2-N-CH_{2a}s), 4.04 (t, 1H, J=9.0 Hz, Ph-N-CH_{2a}), 3.97 (d, 2H, J=8.4 Hz, CO_2-N-CH_{2b}s), 3.77 (dd, 1H, J=6.7 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.68 (m, 5H, NH-CH_2s, OCH_3), 2.03 (s, 3H, O=C-CH_3), 1.61 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 170.9, 160.2 (d, J_{CF}=246 Hz), 157.1, 154.0, 137.8 (d, J_{CF}=11 Hz), 128.5 (d, J_{CF}=15 Hz), 127.0 (d, J_{CF}=7 Hz), 113.1 (d, J_{CF}=3 Hz), 106.3 (d, J_{CF}=27 Hz), 71.8, 60.4, 52.1, 47.2, 41.7, 35.9, 28.0, 22.9; K.F. Water = 1.19%; Anal. Calcd for $C_{18}H_{22}N_3O_5F_1$ plus 1.19% water: C, 56.31; H, 5.91; N, 10.94. Found: C, 56.27; H, 5.93; N, 10.93.

EXAMPLE 4 (S)-N-[[3-[3-Fluoro-4-[1-(methoxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 25 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 8 mL dichloromethane, and cooled to 0°C. The colorless but slightly opaque solution was treated with 0.16 mL triethylamine (1.1 mmol) and 85 µL methoxyacetylchloride (0.90 mmol) with a smokey/haze developing. The cooling bath was removed and the reaction mixture was warmed to room temperatue over two hours. The now clear colorless solution was diluted with 25 mL dichloromethane, washed once with water (15 mL), once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 294 mg of a white foam. This crude material was purified by LC on 27 g (230-400) silica gel eluting with 7% methanol/dichloromethane to afford 240 mg (81%) the title compound as a white amorphous solid. R_f 0.23 (7% methanol/dichloromethane);

$[\alpha]_D$ -20°(c 0.9736, methanol); IR (mull) 1754, 1662, 1654, 1632, 1517, 1437, 1412, 1226, 1194, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, 1H, J=2.1 Hz, J=13.0 Hz, aromatic), 7.15 (dd, 1H, J=2.1 Hz, J=8.5 Hz, aromatic), 7.07 (t, 1H, J=8.5 Hz, aromatic), 6.47 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.51 (d, 1H, J=9.0 Hz, Ph-C-CH_{2a}), 4.35 (d, 1H, J=9.7 Hz, Ph-C-CH_{2b}), 4.25 (d, 1H, J=9.2 Hz, Ph-C-CH_{2a}), 4.05 (m, 4H, O=C-CH_2s, Ph-C-CH_{2b}, Ph-N-CH_{2a}), 3.66 (m, 1H, Ph-N-CH_{2b}), 3.66 (m, 2H, NH-CH_2s), 2.03 (s, 3H, O=C-CH_3), 1.63 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 169.7, 160.4 (d, J_{CF}=246 Hz), 154.2, 138.2 (d, J_{CF}=11 Hz), 128.4 (d, J_{CF}=14 Hz), 127.3 (d, J_{CF}=6 Hz), 113.4, 106.6 (d, J_{CF}=28 Hz), 72.1, 71.5, 62.4, 59.5, 59.2, 47.5, 41.9, 36.9, 28.3, 23.1; K.F. Water = 2.03%; Anal. Calcd for $C_{19}H_{24}N_3O_5F_1$ plus 2.03% water: C, 56.83; H, 6.25; N, 10.47. Found: C, 56.99; H, 6.34; N, 10.49. HRMS Calcd for $C_{19}H_{24}N_3O_5F_1$: 394.1778. Found: 394.1784.

EXAMPLE 5 (S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 25 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-Fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 8 mL dichloromethane, and cooled to 0°C. The colorless but slightly opaque solution was treated with 0.16 mL triethylamine (1.1 mmol) and 73 µL ethyl formate (0.90 mmol) with no observable change. The cooling bath was removed and the reaction mixture was warmed to room temperature for 16 hours. TLC analysis of the now clear solution indicated incomplete consumption of (S)-N-[[3-[3-Fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide. The reaction mixture was treated with an additional 0.14 mL ethyl formate (1.8 mmol) and 8.0 mL 1N sodium hydroxide with vigorous stirring for five minutes. The reaction was diluted with 10 mL water and extracted twice with dichloromethane (25 mL). The combined organics were washed once with water (20 mL), once with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give 253 mg of a white foam. This crude material was purified by LC on 18 g (230-400) silica gel eluting with 6% methanol/dichloromethane to afford 145 mg (55%) the title compound as a white amorphous solid. R_f 0.25 (7% methanol/dichloromethane); $[\alpha]_D$ -20°(c 0.9949, methanol); IR (mull) 1754, 1666, 1631, 1548, 1516, 1478, 1433, 1414, 1227, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H, CHO), 7.47 (dd, 1H, J=2.0 Hz,

J=13.0 Hz, aromatic), 7.16 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.07 (t, 1H, J=8.6 Hz, aromatic), 6.33 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.42 (d, 1H, J=8.2 Hz, Ph-C-CH_{2a}), 4.30 (d, 1H, J=9.9 Hz, Ph-C-CH_{2b}), 4.15 (d, 1H, J=8.3 Hz, Ph-C-CH_{2a}), 4.05 (m, 2H, Ph-C-CH_{2b}, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.67 (m, 2H, NH-CH_2s), 2.03 (s, 3H, O=C-CH_3), 1.64 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.1, 162.3, 160.3 (d, J_{CF}=246 Hz), 154.1, 138.2 (d, J_{CF}=11 Hz), 127.9 (d, J_{CF}=14 Hz), 127.1 (d, J_{CF}=6 Hz), 113.3, 106.4 (d, J_{CF}=27 Hz), 71.9, 59.6, 58.2, 47.3, 41.7, 37.6, 28.0, 23.0; HRMS Calcd for $C_{17}H_{20}N_3O_4F_1$: 349.1438. Found: 349.1444.

EXAMPLE 6 (S)-N-[[3-[3-Fluoro-4-[1-(dichloroacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 25 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-Fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 8 mL dichloromethane, and cooled to 0°C. The colorless but slightly opaque solution was treated with 0.16 mL triethylamine (1.1 mmol) and 87 µL dichloroacetyl chloride (0.90 mmol) with a smokey/haze developing. The cooling bath was removed and the reaction mixture was warmed to room temperature over three hours. The now clear colorless solution was diluted with 15 mL water and extracted twice with dichloromethane (25 mL). The combined organics were washed once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 353 mg of a tan foam. This crude material was purified by LC on 25 g (230-400) silica gel eluting with 5% methanol/dichloromethane to afford 243 mg (75%) the title compound as an off-white amorphous solid. R_f 0.26 (5% methanol/dichloromethane); $[\alpha]_D$ -18°(c 0.9862, methanol); IR (mull) 1752, 1666, 1631, 1545, 1517, 1440, 1412, 1288, 1227, 1193 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, 1H, J=2.1 Hz, J=13.0 Hz, aromatic), 7.18 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.08 (t, 1H, J=8.6 Hz, aromatic), 6.52 (bt, 1H, J=6.1 Hz, NH), 4.81 (m, 1H, methine), 4.70 (d, 1H, J=8.9 Hz, Ph-C-CH_{2a}), 4.48 (d, 1H, J=9.1 Hz, Ph-C-CH_{2b}), 4.41 (d, 1H, J=10.1 Hz, Ph-C-CH_{2a}), 4.13 (d, 1H, J=10.0 Hz, Ph-C-CH_{2b}), 4.06 (t, 1H, J= 9.0 Hz, Ph-N-CH_{2a}), 3. 79 (dd, 1H, J 6.7 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.67 (m, 2H, NH-CH_2s), 2.03 (s, 3H, O=C-CH_3), 1.67 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.3, 163.1, 160.3 (d, J_{CF}=246 Hz), 154.2, 138.4 (d, J_{CF}=11 Hz), 127.6 (d, J_{CF}=15 Hz), 127.1 (d, J_{CF}=6 Hz), 113.4, 106.6 (d, J_{CF}=27 Hz), 72.1, 64.6, 63.1, 60.3, 47.4, 41.8, 36.9, 28.2, 23.0; K.F. Water = 1.3%. Anal. Calcd for $C_{18}H_{20}N_3O_4F_1Cl_2$ plus 1.3% water: C, 49.36; H, 4.75; N,

9.60. Found: C, 48.97; H, 4.80; N, 9.53. HRMS Calcd for $C_{18}H_{20}N_3O_4F_1Cl_2$: 432.0893. Found: 432.0900.

EXAMPLE 7 (S)-N-[[3-[3-Fluoro-4-[1-(3-methoxypropionyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 10 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 4 mL dichloromethane, 81 µL 3-methoxypropionic acid (0.83 mmol), 0.13 mL of distilled diethylcyanophosphonate (0.83 mmol) and cooled to 0°C. The colorless solution was treated with 0.11 mL triethylamine (0.78 mmol) becoming a pinkish color. The cooling bath was removed and the reaction mixture was warmed to room temperature over 66 hours. The now reddish brown solution was diluted with 20 mL dichloromethane and washed once with water (15 mL), once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 297 mg of a red foam. This crude material was purified by LC on 18 g (230-400) silica gel eluting with 7% methanol/dichloromethane to afford 216 mg of an off-white amorphous solid. ^1H NMR indicates this material to be contaminated with 10% (S)-N-[[3-[3-fluoro-4-[1-(formyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide which was removed by catalytic hydrogenolysis with 22 mg 10% palladium on carbon in 30 mL tetrahydrofuran containing 10 drops concentrated hydrochloric acid. The resulting crude material was rechromatographed on 13 g (230-400) silica gel eluting with 7% methanol/dichloromethane to afford 135 mg (44% overall) the title compound as an off-white amorphous solid. R_f 0.23 (7% methanol/dichloromethane); $[\alpha]_D$ -19°(c 0.8324, methanol); IR (mull) 1755, 1644, 1630, 1548, 1516, 1440, 1410, 1226, 1192, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, 1H, J=2.0 Hz, J=12.9Hz, aromatic), 7.15 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.07 (t, 1H, J=8.5 Hz, aromatic), 6.29 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.42 (d, 1H, J=8.0, Ph-C-CH_{2a}), 4.30 (d, 1H, J=9.6 Hz, Ph-C-CH_{2b}), 4.15 (d, 1H, J=8.2 Hz, Ph-C-CH_{2a}), 4.04 (m, 2H, Ph-C-CH_{2b}, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=6.7 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.67 (m, 4H, NH-CH_2s, O-CH_2s), 3.34 (s, 3H, OCH_3), 2.36 (qrt, 2H, J=6.2 Hz, O-(CH_2)-CH_2s), 2.03 (s, 3H, O=C-CH_3), 1.61 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.5, 171.1, 162.5 (d, J_{CF}=246 Hz), 154.2, 138.1 (d, J_{CF}=11 Hz), 128.5 (d, J_{CF}=15 Hz), 127.3 (d, J_{CF}=6 Hz), 113.4, 106.5 (d, J_{CF}=28 Hz), 72.0, 68.4, 61.6, 58.9, 47.5, 41.9, 35.6, 32.2, 28.6, 23.1; HRMS Calcd for $C_{20}H_{26}N_3O_5F_1$: 407.1856. Found: 407.1855.

EXAMPLE 8 (S)-N-[[3-[3-Fluoro-4-[1-(3-hydroxypropionyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

A 10 mL recovery flask equipped with magnetic stirrer was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol) and 1.5 mL water then cooled to 0°C. The colorless but slightly opaque solution was treated with 52 µL β-propiolactone (0.75 mmol) with no observable change. The cooling bath was removed and the reaction mixture was warmed to room temperature for two hours. The visually unchanged reaction mixture was diluted with 10 mL brine and extracted twice with dichloromethane (20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated to give 232 mg of an off-white foam. This crude material was purified by LC on 17 g (230-400) silica gel eluting with 7% methanol/dichloromethane to afford 178 mg (60%) the title coupound as a white amorphous solid. R_f 0.30 (10% methanol/dichloromethane); $[\alpha]_D$ -19°(c 0.9248, methanol); IR (mull) 3288, 1754, 1630, 1554, 1517, 1436, 1412, 1289, 1227, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, 1H, J=2.1 Hz, J=13.0 Hz, aromatic), 7.14 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.07 (t, 1H, J=8.6 Hz, aromatic), 6.55 (bt, 1H, J=6 Hz, NH), 4.81 (m, 1H, methine), 4.41 (d, 1H, J=8.3, Ph-C-CH_{2a}), 4.32 (d, 1H, J=9.6 Hz, Ph-C-CH_{2b}), 4.12 (d, 1H, J=8.4 Hz, Ph-C-CH_{2a}), 4.05 (m, 2H, Ph-C-CH_{2b}, Ph-N-CH_{2a}), 3.88 (bs, 2H, HO-CH_2s), 3.80 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.67 (m, 2H, NH-CH_2s), 3.46 (bs, 1H, HO), 2.37 (qrt, 2H, J=5.6 Hz, HO-(CH_2)-CH_2s), 2.03 (s, 3H, O=C-CH_3), 1.63 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 172.8, 171.2, 160.3 (d, J_{CF}=246 Hz), 154.1, 138.1 (d, J_{CF}=11 Hz), 128.0 (d, J_{CF}=14 Hz), 127.1 (d, J_{CF}=6 Hz), 113.3, 106.5 (d, J_{CF}=27 Hz), 72.0, 61.4, 58.8, 58.3, 47.3, 41.8, 35.7, 32.9, 28.2, 23.0; HRMS Calcd for $C_{19}H_{24}N_3O_5F_1$: 394.1778. Found: 394.1788.

EXAMPLE 9 (S)-N-[[3-[3-Fluoro-4-[1-(4-oxopentanoyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 10 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 4 mL dichloromethane, 100 µL levulinic acid (0.98 mmol), 216 mg EDC•HCL (1.13 mmol), 18 mg dimethylamino pyridine (0.15 mmol) and cooled to 0°C. The colorless solution was treated with 0.31 mL triethylamine (2.25 mmol) becoming a pale yellow color. The cooling bath was removed and the reaction mixture was warmed to room temperature over 16

hours. The visually unchanged solution was diluted with 20 mL water and extracted twice with dichloromethane (25 mL). The combined organics were washed once with saturated sodium bicarbonate (20 mL), brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 332 mg of a light yellow syrup. This crude material was purified by LC on 20 g (230-400) silica gel eluting with 5% methanol/dichloromethane to afford 256 mg of an off-white amorphous solid. ^1H NMR indicates this material to be contaminated with 8% (S)-N-[[3-[3-fluoro-4-[1-(formyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide which was removed by catalytic hydrogenolysis with 26 mg 10% palladium on carbon in 30 mL tetrahydrofuran containing ten drops concentrated hydrochloric acid. The resulting crude material was rechromatographed on 15 g (230-400) silica gel eluting with 5% methanol/dichloromethane to afford 116 mg (37% overall) the title compound as a white amorphous solid. R_f 0.16 (5% methanol/dichloromethane); $[\alpha]_D$ -19°(c 0.9205, methanol); IR (mull) 1754, 1716, 1631, 1548, 1517, 1440, 1411, 1227, 1193, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, 1H, J=2.1 Hz, J=13.0 Hz, aromatic), 7.15 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.07 (t, 1H, J=8.5 Hz, aromatic), 6.32 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.46 (d, 1H, J=8.1, Ph-C-CH_{2a}), 4.27 (d, 1H, J=9.4 Hz, Ph-C-CH_{2b}), 4.19 (d, 1H, J=8.3 Hz, Ph-C-CH_{2a}), 4.01 (m, 2H, Ph-C-CH_{2b}, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.68 (m, 2H, NH-CH_2s), 2.80 (t, 2H, J=6.5 Hz, CH_3CO-CH_2s), 2.35 (m, 2H, N-CO-CH_2), 2.19 (s, 3H, (CH_2)-CO-CH_3), 2.03 (s, 3H, NCO-CH_3), 1.63 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 207.3, 172.0, 170.9, 160.5 (d, J_{CF}=246 Hz), 153.9, 137.8 (d, J_{CF}=11 Hz), 128.2 (d, J_{CF}=14 Hz), 127.0 (d, J_{CF}=6 Hz), 113.1, 106.2 (d, J_{CF}=28 Hz), 71.7, 61.3, 58.6, 47.1, 41.6, 37.6, 35.5, 29.7, 28.0, 24.6, 22.8; K.F. Water = 1.67%. Anal. Calcd for $C_{21}H_{26}N_3O_5F_1$ plus 1.67% water: C, 59.13; H, 6.33; N, 9.85. Found: C, 59.04; H, 6.38; N, 9.80. HRMS Calcd for $C_{21}H_{26}N_3O_5F_1$: 419.1856. Found: 419.1854.

EXAMPLE 10 (S)-N-[[3-[3-Fluoro-4-[1-acetyl-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 25 mL round bottom flask equipped with magnetic spinbar was charged with 75 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.23 mmol), 5 mL dichloromethane, and cooled to 0°C. The colorless but slightly opaque solution was treated with 49 µL triethylamine (0.35 mmol) and 20 µL acetyl chloride (0.28 mmol) becoming a light yellow color. The cooling bath was removed and the reaction mixture was warmed

to room temperature over three hours. The now clear yellow solution was diluted with 10 mL water and extracted twice with dichloromethane (20 mL). The combined organics were washed once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 96 mg of an off-white foam. This crude material was combined with 28900-RLH-017 and purified by LC on 10 g (230-400) silica gel eluting with 7% methanol/dichloromethane to afford 143 mg the title compound as a white amorphous solid. R_f 0.24 (7% methanol/dichloromethane); $[\alpha]_D$ -21°(c 0.9238, methanol); IR (mull) 1754, 1646, 1631, 1552, 1517, 1435, 1413, 1288, 1227, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, 1H, J=2.1 Hz, J=13.1 Hz, aromatic), 7.14 (dd, 1H, J=2.2 Hz, J=8.6 Hz, aromatic), 7.07 (t, 1H, J=8.5 Hz, aromatic), 6.40 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.39 (d, 1H, J=7.9 Hz, Ph-C-CH_{2a}), 4.30 (d, 1H, J=9.5 Hz, Ph-C-CH_{2b}), 4.11 (d, 1H, J=8.2 Hz, Ph-C-CH_{2a}), 4.02 (m, 2H, Ph-C-CH_{2b}, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.66 (m, 2H, NH-CH_2s), 2.03 (s, 3H, HNCO-CH_3), 1.90 (s, 3H, NCO-CH_3), 1.62 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.0, 170.8, 160.3 (d, J_{CF}=246 Hz), 154.0, 138.0 (d, J_{CF}=11 Hz), 128.2 (d, J_{CF}=14 Hz), 127.1 (d, J_{CF}=6 Hz), 113.2, 106.3 (d, J_{CF}=27 Hz), 71.8, 61.7, 58.7, 47.3, 41.7, 35.2, 28.1, 22.9, 18.6; K.F. Water = 1.83%. Anal. Calcd for $C_{18}H_{22}N_3O_4F_1$ plus 1.83% water: C, 58.41; H, 6.20; N, 11.35. Found: C, 58.43; H, 6.45; N, 11.27. HRMS Calcd for $C_{18}H_{22}N_3O_4F_1$: 363.1594. Found: 363.1585.

EXAMPLE 11 (S)-N-[[3-[3-Fluoro-4-[1-(2-fluoroethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 10 mL recovery flask equipped with magnetic spinbar and reflux condenser was charged with 262 mg 2-fluoro-1-tosyl ethanol (1.2 mmol), 321 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (1.0 mmol), 7.0 mL acetonitrile, and 415 mg powdered potassium carbonate (3.0 mmol). The resulting white suspension was heated to reflux for 16 hours. The visually unchanged reaction mixture was cooled to room temperature, volatiles removed *in vacuo*, resulting residue diluted with 20 mL water, and extracted twice with dichloromethane (20 mL). The combined organics were washed once with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give 394 mg of a light brown syrup. This crude material was purified by LC on 19 g (230-400) silica gel eluting with 7% methanol/dichloromethane to afford 260 mg (71%) the title compound as a light peach amorphous solid. R_f 0.30 (7% methanol/dichloromethane); $[\alpha]_D$ -21°(c 0.95445, methanol); IR (mull) 1753, 1660,

1630, 1550, 1515, 1481, 1435, 1411, 1225, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, 1H, J=2.2 Hz, J=12.7 Hz, aromatic), 7.11 (dd, 1H, J=2.3 Hz, J=8.5 Hz, aromatic), 6.98 (t, 1H, J=8.6 Hz, aromatic), 6.23 (bt, 1H, J=6 Hz, NH), 4.79 (m, 1H, methine), 4.47 (dt, 2H, J=4.8 Hz, J_{HF}=47.4 Hz, F-CH_2), 4.04 (t, 1H, J=9.0 Hz, Ph-N-CH_{2a}), 3.77 (dd, 1H, J=6.8 Hz, J=9.2 Hz, Ph-N-CH_{2b}), 3.66 (m, 4H, HN-CH_2s, N-CH_{2a}s), 3.34 (d, 2H, J=7.2 Hz, N-CH_{2b}s), 2.75 (dt, 2H, J=4.9 Hz, J_{HF}=28.2 Hz, F-CH_2-CH_2), 2.03 (s, 3H, O=C-CH_3), 1.64 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 170.8, 159.9 (d, J_{CF}=245 Hz), 153.9, 137.0 (d, J_{CF}=11 Hz), 131.1 (d, J_{CF}=16 Hz), 127.0 (d, J_{CF}=7 Hz), 113.2 (d, J_{CF}=3 Hz), 106.2 (d, J_{CF}=28 Hz), 82.6 (d, J_{CF}=166 Hz), 71.7, 66.0, 58.5 (d, J_{CF}=19 Hz), 47.2, 41.6, 36.8, 27.1, 22.8; K.F. Water = 1.05%; Anal. Calcd for $C_{18}H_3N_3O_3F_2$ plus 1.66% water: C, 57.87; H, 6.39; N, 11.25. Found: C, 57.67; H, 6.43; N, 11.18. HRMS Calcd for $C_{18}H_3N_3O_3F_2$: 368.1786. Found: 368.1789.

EXAMPLE 12 (S)-N-[[3-[3-Fluoro-4-[1-(cyanomethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 10 mL recovery flask equipped with magnetic spinbar and reflux condenser was charged with 321 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (1.0 mmol), 7.0 mL acetonitrile, 76 µL chloroacetonitrile (1.2 mmol), and 415 mg powdered potassium carbonate (3.0 mmol). The resulting white suspension was heated to reflux and quickly darkened to a tan color. TLC after 20 minutes indicates almost complete consumption of (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide, and the reaction was stirred at room temperature for 16 hours. The visually unchanged reaction mixture was cooled to room temperature, volatiles removed *in vacuo,* resulting residue diluted with 20 mL water, and extracted twice with dichloromethane (20 mL). The combined organics were washed once with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give 340 mg of a yellow foam. This crude material was purified by LC on 24 g (230-400) silica gel eluting with 5% methanol/dichloromethane to afford 271 mg (75%) the title compound as a white amorphous solid. R_f 0.30 (5% methanol/dichloromethane); $[\alpha]_D$ -22°(c 0.9252, methanol); IR (mull) 1752, 1661, 1631, 1546, 1516, 1480, 1434, 1412, 1227, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, 1H, J=2.3 Hz, J=12.8 Hz, aromatic), 7.13 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 6.99 (t, 1H, J=8.6 Hz, aromatic), 6.30 (bt, 1H, J=6 Hz, NH), 4.79 (m, 1H, methine), 4.03 (t, 1H, J=9.0 Hz, Ph-N-CH_{2a}), 3.77 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-

N-CH_{2b}), 3.66 (m, 2H, HN-CH_2s), 3.55 (s, 4H, N-CH_2s), 3.49 (s, 2H, NC-CH_2), 2.02 (s, 3H, O=C-CH_3), 1.64 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$); 171.1, 159.9 (d, J_{CF}=246 Hz), 154.1, 137.4 (d, J_{CF}=11 Hz), 129.7 (d, J_{CF}=15 Hz), 126.9 (d, J_{CF}=7 Hz), 114.8, 113.3, 106.2 (d, J_{CF}=28 Hz), 71.8, 63.3, 47.2, 43.9, 41.6, 36.5, 26.9, 22.8; K.F. Water = 1.42%; Anal. Calcd for $C_{18}H_{21}N_4O_3F_1$ plus 1.42% water: C, 59.14; H, 5.95; N, 15.33. Found: C, 58.96; H, 5.88; N, 15.33. HRMS Calcd for $C_{18}H_{21}N_4O_3F_1$: 360.1598. Found: 360.1610.

EXAMPLE 13 (S)-N-[[3-[3-Fluoro-4-[1-(5-nitro-2-thiazolyl)-3-(3-methyl)-azetidinyl-phenyl]-2-oxo-5-oxazolidinyllmethyll-acetamide

An oven-dried 10 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 4 mL dimethylsulfoxide, and 188 mg 2-bromo-5-nitrothiazole. This golden homogenous solution was treated with 207 mg powdered potassium carbonate (1.5 mmol) and stirred at room temperature for 16 hours. The now dark brown suspension was diluted with 40 mL dichloromethane and washed with water (3 x 15 mL), once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 280 mg of an orange foam. This crude material was purified by LC on 18 g (230-400) silica gel eluting with 5% methanol/dichloromethane to afford 191 mg (56%) the title compound as a yellow solid. This material was recrystallized from ethyl acetate/hexane to afford 88 mg of a yellow solid. mp 182-185°C (dec.); R_f 0.29 (5% methanol/dichloromethane); $[\alpha]_D$ -20°(c 0.4062, DMSO); IR (mull) 1747, 1771, 1572, 1517, 1498, 1475, 1439, 1282, 1228, 1199, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J=2.1 Hz, J=13.1 Hz, aromatic), 7.20 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.12 (t, 1H, J=8.5 Hz, aromatic), 4.79 (m, 1H, methine), 4.51 (d, 2H, J=8.9, Ph-C-CH_2s), 4.24 (d, 2H, J=9.4 Hz, Ph-C-CH_2s), 4.07 (t, 1H, J=9.0 Hz, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=7.0 Hz, J=9.5 Hz, Ph-N-CH_{2b}), 3.62 (m, 2H, NH-CH_2s), 2.01 (s, 3H, O=C-CH_3), 1.75 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 201.0, 171.9, 171.8, 160.1 (d, J_{CF}=247 Hz), 154.6, 145.5, 138.4 (d, J_{CF}=11 Hz), 127.1, 126.9 (d, J_{CF}=6 Hz), 113.5, 106.5 (d, J_{CF}=27 Hz), 72.2, 64.0, 47.4, 41.7, 38.1, 28.0, 22.4; K.F. Water = 0.59%. Anal. Calcd for $C_{19}H_{20}N_5O_5F_1S_1$ plus 0.59% water: C, 50.48; H, 4.53; N, 15.49. Found: C, 50.26; H, 4.69; N, 15.29.

EXAMPLE 14 (S)-N-[[3-[3-Fluoro-4-[1-(methanesulfonyl)-3-(3-methyl)-azetidinyll-phenyll-2-oxo-5-oxazolidinyllmethyll-acetamide

An oven-dried 15 mL round bottom flask equipped with magnetic spinbar was charged with 241 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.75 mmol), 8 mL dichloromethane, and cooled to 0°C. The colorless but slightly opaque solution was treated with 0.16 mL triethylamine (1.1 mmol) and 70 µL methanesulfonyl chloride (0.90 mmol) with no visible change. The cooling bath was removed and the reaction mixture was warmed to room temperature over three hours. The now clear solution was concentrated to a colorless syrup. This crude material was purified by LC on 18 g (230-400) silica gel eluting with 5% methanol/ethyl acetate to afford 234 mg (78%) the title compound as a white foam. R_f 0.30 (5% methanol/ethyl acetate); $[\alpha]_D$ -9°(c 0.9701, methanol; IR (mull) 1753, 1664, 1631, 1517, 1436, 1412, 1333, 1228, 1194, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, 1H, J=2.2 Hz, J=13.0 Hz, aromatic), 7.16 (m, 1H, aromatic), 7.00 (t, 1H, J=8.6 Hz, aromatic), 6.30 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.24 (d, 2H, J=7.4 Hz, Ms-N-CH_{2a}s), 4.05 (t, 1H, J=9.0 Hz, Ph-N-CH_{2a}), 3.88 (d, 2H, J=7.6 Hz, Ms-N-CH_{2b}s), 3.79 (m, 1H, Ph-N-CH_{2b}), 3.66 (m, 2H, NH-CH_2s), 2.87 (s, 3H, S-CH_3), 2.03 (s, 3H, O=C-CH_3), 1.68 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 160.2 (d, J_{CF}=246 Hz), 154.2, 138.3 (d, J_{CF}=11 Hz), 128.2 (d, J_{CF}=15 Hz), 126.9 (d, J_{CF}=6 Hz), 113.5 (d, J_{CF}=3 Hz), 106.5 (d, J_{CF}=28 Hz), 72.0, 60.8, 47.4, 41.8, 36.2, 35.0, 27.4, 23.1; Melt solvate = 0.3% ethyl acetate; K.F. Water = 1.05%; Anal. Calcd for $C_{17}H_{22}N_3O_5F_1S_1$ plus 0.3% ethyl acetate and 1.05% water: C, 50.59; H, 5.62; N, 10.38. Found: C, 50.50; H, 5.81; N, 10.29. HRMS Calcd for $C_{17}H_{22}N_3O_5F_1S_1$: 400.1342. Found: 400.1352.

EXAMPLE 15 (S)-N-[[3-[3-Fluoro-4-[1-(benzyloxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

An oven-dried 25 mL round bottom flask equipped with magnetic spinbar was charged with 313 mg (S)-N-[[3-[3-fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.97 mmol), 10 mL dichloromethane, and cooled to 0°C. The colorless but slightly opaque solution was treated with 0.27 mL triethylamine (2.0 mmol) and 0.23 mL benzyloxyacetyl chloride (1.5 mmol) with the reaction mixture becoming clear and a pale yellow color. The cooling bath was removed and the reaction mixture was warmed to room temperature over 16 hours. The visually unchanged solution was diluted with 15 mL saturated sodium bicarbonate and extracted twice with dichloromethane (20 mL). The combined organics were washed once with 15 mL brine, dried over $MgSO_4$, filtered, and

concentrated to give 521 mg of a light yellow foam. This crude material was purified by LC on 27 g (230-400) silica gel eluting with 10% methanol/ethyl acetate to afford 370 mg (81%) the title compound as a white foam. R_f 0.29 (10% methanol/ethyl acetate); $[\alpha]_D$ -17°(c 0.9516, methanol); IR (mull) 1754, 1654, 1631, 1548, 1516, 1438, 1411, 1226, 1193, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, 1H, J=2.2 Hz, J=13.0 Hz, aromatic), 7.33 (m, 5H, aromatic), 7.15 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.04 (t, 1H, J=8.6 Hz, aromatic), 6.42 (bt, 1H, J=6 Hz, NH), 4.79 (m, 1H, methine), 4.57 (s, 2H, Ph-CH_2), 4.50 (d, 1H, J=9.0 Hz, Ph-C-CH_{2a}), 4.33 (d, 1H, J=9.7 Hz, Ph-C-CH_{2b}), 4.23 (d, 1H, J=9.2 Hz, Ph-C-CH_{2b}), 4.04 (m, 4H, Ph-C-CH_{2a}, O-CH_2, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=6.8 Hz, J=9.0 Hz, Ph-N-CH_{2b}), 3.66 (m, 2H, NH-CH_2), 2.02 (s, 3H, O=C-CH_3), 1.61 (s, 3H, Ph-C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.1, 169.6, 160.3 (d, J_{CF}=246 Hz), 154.1, 138.1 (d, J_{CF}=11 Hz), 137.0, 128.4, 128.2, 128.0, 127.9, 127.2 (d, J_{CF}=6 Hz), 113.3, 106.5 (d, J_{CF}=26 Hz), 73.3, 71.9, 69.0, 62.4, 59.4, 47.4, 41.8, 36.7, 28.2, 23.0; HRMS Calcd for $C_{25}H_{28}N_3O_5F_1$: 470.2091. Found: 470.2101.

EXAMPLE 16 (S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

A 250 mL Parr flask was charged with a solution of 310 mg (S)-N-[[3-[3-fluoro-4-[1-(benzyloxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.66 mmol) in 30 mL methanol and 31 mg 10% palladium on carbon. The black suspension was placed under 40 psi hydrogen with shaking for 16 hours with the pressure remaining constant. The reaction was monitored by TLC analysis with several additional equivalents of 10 % palladium on carbon (300 mg total amount) and prolonged time (five days) to fully consume (S)-N-[[3-[3-fluoro-4-[1-(benzyloxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]-methyl]-acetamide. The reaction mixture was filtered through a pad of Celite and concentrated to afford 221 mg (88%) the title compound as an off-white amorphous solid. R_f 0.21 (15% methanol/ethyl acetate); $[\alpha]_D$ -20°(c 0.9432, methanol); IR (mull) 1754, 1655, 1632, 1552, 1517, 1481, 1435, 1412, 1227, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 1H, J=2.1 Hz, J=13.0 Hz, aromatic), 7.15 (dd, 1H, J=2.2 Hz, J=8.5 Hz, aromatic), 7.07 (t, 1H, J=8.6 Hz, aromatic), 6.37 (bt, 1H, J=6 Hz, NH), 4.80 (m, 1H, methine), 4.38 (m, 2H, Ph-C-$CH_{2a\&b}$), 4.01 (m, 5H, Ph-C-$CH_{2a\&b}$, HO-CH_2, Ph-N-CH_{2a}), 3.79 (dd, 1H, J=6.8 Hz, J=9.1 Hz, Ph-N-CH_{2b}), 3.68 (m, 2H, HN-CH_2s), 2.03 (s, 3H, O=C-CH_3), 1.65 (s, 3H, Ph-C-CH) 171.3, 170.9, 160.1 (d, J_{CF}=246 Hz), 153.9, 138.1 (d, J_{CF}=11 Hz), 127.6 (d, J_{CF}=14

Hz), 126.9 (d, J_{CF}=6 Hz), 113.1, 106.3 (d, J_{CF}=28 Hz), 71.8, 60.1, 59.3, 58.5, 47.1, 41.6, 37.0, 28.0, 22.8; HRMS Calcd for $C_{18}H_{22}N_3O_5F_1$: 379.1543. Found: 379.1542.

EXAMPLE 17 (S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: 4-Hydroxy-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1-piperidinecarboxylic acid phenylmethyl ester

To a solution of N-(carbobenzyloxy)-4-bromoaniline (5.00 g) in dry tetrahydrofuran (80 mL) at -78°C under N_2 is added n-butyllithium (21.4 mL, 1.6M in hexanes) dropwise over five minutes. The resulting yellow solution is stirred at -78°C for 30 minutes and is then treated with a solution of N-(carbobenzyloxy)-4-piperidone (3.99 g) in dry tetrahydrofuran (17 mL). The reaction mixture is stirred for three hours, during which the reaction temperature is allowed to rise to 0°C, and is quenched with saturated aqueous ammonium chloride (30 mL). The mixture is then diluted with water (100 mL), the layers are separated, the aqueous phase is extracted with diethyl ether, and the combined organic phase is washed with saline (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is chromato-graphed on silica gel (230 - 400 mesh, 350 g), eluting with ethyl acetate/hexane (25/75), and those fractions with an R_f = 0.38 by TLC (ethyl acetate/hexane, 50/50) are pooled and con-centrated under reduced pressure to give the title compound, mp 156°C - 158°C.

Step 2: 3,6-Dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester

A solution of 4-hydroxy-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 17, Step 1, 2.50 g) in dry methylene chloride under N_2 is treated with trifluoroacetic acid (0.84 mL), stirred at ambient temperature for three hours, diluted with saturated aqueous potassium carbonate (25 mL) to neutralize excess trifluoroacetic acid, and the layers are separated. The organic phase is washed with water (20 mL) and saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue is chromatographed on silica gel (230 - 400 mesh, 300 g), eluting with a gradient of ethyl acetate/hexane (20/80 - 50/50). Pooling of fractions with an R_f = 0.69 by TLC (ethyl acetate/hexane, 50/50) and removal of solvent under reduced pressure gives the title compound, mp 146 - 148°C.

Step 3: (R)-(-)-3,6-Dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-

oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester

A solution of 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 17, Step 2, 0.500 g) in dry tetrahydrofuran (5.7 mL) at -78°C under N_2 is treated with n-butyllithium (0.73 mL, 1.6M in hexanes) dropwise over five minutes. The resulting mixture is stirred at -78°C for 45 minutes and is then treated with (R)-(-)-glycidyl butyrate dropwise. The resulting solution is allowed to warm to ambient temperature over approximately 45 minutes and is stirred for an additional 20 hours, after which the reaction is quenched with saturated aqueous ammonium chloride (10 mL), diluted with water (20 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic phase is washed with saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 40 g), eluting with methanol/methylene chloride (1/99). Pooling and concentration of those fractions with an R_f = 0.37 by TLC (methanol/chloroform, 5/95) gives the title compound, mp 131.5 - 133.5°C.

Step 4: (R)-(-)-3,6-Dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester

A solution of (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 17, Step 3, 970 mg) and triethylamine (0.50 mL) in dry methylene chloride (9.5 mL) at 0°C under N_2 is treated with methanesulfonyl chloride (0.20 mL) dropwise. The resulting mixture is stirred at 0°C for one hour, diluted with methylene chloride (40 mL), washed with water (10 mL), saturated aqueous sodium bicarbonate (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound, mp 166 - 168°C.

Step 5: (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid phenylmethyl ester

A mixture of (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 17, Step 4, 935 mg) and concentrated aqueous ammonium hydroxide (4 mL) in isopropanol (4 mL) and tetrahydrofuran (4 mL) is placed in a sealed tube and immersed in an oil bath maintained at 95°C for 18 hours. The mixture is then diluted with methylene chloride (40 mL), washed with saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the 5-aminomethyl-2-oxazolidinone intermediate (R_f = 0.34 by TLC, methanol/chloroform,

10/90). A solution of this intermediate (783 mg) and pyridine (1.55 mL) in dry methylene chloride (19 mL) at 0°C under N_2 is treated with acetic anhydride (0.90 mL), and the resulting solution is allowed to warm to ambient temperature with stirring over 1.5 hours. The mixture is then diluted with methylene chloride (20 mL), washed with water (10 mL), saturated aqueous sodium bicarbonate (2 x 10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 75 g), eluting with a gradient of methanol/methylene chloride (1/99 - 2/98). Pooling and concentration of those fractions with an R_f = 0.26 by TLC (methanol/chloroform, 5/95) gives the title compound, mp 166 - 169°C.

Step 6: (S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 17, Step 5, 625 mg) and 10% palladium-on-carbon (300 mg) in methanol (100 mL) is shaken on a Parr apparatus under a hydrogen atmosphere at 40 psi for one hour and at 20 psi for 16 hours, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure to give the title compound, mp 169 - 171°C.

EXAMPLE 18 (S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 17, 300 mg) and triethylamine (0.20 mL) in dry methylene chloride (19 mL) at 0°C under N_2 is treated with benzyloxyacetyl chloride (0.18 mL), and the resulting solution is stirred at 0°C for one hour and at ambient temperature for one hour. The reaction mixture is then washed with water (2 x 10 mL), saturated aqueous sodium bicarbonate (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of methanol/methylene chloride (1/99 - 2/98). Pooling and concentration of those fractions with an R_f = 0.28 by TLC (methanol/chloroform, 5/95) gives the title compound, NMR ($CDCl_3$, 400 MHz) 7.45, 7.35, 7.18, 6.26, 4.75, 4.63, 4.22, 4.04, 3.78, 3.70, 3.60, 3.09, 2.70, 2.02, 1.85, 1.60 δ.

EXAMPLE 19 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[3-[4-[1-[(benzyloxy)acetyl]-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 18, 207 mg) and 10% palladium-on-carbon (100 mg) in methanol (9 mL) is shaken on a Parr apparatus under a hydrogen atmosphere at 40 psi for 20 hours, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 20 g), eluting with a gradient of methanol/methylene chloride (5/95 - 10/90). Pooling and concentration of those fractions with an R_f = 0.26 by TLC (methanol/chloroform, 10/90) and recrystallization from methylene chloride/diethyl ether gives the title compound, mp 155 - 157°C.

EXAMPLE 20 (S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: 1-(3-Fluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane

A solution of freshly distilled diisopropylamine (22.9 mL) in dry tetrahydrofuran (175 mL) at -78°C under N_2 is treated with n-butyllithium (1.6M in hexanes, 109 mL) dropwise over 15 minutes, and the resulting mixture is stirred at -78°C for 45 minutes and is then added over ten minutes via cannula to a solution of 3-fluoroaniline (8.00 mL) in dry tetrahydrofuran (166 mL) at -78°C under N_2. The resulting reaction mixture is stirred at -78°C for 50 minutes and is then treated with a solution of 1,1,4,4-tetramethyl-1,4-dichlorodisilethylene (18.3 g) in dry tetrahydrofuran (85 mL). The mixture is allowed to slowly warm to ambient temperature over four hours with stirring and is then washed with water (2 x 200 mL) and saline (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound, NMR ($CDCl_3$, 400 MHz) 7.12, 6.65, 6.58, 0.86, 0.24 δ.

Step 2: 3,6-Dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester

A solution of freshly distilled diisopropylamine (8.70 mL) in dry tetrahydrofuran (133 mL) at -78°C under N_2 is treated with n-butyllithium (1.6M in hexanes, 41.5 mL) dropwise over ten minutes, and the resulting mixture is stirred at -78°C for one hour and is then treated with a solution of 1-(1,1-dimethylethoxycarbonyl)-4-piperidone (12.0 g) in dry tetrahydrofuran (120 mL) dropwise over 10 minutes. The resulting mixture is stirred at -78°C for 40 minutes and is then treated with a solution of N-phenyltrifluoromethanesulfonimide (22.0 g)

in dry tetrahydrofuran (62 mL) over five minutes. The reaction mixture is stirred at -78°C for 10 minutes and at 0°C for four hours and is then quenched with water (200 mL). The layers are separated, the aqueous phase is extracted with diethyl ether (100 mL) and the combined organic phase is washed with saline (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound, NMR ($CDCl_3$, 400 MHz) 5.77, 4.05, 3.64, 2.45, 1.48 δ.

Step 3: 3,6-Dihydro-4-[4-amino-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester

A solution of 1-(3-fluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (EXAMPLE 20, Step 1, 19.1 g) in dry tetrahydrofuran (150 mL) at -78°C under N_2 is treated with sec-butyllithium (1.3M in cyclohexane, 60.3 mL) dropwise over ten minutes, and the resulting mixture is stirred at -78°C for 2.25 hours. A solution of zinc chloride (0.5M in tetrahydrofuran, 150 mL) is then added over 15 minutes, and the mixture is allowed to warm to ambient temperature over one hour with stirring. A solution of 3,6-dihydro-4-[[(trifluoromethyl)-sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 2, 20.8 g) in dry tetrahydrofuran (63 mL) and tetrakis(triphenylphosphine)palladium(0) (1.45 g) is added, and the mixture is degassed, heated up to reflux, refluxed for five minutes, cooled to ambient temperature and stirred for 12 hours. The mixture is then diluted with water (150 mL), the layers are separated, the aqueous phase is extracted with diethyl ether (2 x 100 mL) and the combined organic phase is washed with water (100 mL) and saline (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is then dissolved in methanol (630 mL) and treated with anhydrous potassium carbonate (17.3 g), and the mixture is stirred at ambient temperature for 40 minutes, concentrated under reduced pressure, diluted with water (100 mL) and extracted with diethyl ether (2 x 150 mL). The combined organic phase is washed with water (50 mL) and saline (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 -400 mesh, 1 kg), eluting with a gradient of ethyl acetate/hexane (15/85 - 50/50). Pooling and concentration of those fractions with an R_f = 0.17 by TLC (ethyl acetate/hexane, 25/75) gives the title compound, mp 123 - 125°C.

Step 4: 4-[4-[[(Phenylmethoxy)carbonyl]amino-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

A mixture of 3,6-dihydro-4-[4-amino-2-fluorophenyl]-1(2H)-pyridinecarboxylic

acid

1,1-dimethylethyl ester (EXAMPLE 20, Step 3, 11.44 g) and 10% palladium-on-carbon (4 g) in methanol (400 mL) in four Parr bottles is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for two hours, the catalyst is removed by filtration through Celite, and the filtrate is concentrated under reduced pressure to give the 4-[4-amino-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester intermediate. A mixture of this intermediate (11.17 g) and sodium bicarbonate (6.57 g) in dry tetrahydrofuran (390 mL) is treated with benzyl chloroformate (5.86 mL), and the resulting mixture is stirred at ambient temperature for 15 hours and washed with water (200 mL). The aqueous phase is extracted with methylene chloride (150 mL), and the combined organic phase is washed with saline (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (70 - 230 mesh, 800 g), eluting with a gradient of ethyl acetate/hexane (15/85 - 25/75). Pooling and concentration of those fractions with an R_f = 0.38 by TLC (ethyl acetate/hexane, 25/75) gives the title compound, mp 96 - 98°C.

Step 5: (R)-(-)-4-[4-[5-(Hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

A solution of 4-[4-[[(phenylmethoxy)carbonyl]amino-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 4, 0.500 g) in dry tetrahydrofuran (5.7 mL) at -78°C under N_2 is treated with n-butyllithium (0.73 mL, 1.6M in hexanes) dropwise over five minutes. The resulting mixture is stirred at -78°C for 45 minutes and is then treated with (R)-(-)-glycidyl butyrate dropwise. The resulting solution is allowed to warm to ambient temperature over approximately 45 minutes and is stirred for an additional 20 hours, after which the reaction is quenched with saturated aqueous ammonium chloride (10 mL), diluted with water (20 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic phase is washed with saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 40 g), eluting with methanol/methylene chloride (1/99). Pooling and concentration of those fractions with an R_f = 0.37 by TLC (methanol/chloroform, 5/95) gives the title compound, mp 120 - 122°C.

Step 6: (R)-(-)-4-[4-[5-[[(Methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

A solution of (R)-(-)-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-

fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 5, 970 mg) and triethylamine (0.50 mL) in dry methylene chloride (9.5 mL) at 0°C under N_2 is treated with methanesulfonyl chloride (0.20 mL) dropwise. The resulting mixture is stirred at 0°C for one hour, diluted with methylene chloride (40 mL), washed with water (10 mL), saturated aqueous sodium bicarbonate (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound, mp 163 - 165°C.

Step 7: (R)-(-)-4-[4-[5-(Azidomethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

A mixture of (R)-(-)-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 6, 13.83 g) and sodium azide (7.62 g) in dry dimethylformamide (117 mL) under N_2 is stirred at 60°C for five hours and at ambient temperature for 16 hours. The mixture is then diluted with ethyl acetate (200 mL), washed with water (8 x 100 mL) and saline (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound, mp 109 - 110°C.

Step 8: (S)-(-)-4-[4-[5-(Aminomethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

A solution of (R)-(-)-4-[4-[5-(azidomethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 7, 12.05 g) in dry tetrahydrofuran (96 mL) under N_2 is treated with triphenylphosphine (8.29 g) over five minutes, and the resulting mixture is stirred at ambient temperature for two hours. The mixture is then treated with water (3.1 mL), heated up to 40°C, stirred at 40°C for five hours and at ambient temperature for 12 hours, and then concentrated under reduced pressure to give a viscous oil which is chromatographed on silica gel (70 - 230 mesh, 500 g), eluting with a gradient of methanol/methylene chloride (2.5/97.5 - 15/85). Pooling and concentration of those fractions with an R_f = 0.26 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 136 - 137°C.

Step 9: (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylether ester

A solution of (S)-(-)-4-[4-[5-(aminomethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 8, 9.45 g) in dry methylene chloride (96 mL) under N_2 is treated with pyridine (5.82 mL) and acetic anhydride (3.40 mL), and the resulting mixture is

stirred at ambient temperature for four hours, diluted with methylene chloride (25 mL), washed with water (25 mL), saturated aqueous sodium bicarbonate (25 mL) and saline (25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is then chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/chloroform (2.5/97.5 - 7.5/92.5). Pooling and concentration of those fractions with an R_f = 0.51 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 144 - 146°C.

Step 10: (S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide

A solution of (S)-(-)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 20, Step 9, 10.44 g) in dry methylene chloride (100 mL) at 0°C under N_2 is treated with trifluoroacetic acid (24.0 mL) over one minute, and the resulting mixture is stirred at 0°C for 1.75 hours, concentrated under reduced pressure, diluted with water (100 mL), cooled in an ice bath, adjusted to pH 11 with saturated aqueous potassium carbonate, and extracted with methanol/methylene chloride (5/95, 6 x 100 mL). The combined organic phase is dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound, mp 163 - 164°C.

EXAMPLE 21 (S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]-acetamide (EXAMPLE 20,) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]-methyl]acetamide and purifying the crude product by trituration with chloroform/diethyl ether and filtration, the title compound is obtained, mp 147 - 149°C.

EXAMPLE 22 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[3-[4-[1-[(benzyloxy)acetyl]-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 21, 5.00 g) and 20% palladium hydroxide on carbon (2.80 g) in methanol (500 mL) is stirred under a hydrogen atmosphere (balloon) for four hours, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure, triturated with methylene chloride/diethyl ether and filtered to give the title compound, mp

182 - 183°C.

EXAMPLE 23 (S)-(-)-N-[[3-[4-[1-(Indole-2-carbonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of indole-2-carboxylic acid (79 mg) and 1,1'-carbonyldiimidazole (80 mg) in dry tetrahydrofuran (2.0 mL) is stirred at ambient temperature for one hour, and a solution of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 150 mg) in dry tetrahydrofuran (6.0 mL) is added. The mixture is then stirred at ambient temperature for 19 hours, concentrated under reduced pressure, diluted with methylene chloride (20 mL), washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromagraphed on silica gel (70 - 230 mesh, 10 g), eluting with methanol/methylene chloride (7.5/92.5). Pooling and concentration of those fractions with an R_f = 0.67 by TLC (methanol/chloroform, 10/90) and recrystallization from chloroform/diethyl ether gives the title compound, mp 223 - 225°C.

EXAMPLE 24 (S)-(-)-N-[[3-[4-[1-(Isoxazole-5-carbonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of isoxazole-5-carboxylic acid (79 mg) and 1,1'-carbonyldiimidazole (80 mg) in dry tetrahydrofuran (2.0 mL) is stirred at ambient temperature for one hour, and a solution of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 150 mg) in dry tetrahydrofuran (6.0 mL) is added. The mixture is then stirred at ambient temperature for 19 hours, concentrated under reduced pressure, diluted with methylene chloride (20 mL), washed with saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromagraphed on silica gel (70 - 230 mesh, 10 g), eluting with methanol/methylene chloride (7.5/92.5). Pooling and concentration of those fractions with an R_f = 0.67 by TLC (methanol/chloroform, 10/90) and recrystallization from chloroform/diethyl ether gives the title compound, mp 290 - 292°C.

EXAMPLE 25 (S)-(-)-N-[[3-[4-[1-(Methylsulfonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 125 mg) and pyridine (60 μL) in dry methylene chloride (1.9 mL) at 0°C is treated with methanesulfonyl chloride (32 μL), and the resulting mixture was stirred at 0°C for one hour and at ambient temperature for 16 hours. The reaction mixture is then diluted with methylene chloride (30 mL), washed with water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue is recrystallized from methylene chloride/diethyl ether to give the title compound, mp 240 - 242°C.

EXAMPLE 26 (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid methyl ester

A mixture of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 150 mg) and sodium bicarbonate (75 mg) in dry tetrahydrofuran (6 mL) at 0°C under N_2 is treated with methyl chloroformate (38 μL), and the resulting mixture is stirred at 0°C for one hour. The reaction is then diluted with ethyl acetate (20 mL), washed with water (10 mL) and saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue is recrystallized from methylene chloride/diethyl ether to give the title compound, mp 165 - 166°C.

EXAMPLE 27 (S)-(-)-N-[[3-[4-[1-(Cyanomethyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 150 mg), chloroacetonitrile (31 μL) and anhydrous potassium carbonate (124 mg) in dry acetonitrile (4 mL) under N_2 was stirred at ambient temperature for 20 hours, diluted with methylene chloride (20 mL), washed with water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue is recrystallized from methylene chloride/diethyl ether to give the title compound, mp 165 - 167°C.

EXAMPLE 28 (S)-(-)-N-[[3-[4-[1-(2-Fluoroethyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 27, and making non-critical

variations but substituting 2-flouroethyl 4-toluenesulfonic acid ester for chloroacetonitrile and purifying the crude product by chromatography on silica gel (70 - 230 mesh, 30 g), eluting with methanol/methylene chloride, the title compound is obtained, mp 155 - 157°C.

EXAMPLE 29 (S)-(-)-N-[[3-[4-[1-(Formyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-3-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 150 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (171 mg) and formic acid (34 μL) in dry tetrahydrofuran (6 mL) is stirred at ambient temperature for one hour, diluted with methylene chloride (10 mL), washed with water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue is recrystallized from methylene chloride/diethyl ether to give the title compound, mp 186 - 187°C.

EXAMPLE 30 (S)-(-)-4-[4-[5-[[(2,2-Dichloroacetyl)amino]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

A solution of (S)-(-)-4-[4-[5-(aminomethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 20, Step 8, 400 mg) in dry methylene chloride (4.1 mL) at 0°C under N_2 is treated with triethylamine (0.21 mL) and dichloroacetyl chloride (0.11 mL), and the resulting mixture is stirred at 0°C for three hours, diluted with methylene chloride (10 mL), washed with water (10 mL), saturated aqueous sodium bicarbonate (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is then chromatographed on silica gel (70 - 230 mesh, 50 g), eluting with methanol/chloroform (5/95). Pooling and concentration of those fractions with an R_f = 0.53 by TLC (methanol/chloroform, 10/90), trituration with methylene chloride/diethyl ether and filtration gives the title compound, mp 168 - 170°C.

EXAMPLE 31 (S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 20, Step 10), and making non-critical variations but substituting (S)-(-)-4-[4-[5-[[(2,2-dichloroacetyl)amino]methyl]-

2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 30) for (S)-(-)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.37, 7.22, 7.10, 5.99, 5.29, 4.83, 4.07, 3.78, 3.71, 3.30, 2.98, 2.83, 2.09, 1.81 δ.

EXAMPLE 32 (S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (S)-(-)-2,2-dichloro-N-[[2-oxo-3-[3-fluoro-4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 31) for (S)-(-)-3-N-[4-(4-piperidinyl)phenyl]-5-acetamidomethyl-2-oxazolidinone and acetoxyacetyl chloride for benzyloxyacetyl chloride, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.42, 7.15, 6.24, 4.77, 4.04, 3.77, 3.68, 3.20, 3.07, 2.71, 2.20, 2.02, 1.88, 1.68 δ.

EXAMPLE 33 (S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-(hydroxyacetyl)-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-2,2-dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 32, 110 mg) and anhydrous potassium carbonate (60 mg) in methanol (8.8 mL) is stirred under N_2 at ambient temperature for one hour and then concentrated under reduced pressure and chromatographed on silica gel (70 - 230 mesh, 10 g), eluting with methanol/chloroform (10/90). Pooling and concentration of those fractions with an R_f = 0.41 by TLC (methanol/chloroform, 10/90), repurification by radial chromatography (2000μ silica gel plate) eluting with methanol/methylene chloride, and trituration with chloroform/diethyl ether gives the title compound, NMR ($CDCl_3$, 400 MHz) 7.46, 7.39, 7.15, 5.99, 4.84, 4.74, 4.22, 4.09, 3.77, 3.61, 3.10, 2.79, 1.89, 1.65 δ.

EXAMPLE 34 (S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20,) for (S)-(-)-N-[[2-oxo-3-[4-(4-

piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide and acetoxyacetyl chloride for benzyloxyacetyl chloride, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.42, 7.15, 6.24, 4.77, 4.04, 3.77, 3.68, 3.20, 3.07, 2.71, 2.20, 2.02, 1.88, 1.68 δ.

EXAMPLE 35 (S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)-3,5-difluorophenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: 1-(3,5-Difluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane

Following the general procedure of Step 1 of EXAMPLE 20, and making non-critical variations but substituting 3,5-difluoroaniline for 3-fluoroaniline, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 6.38, 6.31, 0.87, 0.17 δ.

Step 2: 3,6-Dihydro-4-[4-amino-2,6-difluorophenyl]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of Step 3 of EXAMPLE 20, and making non-critical variations but substituting 1-(3,5-difluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane(EXAMPLE 35, Step 1) for 1-(3-fluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane, the title compound is obtained, mp 134 - 135°C.

Step 3: 4-[4-[[(Phenylmethoxy)carbonyl]amino-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of Step 4 of EXAMPLE 20, and making non-critical variations but substituting 3,6-dihydro-4-[4-amino-2,6-difluorophenyl]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 35, Step 2) for 3,6-dihydro-4-[4-amino-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester and purifying the crude product by trituration with ethyl acetate/hexane and filtration, the title compound is obtained, mp 153 -155°C.

Step 4: (R)-(-)-4-[4-[5-(Hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

Following the generel procedure of Step 3 of EXAMPLE 17, and making non-critical variations but substituting 4-[4-[[(phenylmethoxy)carbonyl]amino-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 35, Step 3) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.11, 4.75, 4.22, 3.96, 3.75, 3.06, 2.76, 2.50, 1.98, 1.65, 1.48 δ.

Step 5: (R)-(-)-4-[4-[5-[[(Methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of Step 4 of EXAMPLE 17, and making non-

critical variations but substituting (R)-(-)-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 35, Step 4) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 125 - 126°C.

Step 6: (R)-(-)-4-[4-[5-(Azidomethyl)-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of step 7 of EXAMPLE 20, and making non-critical variations but substituting (R)-(-)-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 35, Step 5) for (R)-(-)-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, mp 125 - 127°C.

Step 7: (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic 1,1-dimethylethyl ester

A mixture of (R)-(-)-4-[4-[5-(azidomethyl)-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester ((EXAMPLE 35, Step 6, 1.51 g) and 10% palladium on carbon (367 mg) in methanol (35 mL) is stirred under a hydrogen atmosphere (balloon) for 18 hours, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure to give the 5-aminomethyl-2-oxazolidinone intermediate (R_f = 0.10 by TLC, methanol/chloroform, 5/95). A solution of this intermediate (1.28 g) and pyridine (2.51 mL) in dry methylene chloride (31 mL) at 0°C under N_2 is treated with acetic anhydride (1.47 mL), and the resulting solution is allowed to warm to ambient temperature with stirring over 1.5 hours. The mixture is then diluted with methylene chloride (15 mL), washed with water (10 mL), saturated aqueous sodium bicarbonate (2 x 10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (70 - 230 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (1/99 - 4/96). Pooling and concentration of those fractions with an R_f = 0.31 by TLC (methanol/chloroform, 5/95), trituration with diethyl ether and filtration gives the title compound, NMR ($CDCl_3$, 400 MHz) 7.06, 6.56, 4.78, 4.22, 4.00, 3.74, 3.65, 3.05, 2.75, 2.02, 1.96, 1.64, 1.47 δ.

Step 8: (S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)-3,5-difluorophenyl]-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-

difluorophenyl]-1-piperidinecarboxylic 1,1-dimethylethyl ester ((EXAMPLE 35, Step 7, 847 mg) and trifluoroacetic acid (12 mL) maintained at 0°C under N_2 is stirred for two hours and then concentrated under reduced pressure to remove excess trifluoroacetic acid. The residue is diluted with saturated aqueous potassium carbonate (70 mL) and methylene chloride (50 mL), and the layers are separated. The aqueous phase is extracted with methylene chloride (2 x 50 mL), and the combined organic phase is dried over anhydrous sodium sulfate, concentrated under reduced pressure, triturated with diethyl ether and recrystallized from ethyl acetate to give the title compound, NMR ($CDCl_3$, 400 MHz) 7.08, 6.10, 4.78, 4.00, 3.74, 3.64, 3.19, 3.07, 2.72, 2.03, 1.99, 1.68 δ.

EXAMPLE 36 (S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3,5-difluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 35) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 169°C - 171°C.

EXAMPLE 37 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[3-[4-[1-[(benzyloxy)acetyl]-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 36, 207 mg) and 10% palladium-on-carbon (100 mg) in methanol (9 mL) is shaken on a Parr apparatus under a hydrogen atmosphere at 40 psi for 20 hours, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 20 g), eluting with a gradient of methanol/methylene chloride (5/95 - 10/90). Pooling and concentration of those fractions with an R_f = 0.26 by TLC (methanol/chloroform, 10/90) and recrystallization from methylene chloride/diethyl ether gives the title compound, NMR ($CDCl_3$, 400 MHz) 7.07, 6.80, 4.78, 4.69, 4.18, 3.99, 3.74, 3.63, 3.60, 3.16, 3.06, 2.90, 2.72, 2.00, 1.97, 1.75 δ.

EXAMPLE 38 (S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-

fluorophenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester

A mixture of (S)-(-)-N-[[3-[4-trimethylstannyl-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (690 mg), 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (step 2 of EXAMPLE 20, 500 mg), tris(dibenzylideneacetone)dipalladium(0) (14 mg) and triphenylarsine (37 mg) in N-methyl-2-pyrrolidinone (7.5 mL) is degassed, stirred under N_2 at ambient temperature for 4.5 days, diluted with ethyl acetate, washed with water (3 x 40 mL) and saline (20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica gel (230 - 400 mesh, 120 g), eluting with a gradient of methanol/methylene chloride (1/99 - 2/98), and those fraction having an R_f = 0.27 by TLC (methanol/chloroform, 2 x 5/95) are pooled and concentrated to give the title compound, ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39, 7.22, 7.13, 7.01, 5.92, 4.82, 4.06, 3.80, 3.67, 3.61, 2.47, 2.03, 1.49 δ.

Step 2: (S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide

A solution of (S)-(-)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 38, Step 1, 1.00g) in dry methylene chloride (9.2 mL) at 0°C under N_2 is treated with trifluoroacetic acid (2.3 mL) over one minute, and the resulting mixture is stirred at 0°C for three hours and added slowly to saturated aqueous potassium carbonate (30 mL) to neutralize excess trifluoroacetic acid. The resultant slurry is filtered and the precipitate is chromatographed on silica gel (70 - 230 mesh, 60 g), eluting with ammonium hydroxide/methanol/methylene chloride (0.25/19.75/80). Those fractions with an R_f = 0.08 by TLC (methanol/chloroform, 20/80) are pooled and concentrated under reduced pressure to give the title compound, ^{1}H NMR (MeOH-d_4, 400 MHz) 7.47, 7.33, 7.25, 6.02, 4.80, 4.15, 3.83, 3.58, 3.47, 3.04, 2.46, 1.98 δ.

EXAMPLE 39 (S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 38) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide and acetoxyacetyl chloride for benzyloxyacetyl chloride, the title compound is obtained, mp 188 -

191°C.

EXAMPLE 40 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 39, 475 mg) and anhydrous potassium carbonate (303 mg) in methanol (44 mL) is stirred under N_2 at ambient temperature for 1.5 hours and then adjusted to pH 7 with aqueous hydrochloric acid (1M) and concentrated under reduced pressure. The residue is chromatographed on silica gel (230 - 400 mesh, 40 g), eluting with a gradient of methanol/chloroform (5/95 - 10/90), and those fractions with an R_f = 0.21 by TLC (methanol/chloroform, 10/90) are pooled and concentrated under reduced pressure. The resulting foam is then triturated with methylene chloride/diethyl ether and the precipitate filtered to give the title compound, Anal. calcd for $C_{19}H_{22}N_3O_5F$: C, 58.31; H, 5.67; N, 10.74. Found: C, 58.15; H, 5.64; N, 10.72.

EXAMPLE 41 (5S)-N-[[3-[3-Fluoro-4-[1-(phenylmethyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: (S)-(-)-N-[[3-[4-Ethenyl-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[3-[4-iodo-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (5.45 g), vinyltributyltin (5.48 g) and bis(triphenylphosphine)palladium(II) chloride (303 mg) in 1,4-dioxane (72 mL) under N_2 is degassed, heated up to reflux, refluxed for seven hours, cooled to ambient temperature and stirred for 12 hours. The mixture is then diluted with ethyl acetate (40 mL) and water (50 mL) and the layers are separated. The aqueous phase is extracted with ethyl acetate (2 x 30 mL), and the combined organic phase is washed with saline (40 mL), dried over anhydrous magnesium sulfate, concentrated under reduced pressure and triturated with diethyl ether. The resultant precipitate is filtered to give the title compound, mp 165 - 166°C.

Step 2: (5S)-N-[[3-[3-Fluoro-4-[1-(phenylmethyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (S)-(-)-N-[[3-[4-vinyl-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 41, Step 1, 3.50 g) and trifluoroacetic acid (0.23 mL) in dry methylene chloride under N_2 is treated with a solution of N-benzyl-N-(methoxymethyl) trimethylsilylmethylamine (6.10 g) in dry methylene

chloride (50 mL) dropwise over 4.5 hours, and the resulting solution was stirred at ambient temperature for 17 hours. The reaction mixture is then washed with saturated aqueous sodium bicarbonate (30 mL), water (30 mL) and saline (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a residue which is chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (1/99 - 10/90). Pooling and concentration of those fractions with an R_f = 0.19 by TLC (methanol/chloroform, 10/90) and trituration with methanol/diethyl ether gives the title compound, NMR ($CDCl_3$, 400 MHz) 7.35, 7.25, 7.13, 6.08, 4.78, 4.03, 3.76, 3.69, 3.62, 2.97, 2.78, 2.56, 2.33, 2.02, 1.85 δ.

EXAMPLE 42 (5S)-N-[[3-[3-Fluoro-4-(3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (5S)-N-[[3-[3-fluoro-4-[1-(phenylmethyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 41, 1.09 g) and 20% palladium hydroxide on carbon (545 mg) in methanol (30 mL) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 1.5 hours and at 10 psi for 18 hours. The catalyst is then removed by filtration through Celite, and the filtrate is concentrated under reduced pressure to give the title compound, NMR ($CDCl_3$, 400 MHz) 7.39, 7.24, 7.11, 6.35, 4.78, 4.04, 3.77, 3.67, 3.44, 3.37, 3.18, 3.11, 2.88, 2.21 2.02, 1.86 δ.

EXAMPLE 43 (5S)-N-[[3-[3-Fluoro-4-[1-[(benzyloxy)acetyl]-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (5S)-N-[[3-[3-fluoro-4-(3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 42) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, HRMS calculated for $C_{25}H_{28}N_3O_5F$: 470.2091. Found: 470.2106.

EXAMPLE 44 (5S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 22, and making non-critical variations but substituting (5S)-N-[[3-[3-fluoro-4-[1-[(benzyloxy)acetyl]-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 43) for

(S)-(-)-N-[[3-[4-[1-[(benzyloxy)acetyl]-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, FAB-HRMS calculated for $C_{18}H_{22}N_3O_5F$ + H: 380.1622. Found: 380.1625.

EXAMPLE 45 (5S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 29, and making non-critical variations but substituting (5S)-N-[[3-[3-fluoro-4-(3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 44) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, HRMS calculated for $C_{17}H_{20}FN_3O_4$: 349.1438. Found: 349.1444.

EXAMPLE 46 (5S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-pyrrolidinecarboxylic acid methyl ester

Following the general procedure of EXAMPLE 26, and making non-critical variations but substituting (5S)-N-[[3-[3-fluoro-4-(3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 44) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, HRMS calculated for $C_{18}H_{22}FN_3O_5$: 379.1543. Found: 379.1546.

EXAMPLE 47 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 3,6-Dihydro-2H-pyran-4-yl trifluoromethanesulfonic acid ester

Following the general procedure of Step 2 of EXAMPLE 20, and making non-critical variations but substituting tetrahydropyran-4-one for 1-(1,1-dimethylethoxycarbonyl)-4-piperidone, the title compound is obtained, ^1H NMR ($CDCl_3$, 400 MHz) 5.82, 4.27, 3.90, 2.47 δ.

Step 2: 3-Fluoro-4-(3,6-dihydro-2H-pyran-4-yl)benzenamine

Following the general procedure of Step 3 of EXAMPLE 20, and making non-critical variations but substituting 3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonic acid ester (EXAMPLE 47, Step1) for 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, mp 86°C- 88°C.

Step 3: 3-Fluoro-4-(3,6-dihydro-2H-pyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester

A mixture of 3-fluoro-4-(3,6-dihydro-2H-pyran-4-yl)benzenamine (EXAMPLE

47, Step 2, 2.28 g) and sodium bicarbonate (1.98 g) in tetrahydrofuran (59 mL) is treated with benzyl chloroformate (1.85 mL), and the resulting slurry is stirred at ambient temperature for six hours. The mixture is then washed with water (50 mL), the aqueous phase is extracted with methylene chloride (50 mL), and the combined organic phase is washed with saline (25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is then chromatographed on silica gel (70 - 230 mesh, 80 g), eluting with ethyl acetate/hexane (15/85), and those fractions with an $R_f = 0.45$ by TLC (ethyl acetate/hexane, 25/75) are pooled and concentrated to give the title compound, mp 75 - 76°C.

Step 4: (R)-(-)-3-[3-Fluoro-4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone

Following the general procedure of Step 3 of EXAMPLE 17, and making non-critical variations but substituting 3-fluoro-4-(3,6-dihydro-2H-pyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 47, Step 3) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 127 - 130°C.

Step 5: (R)-(-)-3-[3-Fluoro-4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

Following the general procedure of Step 4 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[3-fluoro-4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone (EXAMPLE 47, Step 4) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 166 - 169°C (decomp.).

Step 6: (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of Step 5 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[3-fluoro-4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (EXAMPLE 47, Step 5) for (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 148 - 151°C.

EXAMPLE 48 (S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 47, 1.00g) and 10% palladium-on-carbon (637 mg) in methanol (60 mL) is shaken on a Parr apparatus under a hydrogen atmosphere at 40 psi for three hours, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure to give the title compound, mp 191- 192°C.

EXAMPLE 49 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 3,6-Dihydro-2H-thiopyran-4-yl trifluoromethanesulfonic acid ester

Following the general procedure of Step 2 of EXAMPLE 20 , and making non-critical variations but substituting tetrahydrothiopyran-4-one for 1-(1,1-dimethylethoxycarbonyl)-4-piperidone, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 6.01, 3.30, 2.86, 2.62 δ.

Step 2: 3-Fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)benzenamine

Following the general procedure of Step 3 of EXAMPLE 20, and making non-critical variations but substituting 3,6-dihydro-2H-thiopyran-4-yl trifluoromethanesulfonic acid ester (EXAMPLE 49, Step 1) for 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 6.98, 6.40, 6.35, 5.94, 3.73, 3.31, 2.84, 2.62 δ.

Step 3: 3-Fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester

Following the general procedure of Step 3 of EXAMPLE 47, and making non-critical variations but substituting 3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)benzenamine (EXAMPLE 49, Step 2) for 3-fluoro-4-(3,6-dihydro-2H-pyran-4-yl)benzenamine, the title compound is obtained, mp 99 - 101°C.

Step 4: (R)-(-)-3-[3-Fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone

Following the general procedure of Step 3 of EXAMPLE 17, and making non-critical variations but substituting 3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 49, Step 3) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 119 - 122°C.

Step 5: (R)-(-)-3-[3-Fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

Following the general procedure of Step 4 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone (EXAMPLE 49, Step 4) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 138 - 141°C.

Step 6: (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of Step 5 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (EXAMPLE 49, Step 5) for (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 187 - 189°C.

EXAMPLE 50 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide

A solution of (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 49, 300 mg) in water/acetone (25%, 17 mL) is treated with N-methylmorpholine N-oxide (301 mg) followed by osmium tetroxide (2.5 wt% in t-butanol, 0.54 mL), and the resulting mixture is stirred at ambient temperature overnight. The mixture is then quenched with saturated aqueous sodium bisulfite (10 mL) and extracted with methylene chloride (2 x 20 mL). The combined organic phase is washed with saline (10 mL), dried over sodium sulfate and concentrated under reduced pressure to give the crude product which is then chromatographed on silica gel (70 - 230 mesh, 30 g), eluting with a gradient of methanol/methylene chloride (3/97 - 5/95). Pooling of fractions with an R_f = 0.49 by TLC (methanol/chloroform, 10/90) and trituration with methylene chloride/diethyl ether gives the title compound, mp 181 - 182°C.

EXAMPLE 51 (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide

Following the general procedure of EXAMPLE 48, and making non-critical variations but substituting (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (EXAMPLE 50) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide and recrystallizing the product from methylene chloride/diethyl ether, the title compound is obtained, mp 199 - 200°C.

EXAMPLE 52 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-[4-(Hydroxy)tetrahydro-2H-pyran-4-yl]benzenaminecarboxylic acid phenylmethyl ester

Following the general procedure of Step 1 of EXAMPLE 17, and making non-critical variations but substituting tetrahydropyran-4-one for N-(carbobenzyloxy)-4-piperidone, the title compound is obtained, mp 143 - 145°C.

Step 2: 4-(3,6-Dihydro-2H-pyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester

Following the general procedure of Step 2 of EXAMPLE 17, and making non-critical variations but substituting 4-[4-(hydroxy)tetrahydro-2H-pyran-4-yl]benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 52, Step 1) for 4-hydroxy-4-[4-[[(phenylmethoxy)carbonyl] amino]phenyl]-1-piperidinecarboxylic acid phenylmethyl ester and recrystallizing the crude product from ethyl acetate/hexane, the title compound is obtained, mp 145 - 148°C.

Step 3: (R)-(-)-3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone

Following the general procedure of Step 3 of EXAMPLE 17, and making non-critical variations but substituting 4-(3,6-dihydro-2H-pyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 52, Step 2) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester and triturating the crude product with ethyl acetate/hexane (50/50), the title compound is obtained, Anal. Calcd for $C_{15}H_{17}NO_4$: C: 65.44; H, 6.22; N, 5.09. Found: C: 65.05; H, 6.04; N, 4.91.

Step 4: (R)-(-)-3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxymethyl]-2-oxazolidinone

Following the general procedure of Step 4 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone (EXAMPLE 52, Step 3) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 182 - 184°C.

Step 5: (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide

Following the general procedure of Step 5 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (EXAMPLE 52, Step 4) for (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.45, 7.36, 6.63, 6.09, 4.77, 4.31, 4.05, 3.92, 3.80, 3.65, 2.48, 2.01 δ.

EXAMPLE 53 (S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 48, and making non-critical variations but substituting (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 52) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 185°C - 187°C.

EXAMPLE 54 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-[4-(Hydroxy)tetrahydro-2H-thiopyran-4-yl]benzenaminecarboxylic acid phenylmethyl ester

Following the general procedure of Step 1 of EXAMPLE 17, and making non-critical variations but substituting tetrahydrothiopyran-4-one for N-(carbobenzyloxy)-4-piperidone and recrystallizing the product from ethyl acetate/hexane, the title compound is obtained, mp 152 - 154°C.

Step 2: 4-(3,6-Dihydro-2H-thiopyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester

Following the general procedure of Step 2 of EXAMPLE 17, and making non-critical variations but substituting 4-[4-(hydroxy)tetrahydrothiopyran-4-yl]benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 54, Step 1) for 4-hydroxy-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1-piperidinecarboxylic acid phenylmethyl ester and triturating the crude product with diethyl ether or recrystallizing from ethyl acetate/hexane, the title compound is obtained, mp 150 - 152°C.

Step 3: (R)-(-)-3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-5-hydroxymethyl-2-

oxazolidinone

Following the general procedure of Step 3 of EXAMPLE 17, and making non-critical variations but substituting 4-(3,6-dihydro-2H-thiopyran-4-yl)benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 54, Step 2) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester and triturating the crude product with methanol/methylene chloride, the title compound is obtained, mp 182 - 184°C (decomp.).

Step 4: (R)-(-)-3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

Following the general procedure of Step 4 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone (EXAMPLE 54, Step 3) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester and triturating the crude product with methylene chloride/diethyl ether (25/75), the title compound is obtained, mp 171 - 174°C (decomp.).

Step 5: (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of Step 5 of EXAMPLE 17, and making non-critical variations but substituting (R)-(-)-3-[4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (EXAMPLE 54, Step 4) for (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester and acetonitrile for isopropanol, the title compound is obtained, mp 169°C - 173°C (decomp.).

EXAMPLE 55 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide

Following the general procedure of EXAMPLE 50, and making non-critical variations but substituting (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 54) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and triturating the product with ethyl acetate/methylene chloride, the title compound is obtained, mp 185 - 187°C.

EXAMPLE 56 (S)-(-)-N-[[3-[4-[1-(Formyl)-3,6-dihydro-2H-pyridin-4-yl]-3-

fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 29, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 38) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 148 - 151 °C.

EXAMPLE 57 (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester

Following the general procedure of EXAMPLE 26, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 38) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.35, 7.18, 7.10, 6.85, 5.89, 4.78, 4.08, 4.02, 3.78, 3.71, 3.64, 2.45, 2.00 δ.

EXAMPLE 58 (S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of step 1 of EXAMPLE 38, and making non-critical variations but substituting (S)-(-)-N-[[3-[4-(trimethylstannyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide for (S)-(-)-N-[[3-[4-(trimethylstannyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.45, 7.35, 6.55, 6.00, 4.77, 4.05, 3.80, 3.63, 2.49, 2.01, 1.48 δ.

Step 2: (S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide

A solution of (S)-(-)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 58, step 1, 0.92g) in dry methylene chloride (8.8 mL) at 0°C under N_2 is treated with trifluoroacetic acid (2.2 mL) over one minute, and the resulting mixture is stirred at 0°C for four hours and added slowly to saturated aqueous potassium carbonate (30 mL) at 0°C to neutralize excess trifluoroacetic acid. The mixture is then diluted with water (50 mL) and saline (50 mL), extracted with

methanol/methylene chloride (3 x 150 mL, 25/75), and the combined organic phase is dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound, mp 164 - 166°C (decomp.).

EXAMPLE 59 (S)-(-)-N-[[2-Oxo-3-[4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 18, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 58) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide and acetoxyacetyl chloride for benzyloxyacetyl chloride, the title compound is obtained, HRMS calcd for $C_{21}H_{25}N_3O_6$: 415.1743. Found: 415.1752.

EXAMPLE 60 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 40, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 59) for (S)-(-)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, HRMS (FAB) calcd for $C_{19}H_{23}N_3O_5$ + H: 374.1716. Found: 374.1713.

EXAMPLE 61 (S)-(-)-N-[[3-[4-[1-(Formyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 29, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 58) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 149 - 152°C.

EXAMPLE 62 (S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester

Following the general procedure of EXAMPLE 26, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 58) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound

is obtained, mp 142 - 145°C.

EXAMPLE 63 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide

A solution of sodium periodate (192 mg) in water at 0°C is treated with a slurry of (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 49, 300 mg) in methanol (10 mL), and the resulting mixture is allowed to slowly warm to ambient temperature over approximately one hour and is stirred overnight. The mixture is then concentrated to remove methanol, diluted with water (20 mL) and extracted with methanol/chloroform (3 x 30 mL, 5/95). The combined organic phase is washed with saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is then chromatographed on silica gel (30 g, 70-230 mesh), eluting with methanol/methylene chloride (5/95). Those fractions an R_f = 0.39 by TLC (methanol/chloroform, 10/90) were pooled and concentrated and the residue was recrystallized from methylene chloride/diethyl ether to give the title compound, mp 150 - 151°C.

EXAMPLE 64 (S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide

Following the general procedure of EXAMPLE 63, and making non-critical variations but substituting (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 54) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 158 -162°C (decomp.).

EXAMPLE 65 (S)-(-)-N-[[3-[4-(Tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide

A mixture of (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (EXAMPLE 55, 75 mg) and 10% palladium-on-carbon (44 mg) in tetrahydrofuran (20 mL) is stirred under a hydrogen atmosphere (balloon) for one hour, the catalyst is removed by filtration through Celite, the filtrate is concentrated under reduced pressure and the residue is recrystallized from methylene chloride/diethyl ether to give the title compound, mp 190 - 192°C (decomp.).

EXAMPLE 66 3-(4-amino-2-fluorophenyl)pyrrolidine

Step 1: 2-(2-fluoro-4-nitrophenyl)-dimethylmalonate

A flame-dried 500 mL round bottom flask equipped with spinbar and addition funnel was charged with sodium hydride (4.0 g, 0.10 mol). This oil dispersion was washed three times with pentane (30 mL), dried under house vacuum, diluted with 50 mL of freshly distilled tetrahydrofuran, and cooled to 0°C. The grey suspension was drop-wise treated with a 100 mL THF solution of dimethylmalonate (5.7 mL, 50 mmol) with copious gas evolution. The resulting thick suspension was treated with a 100 mL THF solution of 3,4-difluoronitrobenzene, quickly turning golden in color and was warmed to 50°C for 16 hours. At this time, the deep red wine homogenous solution was cooled to RT, quenched with 300 mL 1M hydrochloric acid, and volatiles removed *in vacuo*. The resulting aqueous acidic residue was extracted three time with ethyl acetate (200 mL) with the combined organics washed once with brine (200 mL), dried over $MgSO_4$, filtered and concentrated to give 13.58 g of a brown solid. This material was triturated with a mixture of ethyl acetate/hexane/dichloromethane to afford 7.60 g of the title compound as a light yellow solid. The filtrate was concentrated and purified by Prep 500 HPLC on a single silica gel cartridge eluting with 25% ethyl acetate/hexane to afford and additional 3.95 g of the title compound. Total yield 10.60 g (78%), mp 108-109. mp 108-109°C; R_f 0.38 (25% ethyl acetate/hexane); IR (mull) 1744, 1736, 1532, 1438, 1357, 1345, 1273, 1243, 1232, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (dt, 1H, J=2.2 & J=7.8 Hz, aromatic), 7.99 (ddd, 1H, J=2.3 & 9.4 Hz, aromatic), 7.74 (dd, 1H, J=7.1 & J=8.6 Hz, aromatic), 5.08 (s, 1H, methine), 3.81 (s, 6H, methyls); Anal. Calcd for $C_{11}H_{10}N_1O_6F_1$: C, 48.74; H, 3.72; N, 5.17. Found: C, 48.74; H, 3.84; N, 5.14.

Step 2: 2-(2-fluoro-4-nitrophenyl)-2-(cyanomethyl)-dimethylmalonate

An oven-dried 100 mL round bottom flask equipped with spinbar and reflux condenser was charged with 2-(2-fluoro-4-nitrophenyl)-dimethylmalonate (EXAMPLE 66, Step 1, 3.25 g, 12.0 mmol) and 60 mL acetone. This yellow homogenous solution was treated with a single portion of powdered potassium carbonate (4.98 g, 36 mmol) instantly turning red in color. This suspension was added to by bromoacetonitrile (1.3 mL, 18 mmol) and heated to reflux for 16 hours. At this time, the now brown suspension was cooled to RT, diluted with 100 mL 1M hydrochloric acid, and extracted twice with ethyl acetate (150 mL). The combined organics were washed once with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to give 4.10 g of a crude brown foam. This material was

purified by Prep 500 HPLC on a single silica gel cartridge eluting with 30% ethyl acetate/hexane to afford 3.60 g of an off-white solid. This material was recrystallized from ethyl acetate/hexanes to give 3.14 g (84%) of the title compound as white needles. mp 137-138°C; R_f 0.26 (30% ethyl acetate/hexanes); IR (mull) 1749, 1730, 1527, 1355, 1290, 1276, 1262, 1234, 812, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.12 (ddd, 1H, J_{HF}=0.8, J=2.2, J=8.6 Hz, aromatic), 8.01 (dd, 1H, J=2.3 & 10.8 Hz, aromatic), 7.48 (dd, 1H, J=7.5 & J=8.7 Hz, aromatic), 3.92 (s, 6H, methyls), 3.34 (s, 2H, methine); ^{13}C NMR (75 MHz,$CDCl_3$) 166.5, 159.5 (J_{CF}=253 Hz), 148.7, 130.2 (J_{CF}=3 Hz), 129.9 (J_{CF}=13 Hz), 119.4 (J_{CF}=3 Hz), 11.9 (J_{CF}=28 Hz), 58.0, 54.1, 24.2; Anal. Calcd for $C_{13}H_{11}N_2O_6F_1$: C, 50.33; H, 3.57; N, 9.03. Found: C, 50.23; H, 3.73; N, 9.06.

Step 3: 2-(4-amino-2-fluorophenyl)-2-carbomethoxypyrrolidinone.

A 500 mL Parr flask was charged with a solution of 2-(2-fluoro-4-nitrophenyl)-2-(cyanomethyl)-dimethylmalonate (EXAMPLE 66, Step 2, 1.236 g, 4.0 mmol) in 100 mL methanol and 1.17 g 10% palladium on carbon. The black suspension was placed under 40 psi hydrogen with shaking for 64 hours. The Parr was removed from the hydrogentaor, the reaction mixture was filtered through a pad of CELITE and concentrated to afford 1.02 g of a white foam. This material was purified by LC on 70 g (230-400) silica gel eluting with ethyl acetate to afford 824 mg (82%) of the compound as a white amorphous solid. R_f 0.20 (75% ethyl acetate/hexanes); IR (mull) 3359, 3233, 1738, 1695, 1694, 1634, 1515, 1254, 1276, 1128, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, 1H, J=9.0 Hz, aromatic), 6.58 (bs, 1H, O=C-NH), 6.41 (m, 2H, aromatic), 3.80 (bs, 2H, NH_2), 3.77 (s, 3H, CH_3), 3.49 (m, 1H, N-CH_{2a}), 3.25 (m, 2H, C-CH_2s), 2.28 (m, 1H, N-CH_{2b}); ^{13}C NMR (75 MHz, $CDCl_3$) 173.6, 170.9, 161.4 (J_{CF}=245 Hz), 147.7 (J_{CF}=11 Hz), 128.9 (J_{CF}=5 Hz), 115.7 (J_{CF}=14 Hz), 110.2, 102.5, (J_{CF}=25 Hz), 56.9, 53.2, 39.4, 34.3; K.F. Water = 0.87%; Anal. Calcd for $C_{12}H_{13}N_2O_3F_1$ with 0.87% water: C, 56.64; H, 5.25; N, 11.01. Found: C, 56.78; H, 5.34; N, 11.01. HRMS Calcd for $C_{12}H_{13}N_2O_3F_1$: 252.0910. Found: 252.0902.

Step 4: 2-(4-amino-2-fluorophenyl)-2-carbomethoxypyrrolidinone

A 100 mL recovery flask containing 2-(4-amino-2-fluorophenyl)-2-carbomethoxypyrrolidinone (EXAMPLE 66, Step 3, 930 mg, 3.7 mmol) was charged with 26 mL DMSO and sodium cyanide (542 mg, 11.1 mmol). This rose colored suspension was heated to 150°C for 30 minutes becoming reddish/brown in color with some gas evolution. At this time, the reaction was cooled to RT, DMSO

removed under reduced pressure (approx. 60°C, 0.1 mm Hg), with the resulting residue diluted with 30 mL brine and extracted three times with dichloromethane (30 mL). The combined organics were washed once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give 521 m g of a red/brown oil. TLC indicated remaining product in the brine layers and they were combined and extracted three times with ethyl acetate (30 mL). These combined organics were washed once with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give an additional 230 m g of a red/brown oil. These crude extracts were purified by LC on 49 g (230-400) silica gel eluting with 5% methanol/ethyl acetate to afford 628 mg (88%) of the title compound as a light yellow solid. mp 157-160°C; R_f 0.24 (ethyl acetate); IR (mull) 3465, 3363, 1680, 1630, 1614, 1515, 1447, 1285, 830, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (bs, 1H, O=C-NH), 6.85 (t, 1H, J=8.4 Hz, aromatic), 6.31 (m, 2H, aromatic), 5.28 (bs, 2H, NH_2), 3.48 (t, 1H, J=9.4 Hz, Ph-CH), 3.24 (m, 2H, C-CH_2s), 2.35 (m, 1H, N-CH_{2a}), 1.95 (m, 1H, N-CH_{2b}); ^{13}C NMR (75 MHz, $CDCl_3$) 178.8, 161.9 (J_{CF}=244 HZ), 147.5 (J_{CF}=11 Hz), 130.4 (J_{CF}=6 Hz), 115.7 (J_{CF}=15 Hz), 111.1 (J_{CF}=2 Hz), 102.3 (J_{CF}=25 Hz), 41.5, 40.5, 30.1; HRMS Calcd for $C_{10}H_{11}N_2O_1F_1$ + H: 195.0134. Found: 195.0937.

Step 5: 3-(4-amino-2-fluorophenyl)pyrrolidine

100 mL round bottom flask equipped with spinbar and reflux condenser was charged with 2-(4-amino-2-fluorophenyl)-2-carbomethoxypyrrolidinone (EXAMPLE 66, Step 4, 430 mg, 2.2 mmol) and 22 mL freshly distilled THF followed by cooling to 0°C. This light yellow homogeneous solution was treated with a 1M solution of lithium aluminumhydride (11 mL, 11 mmol) instantly becoming an opaque light rose color with copious gas evolution. The reaction was warmed to RT then heated to reflux with the formation of a gelatinous precipitate. After 20 hours, the now green/yellow thick suspension was successively quenched by the addition of 0.42 mL water, 0.38 mL 5N sodium hydroxide, and 1.5 mL water. The resulting thick gelatinous suspension was diluted with ethyl acetate, filtered through a pad of *Celite*, and concentrated to give 392 mg of a yellow oil. This material was purified by LC on 25 g (230-400) silica gel eluting with 2:17:81 sat. NH_4OH:methanol:dichloromethane to afford 295 mg (74%) of the title compound as a light yellow oil. This material was dissolved in a mixture of methanol/ethylacetate and treated with gaseous HCl with no observable change. This solution was concentrated to afford a peach colored foam that failed to recrystallize from many different solvent combinations. R_f 0.20 (2:17:81 sat NH_4OH:methanol:dichloromethane); IR (mull) 3139, 3042, 3016, 2766, 2562, 1514,

1485, 1444, 1266, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (t, 1H, J=8.2 Hz, aromatic), 6.39 (m, 2H, aromatic), 3.70 (bs, 2H, Ph-NH_2s), 3.27 (m, 2H, methine, N-CH_{2a}-CH), 3.11 (m, 2H, N-CH_2s-CH2), 2.80 (dd, 1H, J=6.2 & 8.9 Hz, N-CH_{2b}-CH), 2.30 (bs, 1H, NH), 2.14 (m, 1H, N-CH_2-CH_{2a}), 1.81 (m, 1H, N-CH_2-CH_{2b}); ^{13}C NMR (75 MHz, $CDCl_3$) 161.4 (J_{CF}=243 Hz), 146.0 (J_{CF}=11 Hz), 128.4 (J_{CF}=7 HZ), 119.9 (J_{CF}=152 HZ), 110.5 (J_{CF}=2 HZ), 102.1 (J_{CF}=26 HZ), 53.6, 47.0, 38.1, 32.9; Anal. Calcd for $C_{10}H_{13}N_2F_1$: C, 47.45; H, 5.93; N, 11.07. Found: C, 47.10; H, 6.10; N, 10.74. HRMS Calcd for $C_{10}H_{13}N_2F_1$: 180.1063. Found: 180.1060.

EXAMPLE 67 (S)-(-)-N-[[3-[3-Fluoro-4-(dihydrothien-3-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 3-Fluoro-4-[3-(hydroxy)tetrahydrothiophen-3-yl]benzenaminecarboxylic acid phenylmethyl ester

A solution of 1-(3-fluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (EXAMPLE 20, Step 1, 1.00 g) in dry tetrahydrofuran (16 mL) at -78°C under N_2 is treated with sec-butyllithium (1.3 M in cyclohexane, 3.30 mL) dropwise over 2 mins, and the resulting mixture is stirred at -78°C for 2 hrs. The mixture is then treated with a solution of tetrahydrothiophen-3-one (423 mg) in dry tetrahydrofuran (4.1 mL) dropwise over 2 mins and is stirred at -78°C, allowing the cooling bath to expire over 4 hrs. The mixture is then quenched with saturated aqueous ammonium chloride (25 mL), diluted with water (25 mL), the layers are separated, and the combined organic phase is washed with saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is dissolved in methanol (16 mL) and treated with anhydrous potassium carbonate (1.09 g), and the mixture is stirred at ambient temperature for 30 mins, concentrated under reduced pressure, diluted with water (20 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic phase is washed with saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude 3-fluoro-4-[3-(hydroxy)tetrahydrothiophen-3-yl]benzenamine intermediate (R_f = 0.37 by TLC, ethyl acetate/hexane (50/50)). A solution of this intermediate in tetrahydrofuran (16 mL) and water (8 mL) is then treated with sodium bicarbonate (662 mg) and benzyl chloroformate (0.56 mL), and the resulting mixture is stirred at ambient temperature for 4 hrs, diluted with water (8 mL), the layers are separated, and the organic phase is washed with saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica gel (230 - 400 mesh, 150 g),

eluting with ethyl acetate/hexane (25/75), and those fractions with an R_f = 0.19 by TLC (ethyl acetate/hexane, 25/75) are pooled and concentrated to give the title compound, mp 134 - 135°C.

Step 2: 3-Fluoro-4-(dihydrothien-3-yl)benzenaminecarboxylic acid phenylmethyl ester

Following the general procedure of EXAMPLE 17, Step 2, and making non-critical variations but substituting 3-fluoro-4-[3-(hydroxy)tetrahydrothiophen-3-yl]benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 67, Step 1) for 4-hydroxy-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1-piperidinecarboxylic acid phenylmethyl ester, the title compound is obtained as a mixture of the 2,5- and 4,5-dihydro regioisomers. NMR ($CDCl_3$, 400 MHz) 7.40, 7.21, 7.14, 7.02, 6.73, 6.69, 6.31, 5.21, 4.10, 3.94, 3.33 and 3.15 δ.

Step 3: (R)-3-[3-Fluoro-4-(dihydrothien-3-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone

Following the general procedure of EXAMPLE 17, Step 3, and making non-critical variations but substituting 3-fluoro-4-(dihydrothien-3-yl)benzenaminecarboxylic acid phenylmethyl ester (EXAMPLE 67, Step 2, mixture of the 2,5- and 4,5-dihydro regioisomers) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl] amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained as a mixture of the 2,5- and 4,5-dihydro regioisomers. HRMS calculated for $C_{14}H_{14}N_1F_1O_3S_1$: 295.0678. Found: 295.0676.

Step 4: (R)-3-[3-Fluoro-4-(dihydrothien-3-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

Following the general procedure of EXAMPLE 17, Step 4, and making non-critical variations but substituting (R)-3-[3-fluoro-4-(dihydrothien-3-yl)phenyl]-5-hydroxymethyl-2-oxazolidinone (EXAMPLE 67, Step 3, mixture of the 2,5- and 4,5-dihydro regioisomers) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained as a mixture of the 2,5- and 4,5-dihydro regioisomers. HRMS calculated for $C_{15}H_{16}N_1F_1O_5S_2$: 373.0454. Found: 373.0440.

Step 5: (S)-N-[[3-[3-Fluoro-4-(dihydrothien-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 17, Step 5, and making non-critical variations but substituting (R)-3-[3-fluoro-4-(dihydrothien-3-yl)phenyl]-5-

[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (EXAMPLE 67, Step 4, mixture of the 2,5- and 4,5-dihydro regioisomers) for (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained as a mixture of the 2,5- and 4,5-dihydro regioisomers. Anal. calculated for $C_{16}H_{17}F_1N_2O_3S_1$: C, 57.13; H, 5.09; N, 8.33. Found: C, 56.89; H, 5.18; N, 8.24.

EXAMPLE 68 (5S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1-oxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (68a) and (5S)-N-[[3-[3-Fluoro-4-(4,5-dihydro-1-oxido-3-thienyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (68b)

Following the general procedure of EXAMPLE 63, and making non-critical variations but substituting (S)-N-[[3-[3-fluoro-4-(dihydrothien-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 67, Step 5, mixture of the 2,5- and 4,5-dihydro regioisomers) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and separating the regioisomers by chromatography on silica gel (230 - 400 mesh, methanol/methylene chloride (4/96) eluent), the title compounds are obtained. mp (68a) 208 - 210°C (decomp.); NMR (68b) ($CDCl_3$, 400 MHz) 7.55, 7.46, 7.27, 7.13, 6.11, 4.82, 4.07, 3.82 - 3.62, 3.43, 3.23, 3.10 and 2.03 δ.

EXAMPLE 69 (S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (69a) and (S)-N-[[3-[3-Fluoro-4-(4,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (69b)

Following the general procedure of EXAMPLE 50, and making non-critical variations but substituting (S)-N-[[3-[3-fluoro-4-(dihydrothien-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 67, Step 5, mixture of the 2,5- and 4,5-dihydro regioisomers) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and separating the regioisomers by HPLC (Chiralpak AD, 10% isopropanol/methanol (0.05% diethylamine), 0.5 mL/min), the title compounds are obtained. mp (69a) 183 - 185°C (decomp.); (69b) 238 - 239°C (decomp.).

EXAMPLE 70 (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-3-yl]phenyl]-5-oxazolidinyl]-

methyllacetamide

Step 1: 5,6-Dihydro-3-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of EXAMPLE 20, Step 2, and making non-critical variations but substituting 1-(1,1-dimethylethoxycarbonyl)-3-piperidone for 1-(1,1-dimethylethoxycarbonyl)-4-piperidone and isolating the desired regioisomer by chromatography on silica gel (70 - 230 mesh, ethyl acetate/hexane (10/90) eluent), the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 5.92, 4.04, 3.49, 2.30 and 1.47 δ.

Step 2: (S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-5,6-dihydro-1(2H)-pyridine-1-carboxylic acid 1,1-dimethylethyl ester

Following the general procedure of EXAMPLE 38, Step 1, and making non-critical variations but substituting 5,6-dihydro-3-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 70, Step 1) for 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.41, 7.25, 7.17, 6.06, 4.79, 4.19, 4.06, 3.78, 3.75 - 3.59, 3.57, 2.32, 2.03 and 1.49 δ.

Step 3: (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-3-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

A solution of (S)-3-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-5,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 70, Step 2, 158 mg) in dry acetonitrile under N_2 is treated with iodotrimethylsilane (62 μL) dropwise, and the resulting solution is stirred at ambient temperature for 50 mins, during which additional iodotrimethylsilane (25 μL) is added. The reaction is then treated with methanol (59 μL), stirred for 5 mins and concentrated under reduced pressure to give the deprotected intermediate. A mixture of this intermediate and triethylamine (0.122 mL) in dry methylene chloride (3.6 mL) at 0°C under N_2 is treated with acetoxyacetyl chloride (47 μL), and the resulting mixture is stirred at 0°C for 2 hrs and at ambient temperature for 2 hrs and then diluted with methylene chloride (20 mL), washed with water (10 mL), saturated aqueous sodium bicarbonate (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica gel (70 - 230 mesh, 15 g), eluting with methanol/methylene chloride (5/95), and those fractions with an Rf = 0.5 by TLC (methanol/chloroform, 10/90) are pooled and concentrated to give the title

compound, HRMS calculated for $C_{21}H_{24}N_3F_1O_6 + H_1$: 434.1727. Found: 434.1741.

EXAMPLE 71 (S)-N-[[3-[4-[1-(Hydroxyacetyl)-5,6-dihydro-2H-pyridin-3-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-3-yl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 70, Step 3, 105 mg) and anhydrous potassium carbonate (67 mg) in methanol (4.8 mL) is stirred under N_2 at ambient temperature for 2 hrs and is then neutralized with hydrochloric acid (1 M), diluted with water (10 mL) and methylene chloride (40 mL), and the layers are separated. The organic phase is washed with saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which is then chromatographed on silica gel (70 - 230 mesh, 15 g), eluting with methanol/methylene chloride (5/95). Pooling and concentration of those fractions with an R_f = 0.30 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 188 - 190°C.

EXAMPLE 72 (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,4-dihydro-2H-pyridin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: 3-Hydroxy-3-[4-[[(phenylmethoxy)carbonyl]amino]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester

Following the general procedure of EXAMPLE 67, Step 1, and making non-critical variations but substituting N-(carbobenzyloxy)-3-piperidone for tetrahydrothiophen-3-one, the title compound is obtained, mp 137 - 139°C.

Step 2: 3,4-Dihydro-5-[4-[[(phenylmethoxy)carbonyl]amino]-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester

Following the general procedure of EXAMPLE 17, Step 2, and making non-critical variations but substituting 3-hydroxy-3-[4-[[(phenylmethoxy)carbonyl]amino]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 72, Step 1) for 4-hydroxy-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1-piperidinecarboxylic acid phenylmethyl ester, the title compound is obtained, mp 138 - 139°C.

Step 3: (R)-3,4-Dihydro-5-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester

Following the general procedure of EXAMPLE 17, Step 3, and making non-critical variations but substituting 3,4-Dihydro-5-[4-

[[(phenylmethoxy)carbonyl]amino] -2-fluorophenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 72, Step 2) for 3,6-dihydro-4-[4-[[(phenylmethoxy)carbonyl]amino]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, HRMS calculated for $C_{23}H_{23}N_2F_1O_5$: 426.1591. Found: 426.1594.

Step 4: (R)-3,4-Dihydro-5-[4-[5-[[(methylsulfonyl)oxylmethyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester

Following the general procedure of EXAMPLE 17, Step 4, and making non-critical variations but substituting (R)-3,4-Dihydro-5-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 72, Step 3) for (R)-(-)-3,6-dihydro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.39, 7.27, 7.18, 5.23, 4.93, 4.47, 4.15, 3.95, 3.71, 3.11, 2.44 and 1.97 δ.

Step 5: (S)-(-)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,4-dihydro-1(2H)-pyridinecarboxylic acid phenylmethyl ester

Following the general procedure of EXAMPLE 17, Step 5, and making non-critical variations but substituting (R)-3,4-Dihydro-5-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 72, Step 4) for (R)-(-)-3,6-dihydro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]-1(2H)-pyridinecarboxylic acid phenylmethyl ester, the title compound is obtained, HRMS calculated for $C_{25}H_{26}F_1N_3O_5$: 467.1856. Found: 467.1862.

Step 6: (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,4-dihydro-2H-pyridin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 70, Step 3, and making non-critical variations but substituting (S)-(-)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,4-dihydro-1(2H)-pyridinecarboxylic acid phenylmethyl ester (EXAMPLE 72, Step 5) for (S)-(-)-5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, mp 146 - 148°C.

EXAMPLE 73 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,4-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,4-dihydro-2H-

pyridin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 72, Step 6, 238 mg) and anhydrous potassium carbonate (151 mg) in methanol (27 mL) is stirred under N_2 at ambient temperature for 2 hrs and is then neutralized with hydrochloric acid (1 M) and concentrated under reduced pressure. The residue is then diluted with methylene chloride (100 mL) and saline (50 mL) and the resultant insoluble product is removed by filtration and dried under reduced pressure. The layers in the filtrate are separated and the organic phase is dried over anhydrous sodium sulfate and concentrated under reduced pressure to give additional quantities of the title compound, mp 171 - 173°C.

EXAMPLE 74 (S)-(-)-N-[[3-[4-[1-Formyl-4-fluoro-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-Hydroxy-4-[2-fluoro-4-[[(phenylmethoxy)carbonyl]amino] phenyl]-1-piperidinecarboxylic acid phenylmethyl ester

A solution of 1-(3-fluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (EXAMPLE 20, Step 1, 1.00 g) in dry tetrahydrofuran (9.8 mL) at -78°C under N_2 is treated with sec-butyllithium (1.3 M in cyclohexane, 3.64 mL) dropwise over 3 mins, and the resulting mixture is stirred at -78°C for 2 hrs. The mixture is then treated with a solution of N-(carbobenzyloxy)-4-piperidone (919 mg) in dry tetrahydrofuran (3.9 mL) dropwise over 2 mins and is stirred at -78°C for 2 hrs. The mixture is then warmed to -20°C over 1 hr and quenched with saturated aqueous ammonium chloride (5 mL), diluted with water (20 mL), the layers are separated, the aqueous phase is extracted with diethyl ether (20 mL), and the combined organic phase is washed with saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is dissolved in methanol (15 mL) and treated with anhydrous potassium carbonate (544 mg, 3.94 mmol), and the mixture is stirred at ambient temperature for 30 mins, concentrated under reduced pressure, diluted with diethyl ether (30 mL), washed with water (20 mL) and saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude 4-(hydroxy)piperidinyl benzenamine intermediate (R_f = 0.25 by TLC, ethyl acetate/hexane (50/50)). A mixture of this intermediate and N,N-dimethylaniline (1.00 mL) in tetrahydrofuran (20 mL) is cooled to -20°C and treated with benzyl chloroformate (0.59 mL), and the resulting mixture is stirred at -20°C for 1 hr. The mixture is then diluted with saturated aqueous potassium carbonate (5 mL), water (25 mL) and diethyl ether (25 mL), the layers are separated, and the organic phase is washed with water (20 mL)

and saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of ethyl acetate/hexane (25/75 - 50/50), and those fractions with an R_f = 0.47 by TLC (ethyl acetate/hexane, 50/50) are pooled and concentrated to give the title compound, NMR (400 MHz, $CDCl_3$) 7.35, 7.00, 6.92, 5.20, 5.16, 4.10, 3.32, 2.15 and 1.79 δ and Anal. calculated for $C_{27}H_{27}FN_2O_5$: C, 67.77; H, 5.69; N, 5.85. Found: C, 67.44; H, 5.83; N, 5.65.

Step 2: 4-Fluoro-4-[4-[[(phenylmethoxy)carbonyl]amino]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester

To a solution of diethylaminosulfur trifluoride (DAST, 0.65 mL) in dry methylene chloride (49 mL) at -78°C under N_2 is added a solution of 4-hydroxy-4-[4-[[(phenylmethoxy)carbonyl]amino]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 74, Step 1, 2.25 g) in dry methylene chloride (47 mL) over 2 mins. The resulting mixture is stirred at -78°C for 1 hr and at ambient temperature for 30 mins and is then adjusted to pH 8 with saturated aqueous sodium bicarbonate (50 mL), diluted with water (50 mL), and the layers are separated. The organic phase is washed with water (25 mL) and saline (25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with methanol/methylene chloride (0.5/99.5). Those fractions with an R_f = 0.27 by TLC (ethyl acetate/hexane, 25/75) are pooled and concentrated to give the title compound (contaminated with approx. 15% of the elimination side product). An analytical sample is prepared by radial chromatography (1000μ silica gel rotor, ethyl acetate/hexane (20/80) eluent), mp 116 - 118°C.

Step 3: (R)-4-Fluoro-4-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester

A solution of 4-fluoro-4-[4-[[(phenylmethoxy)carbonyl]amino]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 74, Step 2, 2.03 g, contaminated with the elimination side product) in dry tetrahydrofuran (21 mL) at -78°C under N_2 is treated with n-butyllithium (2.80 mL, 1.6 M in hexanes) dropwise over 5 mins. The resulting mixture is stirred at -78°C for 1.25 hrs and is then treated with (R)-(-)-glycidyl butyrate (0.63 mL) dropwise. The resulting solution is stirred at -78°C for 1 hr, warmed to ambient temperature and stirred for an additional 20 hrs, after which the reaction is quenched with saturated aqueous ammonium chloride (10 mL), diluted with water (10 mL), and the layers are

separated. The organic phase is washed with saline (10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 250 g), eluting with methanol/methylene chloride (3/97). Pooling and concentration of those fractions with an R_f = 0.51 by TLC (methanol/chloroform, 10/90) and repurification by silica gel chromatography (230 - 400 mesh, 100 g, methanol/methylene chloride (4/96) eluent) gives the title compound (contaminated with the elimination side product from the starting material). An analytical sample is prepared by radial chromatography (2000μ silica gel rotor, ethyl acetate/hexane (60/40) eluent), NMR (400 MHz, $CDCl_3$) 7.45, 7.34, 7.18, 5.16, 4.74, 4.17, 3.97, 3.72, 3.22, 2.25 and 1.90 δ and HRMS calculated for $C_{23}H_{24}F_2N_2O_5$: 446.1653. Found: 446.1660.

Step 4: (R)-4-Fluoro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester

A solution of (R)-4-fluoro-[4-[5-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 74, Step 3, 0.17 g) and triethylamine (0.080 mL) in dry methylene chloride (2 mL) at 0°C under N_2 is treated with methanesulfonyl chloride (0.031 mL) dropwise. The resulting mixture is stirred at 0°C for 12 hrs and at ambient temperature for 1.5 hrs, diluted with methylene chloride (10 mL), washed with water (5 mL), saturated aqueous sodium bicarbonate (5 mL) and saline (5 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound, HRMS calculated for $C_{24}H_{26}F_2N_2O_7S+H_1$: 525.1507. Found: 525.1522.

Step 5: (S)-N-[[2-Oxo-3-[4-(4-fluoro-4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide

A mixture of (R)-4-fluoro-4-[4-[5-[[(methylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid phenylmethyl ester (EXAMPLE 74, Step 4, 0.190 g) and concentrated aqueous ammonium hydroxide (2 mL) in isopropanol (1 mL) and acetonitrile (2 mL) is placed in a sealed tube and immersed in an oil bath maintained at 95°C for 18 hrs. The mixture is then diluted with methylene chloride (20 mL), washed with water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude 5-aminomethyl-2-oxazolidinone intermediate (R_f = 0.13 by TLC, methanol/chloroform, 5/95). A solution of this intermediate and pyridine (0.088 mL) in dry methylene chloride (3.6 mL) under N_2 is treated with acetic anhydride (0.051 mL), and the resulting solution is stirred at ambient temperature for 18 hrs. The

mixture is then diluted with methylene chloride (10 mL), washed with water (5 mL), saturated aqueous sodium bicarbonate (5 mL) and saline (5 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude acetamide intermediate which, after being combined with approx. 1.5 g of crude product from previous reaction workups, is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (1/99 - 2/98). Pooling and concentration of those fractions with an R_f = 0.18 by TLC (methanol/chloroform, 5/95) gives 0.80 g (approx. 70% from the mesylate) of the product (contaminated with the elimination side product) as an amorphous, white solid which is used without further purification. A mixture of this intermediate (0.75 g) and 20% palladium hydroxide on carbon (200 mg) in methanol (30 mL) is shaken on a Parr apparatus under a hydrogen atmosphere at 40 psi for 1 hr, the catalyst is removed by filtration through Celite and the filtrate is concentrated under reduced pressure. The residue is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of triethylamine/methanol/methylene chloride (1/9/90 - 1/4/95), and those fractions having an R_f = 0.19 by TLC (triethylamine/methanol/chloroform, 1/9/90) are pooled and concentrated to give the title compound, mp 163 - 165°C.

Step 6: (S)-(-)-N-[[3-[4-[1-Formyl-4-fluoro-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-3-N-[[2-oxo-3-[4-(4-fluoro-4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 74, Step 5, 205 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145 mg) and formic acid (28 μL) in dry tetrahydrofuran (11.6 mL) is diluted with water to solubilize all reactants and stirred at ambient temperature for 6 hrs. The reaction is then diluted with methylene chloride (30 mL), washed with water (20 mL) and saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue is chromatographed on silica gel (230 - 400 mesh, 40 g), eluting with a gradient of methanol/methylene chloride (3/97 - 5/95). Those fractions with an R_f = 0.40 by TLC (methanol/chloroform, 10/90) are pooled and concentrated and the residue is recrystallized from chloroform/diethyl ether to give the title compound, mp 180 - 181°C (decomp.).

EXAMPLE 75 (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: 2,3,4,7-Tetrahydro-5-[[(trifluoromethyl)sulfonyl]oxyl-1*H*-azepine-1-carboxylic acid 1,1-dimethylethyl ester (a) and 2,3,6,7-Tetrahydro-4-[[(trifluoromethyl)sulfonyl]oxyl-1*H*-azepine-1-carboxylic acid 1,1-dimethylethyl ester (b)

Following the general procedure of EXAMPLE 20, Step 2, and making non-critical variations but substituting 1-(1,1-dimethylethoxycarbonyl)-1,2,3,5,6,7-hexahydroazepin-4-one for 1-(1,1-dimethylethoxycarbonyl)-4-piperidone and isolating the regioisomers by chromatography on silica gel (230 - 400 mesh, ethyl acetate/hexane (5/95) eluent), the title compounds are obtained, (a) NMR ($CDCl_3$, 400 MHz) 5.87, 3.95, 3.55, 2.57, 1.95 and 1.46 δ and (b) NMR ($CDCl_3$, 400 MHz) 5.90, 3.54, 2.69, 2.35 and 1.47 δ.

Step 2: (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-2,3,4,7-tetrahydro-1H-azepinecarboxylic acid 1,1-dimethylethyl ester

Following the general procedure of EXAMPLE 38, Step 1, and making non-critical variations but substituting 2,3,4,7-tetrahydro-5-[[(trifluoromethyl)sulfonyl]oxy]-1(1H)-azepinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 75, Step 1(A)) for 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz) 7.31, 7.12 - 6.95, 5.84, 4.76, 4.00, 3.98, 3.76, 3.61, 3.58, 2.51, 1.97, 1.85 and 1.42 δ.

Step 3: (S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 70, Step 3, and making non-critical variations but substituting (S)-5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-2,3,4,7-tetrahydro-1H-azepine-1-carboxylic acid 1,1-dimethylethyl ester (EXAMPLE 75, Step 2) for (S)-(-)-3-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-5,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, HRMS calculated for $C_{22}H_{26}F_1N_3O_6$: 448.1884. Found: 448.1888.

EXAMPLE 76 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 71, and making non-critical variations but substituting (S)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,4,7-tetrahydro-1H-azepin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 75, Step 3) for (S)-(-)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-

3-yl]phenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, NMR ($CDCl_3$, 400 MHz, mixture of rotamers) 7.41, 7.09 - 7.18, 6.07, 6.00, 5.87, 4.78, 4.25, 4.21, 4.05, 3.92, 3.87, 3.78, 3.67, 3.51, 2.63, 2.03 and 1.97 δ and HRMS calculated for $C_{20}H_{24}F_1N_3O_5$: 405.1700. Found: 405.1694.

EXAMPLE 77 (S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Step 1: (S)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-2,3,6,7-tetrahydro-1H-azepine-1-carboxylic acid 1,1-dimethylethyl ester

Following the general procedure of EXAMPLE 38, Step 1, and making non-critical variations but substituting 2,3,6,7-tetrahydro-4-[[(trifluoromethyl)sulfonyl] oxy]-1(1H)-azepinecarboxylic acid 1,1-dimethylethyl ester (EXAMPLE 75, Step 1(B)) for 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, mp 164 - 165°C.

Step 2: (S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 70, Step 3, and making non-critical variations but substituting (S)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-2,3,6,7-tetrahydro-1H-azepine-1-carboxylic acid 1,1-dimethylethyl ester (EXAMPLE 77, Step 1) for (S)-(-)-3-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-5,6-dihydro-1(2H)-pyridinecarboxylic acid 1,1-dimethylethyl ester, the title compound is obtained, NMR ($CDCl_3$, 400 MHz, mixture of rotamers) 7.39, 7.15, 6.22, 5.90, 4.79, 4.04, 3.80 - 3.50, 2.70, 2.50, 2.19 and 2.02 δ and Anal. calculated for $C_{22}H_{26}F_1N_3O_6$: C, 59.05; H, 5.86; N, 9.39. Found: C, 58.70; H, 5.80; N, 9.43.

EXAMPLE 78 (S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 71, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,6,7-tetrahydro-1H-azepin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 77, Step 2) for (S)-(-)-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-3-yl]phenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, NMR ($CDCl_3$, 400 MHz, mixture of rotamers) 7.41, 7.13, 6.08, 5.90, 4.78, 4.22, 4.04, 3.85 - 3.59, 3.51 - 3.41, 2.70, 2.52 and 2.02 δ and Anal. calculated for $C_{20}H_{24}F_1N_3O_5$: C,

59.25; H, 5.97; N, 10.36. Found: C, 58.91; H, 6.04; N, 10.19.

EXAMPLE 79 (5S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)hexahydro-1H-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (as a mixture of diastereomers)

Following the general procedure of EXAMPLE 48, and making non-critical variations but substituting (S)-(-)-N-[[3-[4-[1-(hydroxyacetyl)-2,3,4,7-tetrahydro-1H-azepin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 76, Step 3) for (S)-(-)-N-[[3-[4-(3,6-dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and purifying the product by chromatography on silica gel (70 - 230 mesh, methanol/methylene chloride (7.5/92.5) eluent), the title compound is obtained, HRMS calculated for $C_{20}H_{26}F_1N_3O_5 + H_1$: 408.1935. Found: 408.1928.

EXAMPLE 80 (*S*)-N-[[3-[3-Fluoro-4-(3,4-dihydro-2H-pyran-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 6-(tributylstannyl)-3,4-dihydro-2H-dihydropyran

A solution of 3,4-dihydro-2H-dihydropyran (2.000 g, 23.8 mmol) and N,N,N',N'-tetramethylethylenediamine (0.50 mL, 3.09 mmol) under a nitrogen atmosphere was cooled to 0 °C and treated with *n*-butyllithium (19.30 mL of a 1.6 M solution in hexane, 30.94 mmol). The mixture was then warmed to ambient temperature overnight. The resultant mixture was cooled to -78 °C, dry tetrahydrofuran (20 mL) was added, and then tributyltin chloride (6.40 mL, 23.8 mmol). The mixture was stirred at -78 °C for 1 h and then warmed to ambient temperature for 2 h. The reaction mixture was diluted with diethyl ether (50 mL), transferred to a separatory funnel and washed with 5% aqueous ammonnium hydroxide and brine. The organic layer was then dried, filtered and concentrated to give a crude product. Distillation of the residue under reduced pressure afforded 1.80 g (47%) of the title compound with a purity of 55%.

Step 2: (*S*)-N-[[3-[3-Fluoro-4-(3,4-dihydro-2H-pyran-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (*S*)-N-[[3-[3-fluoro-4-iodophenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (0.200 g, 0.53 mmol) in 1-methyl-2-pyrrolidinone (5 mL) under a nitrogen atmosphere was treated with Pd_2dba_3 (0.018 g, 0.02 mmol) and tri(2-furyl)phosphine (0.009 g, 0.04 mmol). After stirring 10 min at ambient temperature, the mixture was treated with 6-(tributylstannyl)-3,4-dihydro-2H-

dihydropyran (0.538 g, 55% purity, 0.80 mmol). The atmosphere was evacuated and filled with nitrogen three times and then the mixture heated to 90 °C for 24 h. At this time the reaction mixture was cooled to ambient temperature and poured into ethyl acetate. A precipitate was noticed and removed by filtering the mixture through Celite. The filtrate was transferred to a separatory funnel and washed with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with hexane, 20% acetone/hexane, and finally 5% methanol/dichloromethane. Appropriate fractions were combined and concentrated *in vacuo* to give 0.196 g of a material containing a small amount of 1-methyl-2-pyrrolidinone. Recrystallization provided 0.128 g (68%) of the title compound. mp 161-163 °C; MS(EI): m/z 334.

EXAMPLE 81 (S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

Step 1: 3-(4-Amino-2-fluorophenyl)-3-hydroxy-1-(1,1-diphenylmethyl)azetidine

Sec. butyllithium (22.5 mL of a 1.3M solution in cyclohexane, 29.5 mmol) was added dropwise to a stirred solution of 1-(3-fluorophenyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (Example 20, Step 1) (6.0 g, 23.7 mmol) at -78°C under nitrogen in dry THF (75 mL). After 2 hr a solution of 1-(1,1-diphenylmethyl)azetidin-3-one (5.6 g, 23.6 mmol) in dry THF (60 mL) was added dropwise and stirring continued at -78° for 2 hr, when the cooling bath was removed. After reaching room temperature, a solution of saturated ammonium chloride (75 mL) was added followed by water (200 mL). The mixture was extracted with ether (500 mL), washed with brine (100 mL), dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in methanol (150 mL) and anhydrous potassium carbonate (6.0 g, 43.5 mmol) added and then stirred overnight. The suspension was filtered and the filtrate evaporated. The residue was partitioned between ether (500 mL) and water (200 mL). The water was extracted with additional ether (200 mL) and the combined ether extracts washed with brine (100 mL), dried over magnesium sulfate, filtered and evaporated to afford an orange foam. Chromatography over silica gel (150 g, 40-60 μm) eluting with 25-50% ethyl acetate-hexane gave the title compound as a pale yellow foam. ^{1}H NMR δ ($CDCl_3$): 2.62, 3.53, 3.78, 4.41, 6.36, 6.41, 7.03, 7.14-7.30, 7.39-7.47.

Step 2: 3-(N-Carbobenzyloxy-3-fluoroanilin-4-yl)-3-hydroxy-1-(1,1-diphenylmethyl)azetidine

To a solution of 3-(4-amino-2-fluorophenyl)-3-hydroxy-1-(1,1-diphenylmethyl)azetidine (Example 81, Step 1, 5.10 g, 14.7 mmol) in acetone (75 mL) was added a solution of sodium bicarbonate (2.52 g, 30.0 mmol) in water (40 mL) to give a creamy suspension. Benzyl chloroformate (2.57 g, 15.1 mmol) was added and stirring continued overnight. The suspension was filtered and the acetone evaporated. The residue was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and evaporated to leave an amber foam. Chromatography over silica gel (150 g, 40-60 μM) eluting with 1-2% methanol-methylene chloride gave the title compound as a cream foam. HRMS: meas. 483.2087, theory 483.2084.

Step 3: N-Carbobenzyloxy-3-(N-carbobenzyloxy-3-fluoroanilin-4-yl)-3-hydroxyazetidine

Benzyl chloroformate (3.8 mL, 26.6 mmol) was added to a solution of 3-(N-carbobenzyloxy-3-fluoroanilin-4-yl)-3-hydroxy-1-(1,1-diphenylmethyl)azetidine (Example 81, Step 2, 1.60 g, 3.32 mmol) in benzene (30 mL) and then heated under reflux under nitrogen for 2 hr. The benzene was evaporated and the residue chromatographed over silica gel (150 g, 40-60 μm) eluting with 20-60% ethyl acetate-hexane. The title compound was obtained as a white foam. ^{1}H NMR δ ($CDCl_3$): 3.32, 4.19, 4.42, 5.08, 5.17, 6.98, 7.11, 7.19, 7.24-7.43.

Step 4: N-Carbobenzyloxy-3-(N-carbobenzyloxy-3-fluoroanilin-4-yl)azetidine.

Triethylsilane (30 mL) and trifluoroacetic acid (12 mL) were added to a solution of N-carbobenzyloxy-3-(N-carbobenzyloxy-3-fluoroanilin-4-yl)-3-hydroxyazetidine (Example 81, Step 3, 4.3 g, 9.55 mmol) in methylene chloride (40 mL) and stirred for 2 days. Removal of the solvents at 45°/0.75 mm gave an amber oil. Chromatography over silica gel (150 g, 40-60 μm) eluting with 1-3% methanol-chloroform yielded the title compound as a solid, m.p. 95°.

Step 5: (R)-(-)-N-Carbobenzyloxy-3-[2-fluoro-4-[5-hydroxymethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine

n-Butyllithium (5.25 mL of a 1.6 M solution in hexane, 8.40 mmol) was added dropwise to a stirred solution of N-carbobenzyloxy-3-(N-carbobenzyloxy-3-fluoroanilin-4-yl)azetidine (Example 81, Step 4, 3.63 g, 8.36 mmol) at -78° under nitrogen in dry THF (30 mL), then stirred for 2 hr. A solution of R-glycidyl butyrate (1.21 g, 8.40 mmol) in dry THF (3.0 mL) was added and the cooling bath removed after 15 min. After 18 hr, the solvent was removed and the residue partitioned between ethyl acetate (150 mL) and saturated ammonium chloride

solution (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered and evaporated leaving an amber oil. Chromatography over silica gel (150 g, 40-60 μm) eluting with 2-5% methanol-chloroform gave the title compound as a sticky foam. FAB-HRMS: theory 401.1513 (M+1); meas 401.1521.

Step 6: (R)-(-)-N-Carbobenzyloxy-3-[2-fluoro-4-[5-[[(3-nitrophenylsulfonyl)oxy]methyl]-2-oxo-3-oxazolidinyl]phenyl]azetidine

3-Nitrobenzenesulfonyl chloride (1.70 g, 7.67 mmol) was added to an ice cooled solution of (R)-(-)-N-carbobenzyloxy-3-[2-fluoro-4-[5-hydroxymethyl-2-oxo-3-oxazolidinyl]-phenyl]azetidine (Example 81, Step 5, 2.79 g, 6.97 mmol) and triethylamine (1.41 g, 14.0 mmol) in methylene chloride (40 mL). After 16 hr, water (50 mL) and methylene chloride (100 mL) were added. The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and evaporated. The residue was chromatographed over silica gel (150 g, 40-60 μm) eluting with 25-100% ethyl acetate-hexane to give the title compound as a sticky foam. FAB-HRMS: theory 586.1290 (M+1); meas 586.1295.

Step 7: (S)-(-)-N-Carbobenzyloxy-3-[2-fluoro-4-[5-azidomethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine

A mixture of sodium azide (1.44 g, 22.1 mmol) and (R)-(-)-N-carbobenzyloxy-3-[2-fluoro-4-[5-[[(3-nitrophenylsulfonyl)oxy]-methyl]-2-oxo-3-oxazolidinyl]phenyl]azetidine (Example 81, Step 6, 2.60 g, 4.44 mmol) in DMF (30 mL) was stirred for 16 hr, then filtered. The solvent was removed at 38°/0.75 mm and the residue extracted with ethyl acetate (100 mL) and washed with water (3 x 50 mL) and brine (50 mL). After drying over magnesium sulfate, filtration and evaporation gave a yellow oil. Chromatography over silica gel (150 g, 40-60 μm) eluting with 1-3% methanol-methylene chloride gave the title compound as a pale yellow foam. FAB-HRMS: theory 426.1577 (M+1); meas. 426.1580.

Step 8: (S)-(-)-N-Carbobenzyloxy-3-[2-fluoro-4-[5-aminomethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine

To a stirred solution of (S)-(-)-N-carbobenzyloxy-3-[2-fluoro-4-[5-azidomethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine (Example 81, Step 7, 1.63 g, 3.84 mmol) in dry THF (20 mL) was added triphenylphosphine (1.11 g, 4.23 mmol). After 3 hr, water (0.69 mL, 38.4 mmol) was added and the reaction stirred for 2 days at which time the solvents were evaporated. The residue was chromatographed over silica gel (150 g, 40-60 μm) eluting with 5-10% methanol-chloroform. The title compound was isolated as a viscous colorless oil. FAB-HRMS: theory 400.1672 (M+1); meas.

400.1676.

Step 9: (S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Pyridine (1.0 mL), acetic anhydride (1.0 mL) and a few crystals of 4-dimethylaminopyridine were added to a stirred solution of (S)-(-)-N-carbobenzyloxy-3-[2-fluoro-4-[5-aminomethyl-2-oxo-3-oxazolidinyl]phenyl]azetidine (Example 81, Step 8, 1.42 g, 3.56 mmol) in methylene chloride (30 mL), then stirred for 1 hr. The solvents were removed at 38°/0.75 mm and the residue chromatographed over silica gel (50 g, 40-60 μm) eluting with 1-2% methanol-chloroform. The title compound was isolated as a white foam. FAB-HRMS: theory 442.1778 (M+1); meas. 442.1777.

EXAMPLE 82 (S)-N-[[3-[3-Fluoro-4-[3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (S)-N-[[3-[3-fluoro-4-[1-(carbobenzyloxy)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 81, Step 9, 1.44 g, 3.26 mmol) in ethyl acetate (25 mL) and absolute ethanol (50 mL) was added to 10% Pd/C (1.0 g) and hydrogenated at 30 psi for 7 hr. Filtration and evaporation gave the title compound as a white glassy solid. FAB-HRMS: theory 308.1410 (M+1); meas. 308.1408.

EXAMPLE 83 (S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Triethylamine (150 μL, 1.08 mmol) and methyl chloroformate (65 μL, 0.84 mmol) were added to a chloroform (5 mL) suspension of (S)-N-[[3-[3-fluoro-4-[3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 82, 153 mg, 0.50 mmol) and stirred overnight. Additional chloroform (25 mL) was added and the solution washed with water (15 mL) and brine (15 mL). Drying over magnesium sulfate, filtration, and evaporation gave a foam. Chromatography over silica gel (50 g, 40-60 μm) eluting with 1-3% methanol-chloroform gave the title compound as a white solid. FAB-HRMS: theory 366.1465 (M+1); meas. 366.1468.

EXAMPLE 84 (S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

N-Formylbenzotriazole (115 mg, 0.78 mmol) was added to a stirred suspension of (S)-N-[[3-[3-fluoro-4-[3-azetidinyl]phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide (Example 82, 153 mg, 0.50 mmol) in THF (5 mL) and stirred overnight. The solvent was removed and the residue chromatographed over silica gel (50 g, 40-60 μm) eluting with 2-5% methanol-chloroform to give the title compound as a white foam. FAB-HRMS: theory 336.1356 (M+1); meas. 336.1357.

EXAMPLE 85 (S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 310 mg), methyl thiocyanatoacetate (121 mg, *Bull. Chem. Soc. Jpn.* **1972**, *45(5)*, 1507) and glacial acetic acid (55 mg) in absolute ethanol (5 mL) is stirred at reflux under N_2 for 4 hrs and then cooled to ambient temperature, diluted with methylene chloride (45 mL), washed with water (2 x 15 mL) and saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with methanol/methylene chloride (4/96), and those fractions with an R_f = 0.47 by TLC (methanol/chloroform, 10/90) are pooled and concentrated to give the title compound, mp 222 - 224°C (decomp.).

EXAMPLE 86 (S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-3,6-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 85, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 38) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 209 - 211°C (decomp.).

EXAMPLE 87 (S)-(-)-N-[[3-[4-[1-[5-Methyl-1,3,4-thiadiazol-2-yl]-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 2-Bromo-5-methyl-1,3,4-thiadiazole

To a solution of aqueous hydrobromic acid (48%, 40 mL) containing a trace amount of copper powder at -10°C is added a mixture of 2-amino-5-methyl-1,3,4-thiadiazole (2.88 g) and sodium nitrite (7.76 g) portionwise over 45 mins with vigorous stirring. The resulting mixture is stirred at -10°C for 1.5 hrs and at ambient temperature for an additional 1.5 hrs and is then cooled in an ice bath, neutralized with aqueous sodium hydroxide (50%), diluted with saturated aqueous

sodium hydrogensulfite till the mixture no longer turns potassium iodide-starch test paper blue and filtered to remove insoluble material (rinsing with hot water). The filtrate is extracted with methylene chloride (4 x 100 mL), and the combined organic phase is dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is then chromatographed on silica gel (70 - 230 mesh, 75 g), eluting with ethyl acetate/hexane (50/50). Pooling and concentration of those fractions with an R_f = 0.78 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 107 - 108°C.

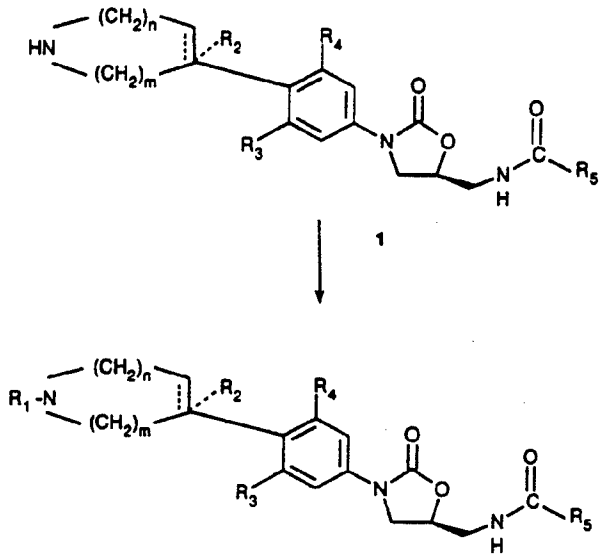
Step 2: (S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 20, 550 mg), 2-bromo-5-methyl-1,3,4-thiadiazole (EXAMPLE 87, Step 1, 323 mg) and potassium hydrogenphosphate (571 mg) in dimethyl sulfoxide (16 mL) is stirred under N_2 at 100°C for 2 hrs, cooled to ambient temperature, diluted with water (20 mL) and extracted with methylene chloride (3 x 20 mL). The combined organic phase is washed with water (20 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated to give the crude product which is then chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of methanol/methylene chloride (2/98 - 3/97). Pooling and concentration of those fractions with an R_f = 0.44 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 193 - 195°C.

EXAMPLE 88 (S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 87, Step 2, and making non-critical variations but substituting (S)-(-)-N-[[2-oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide (EXAMPLE 38) for (S)-(-)-N-[[2-oxo-3-[4-(4-piperidinyl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 229 - 231°C (decomp.).

CHART A



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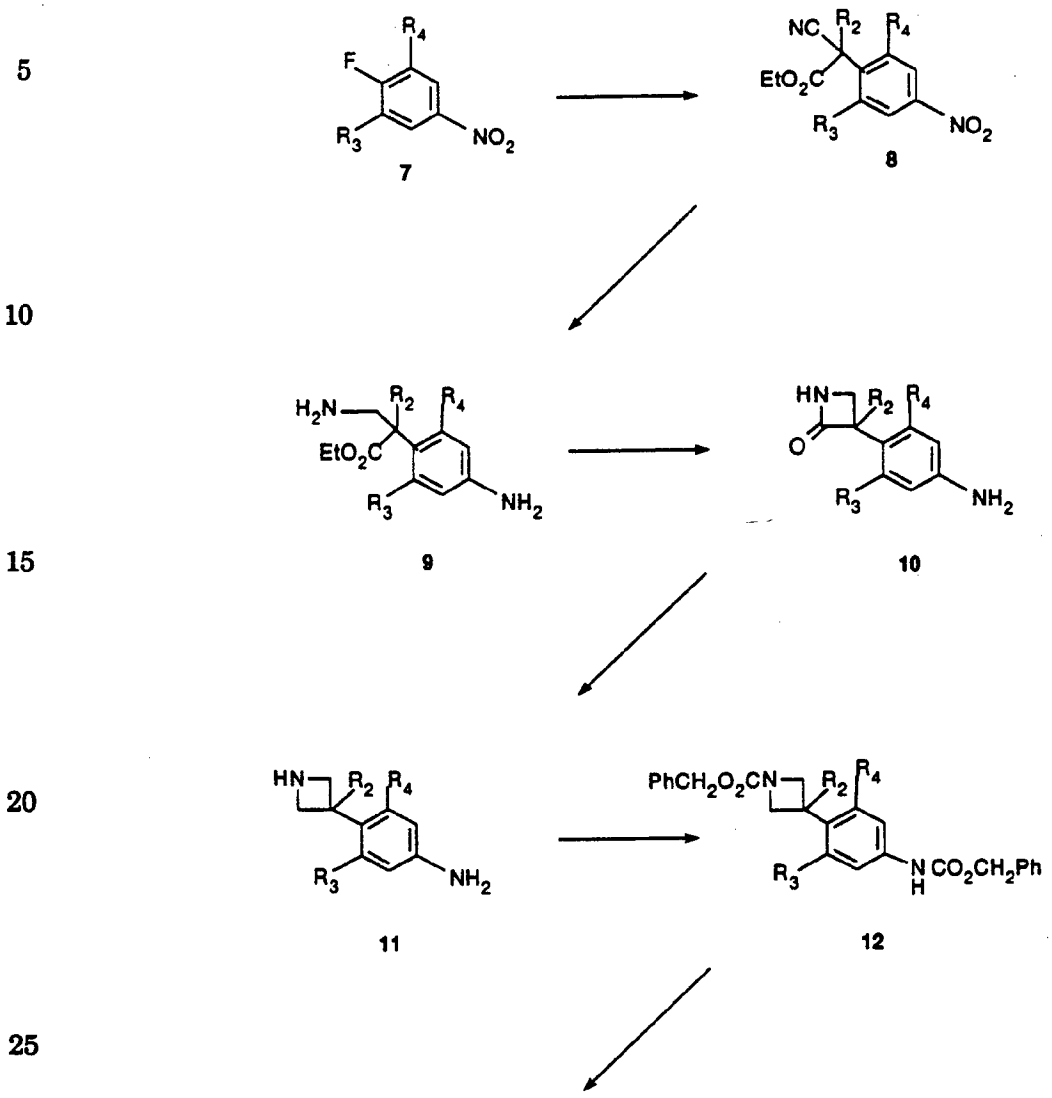
R_1	=	$-C(=O)(CH_2)_hOH$	**2'**
R_1	=	$-C(=O)R_{1-1}$, or $-C(=O)_i$-Het	**3**
R_1	=	$-C(=O)OR_{1-2}$	**4**
R_1	=	C_{1-6} alkyl optionally having one or more substituents	**5**
R_1	=	$-SO_2(CH_2)_h$-aryl	**6**

CHART B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R2
R4
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NH2
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HN
R2
R4
O
R3
NH2
10
HN
R2
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CO2CH2Ph
12

CHART B (Continued)

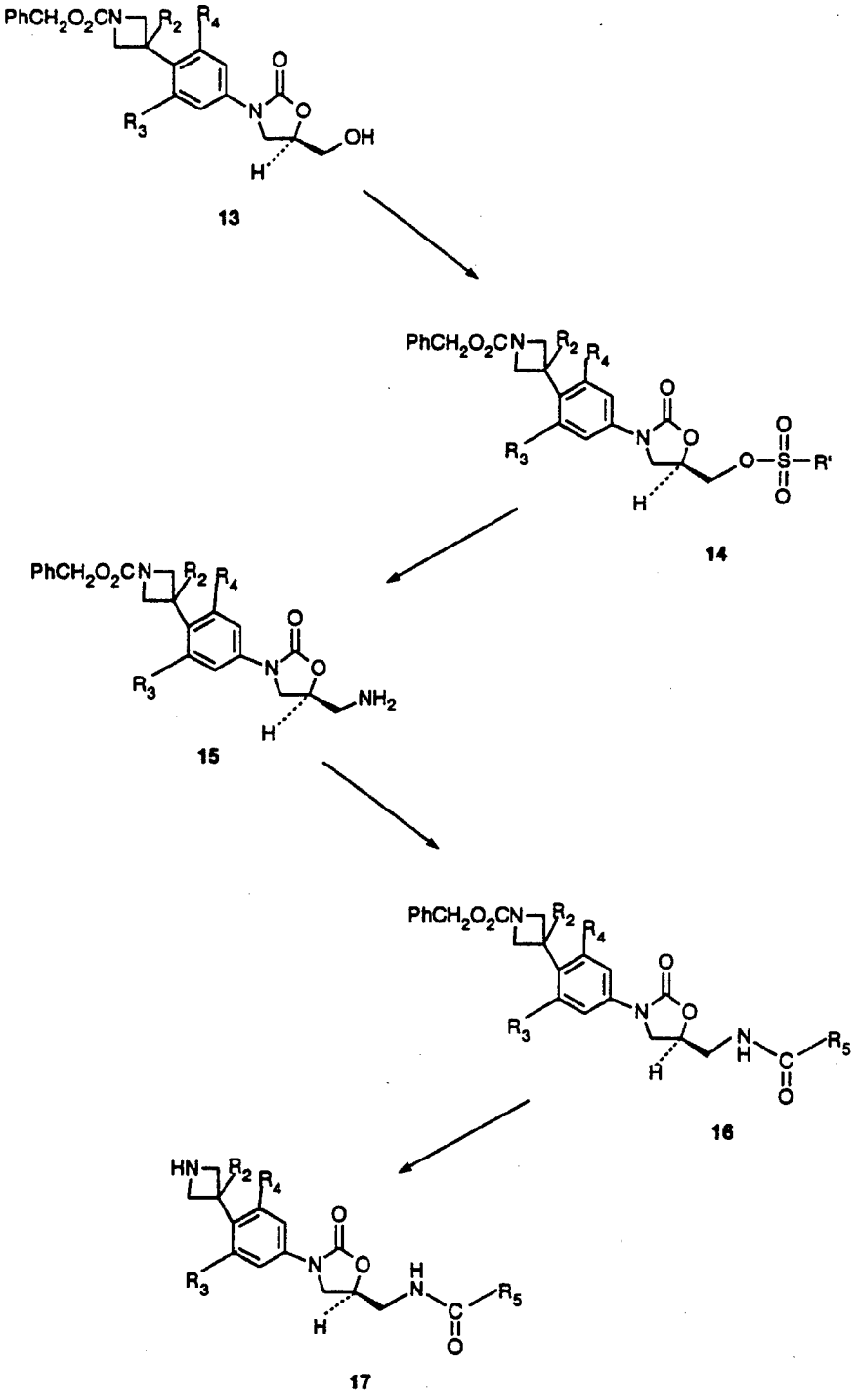

CHART C

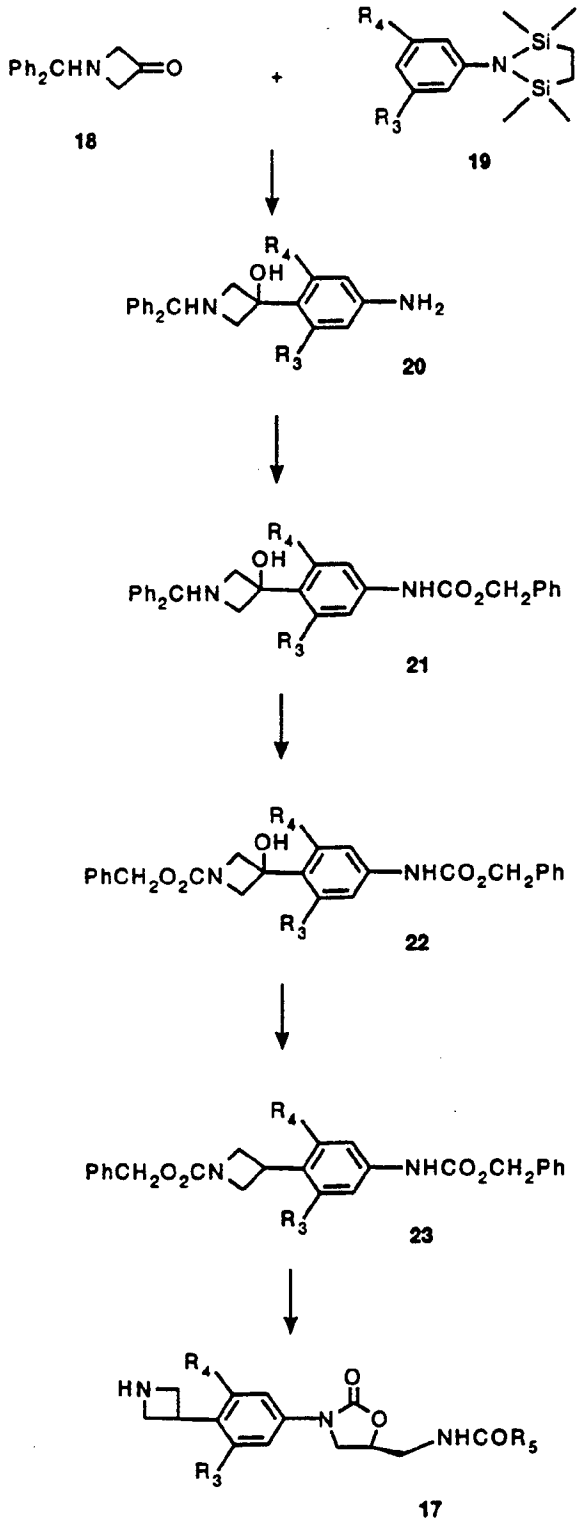
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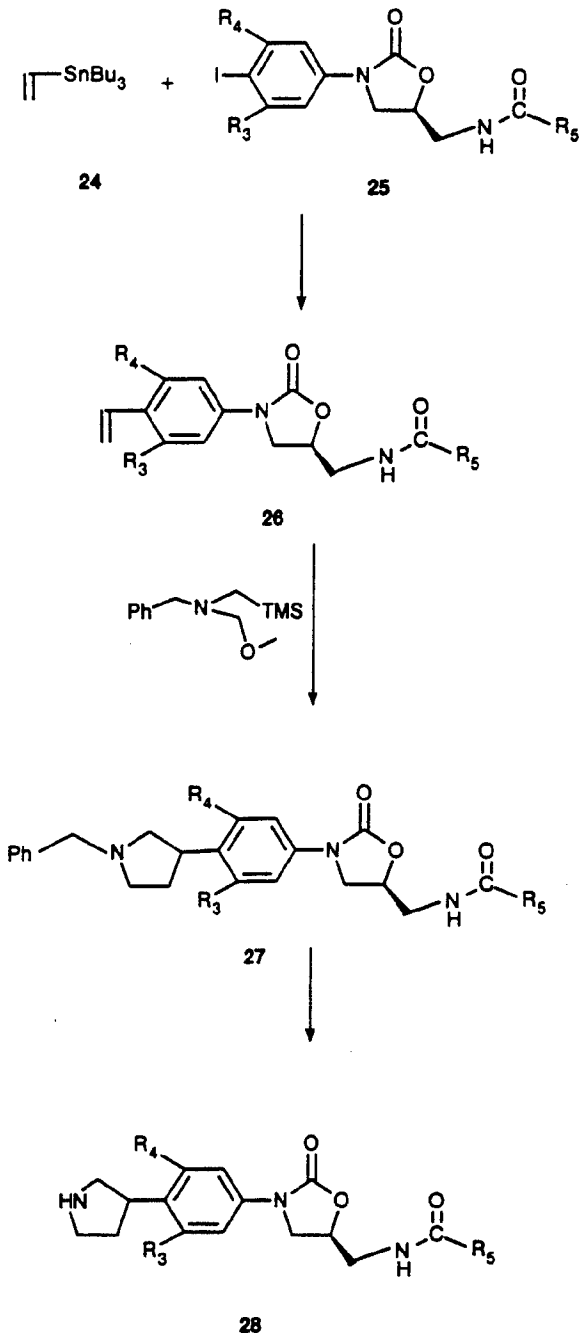
CHART D



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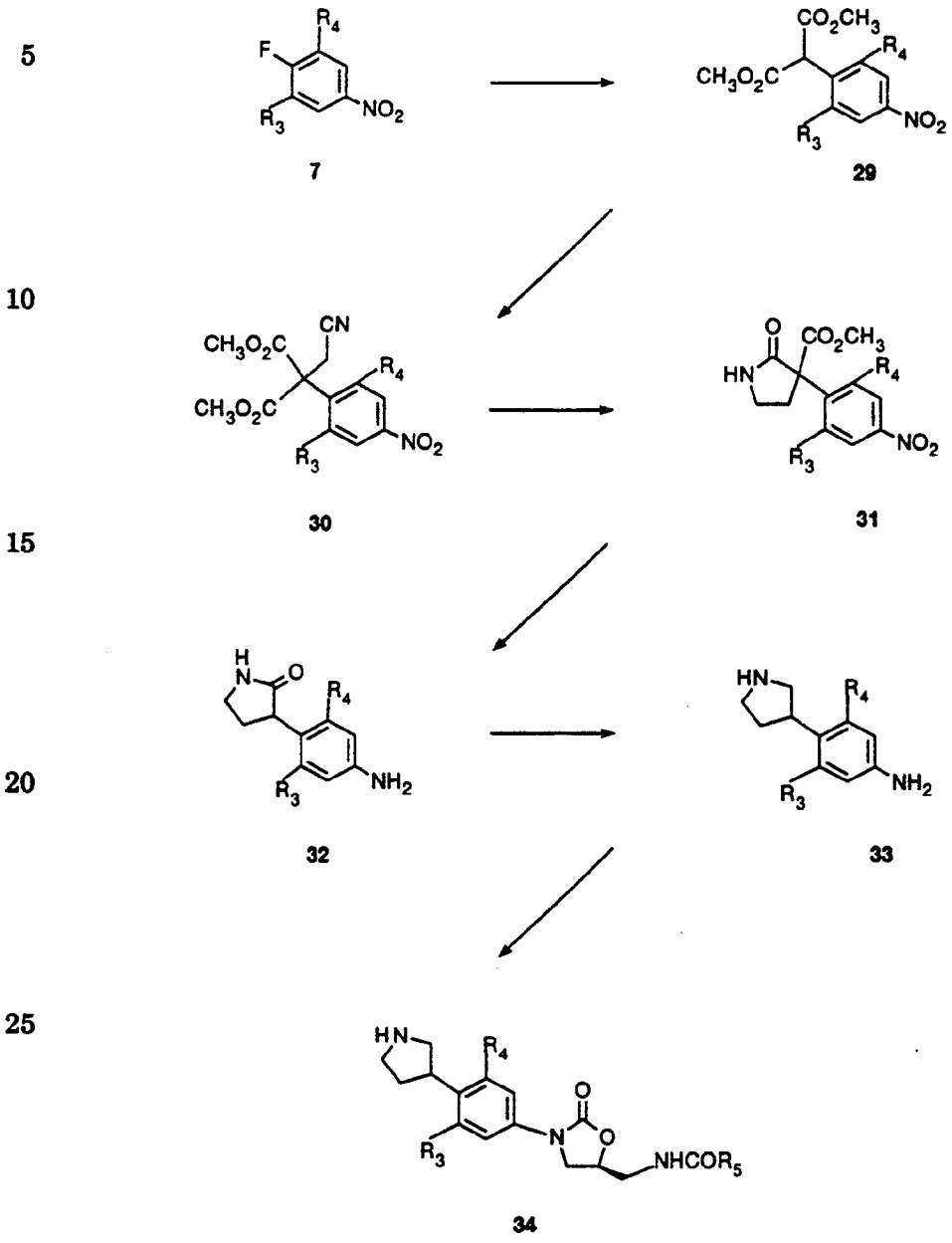
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NO2
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O
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HN
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R3
NO2
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N
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R4
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CHART F

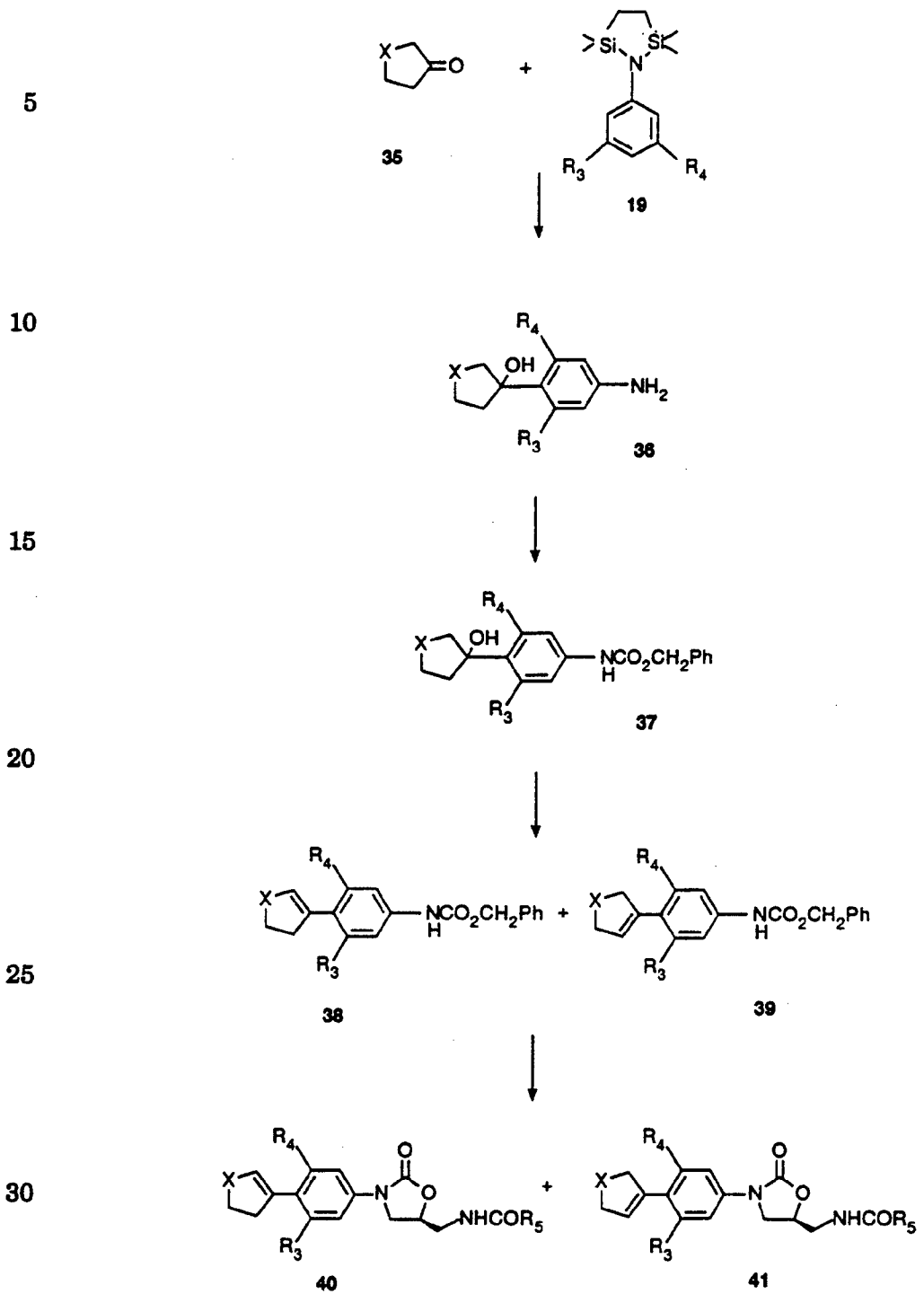

CHART G

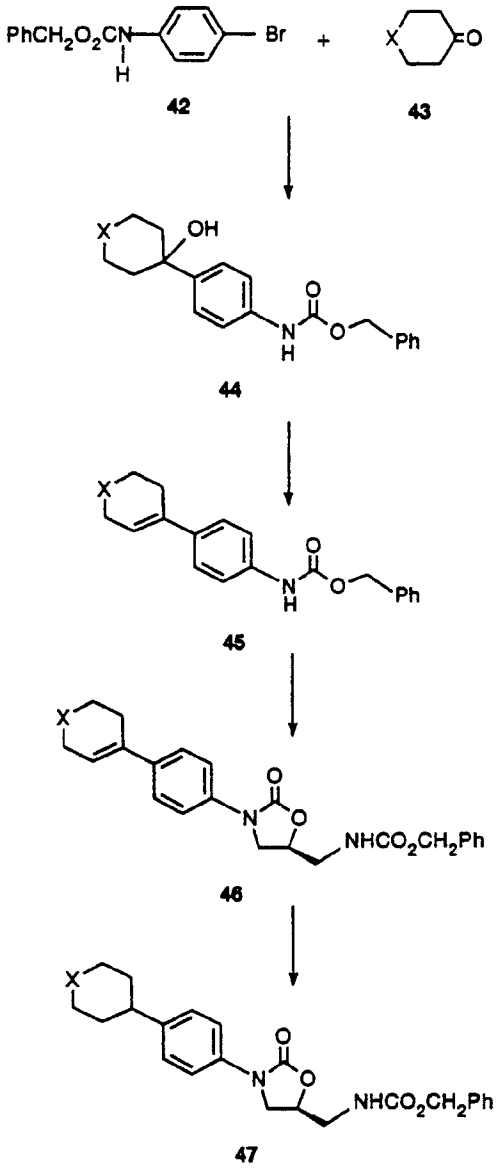
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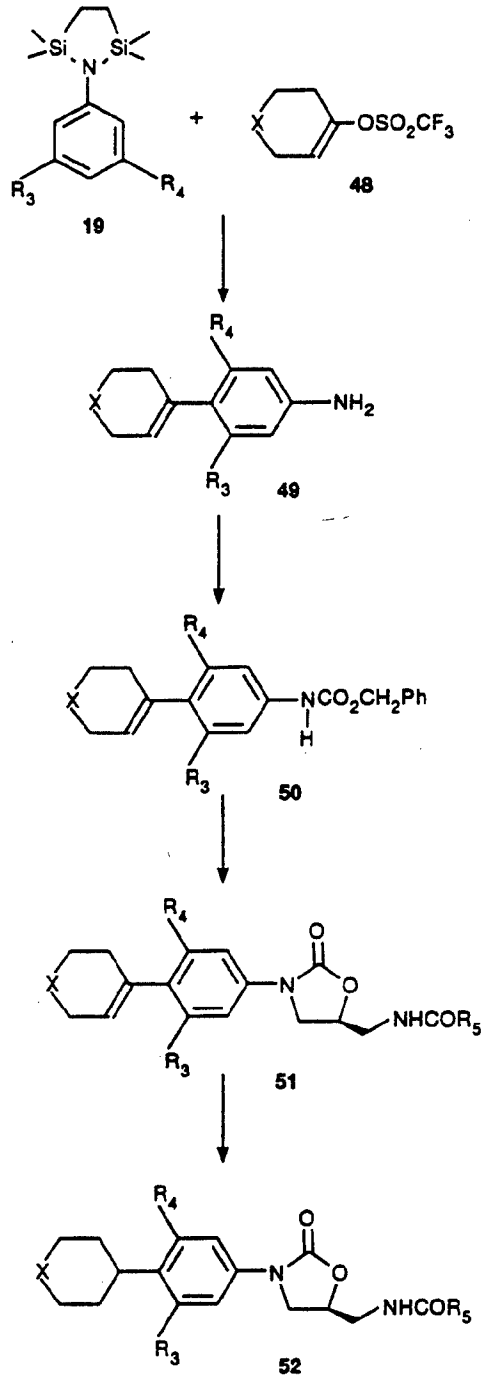
CHART H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R3
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CHART I

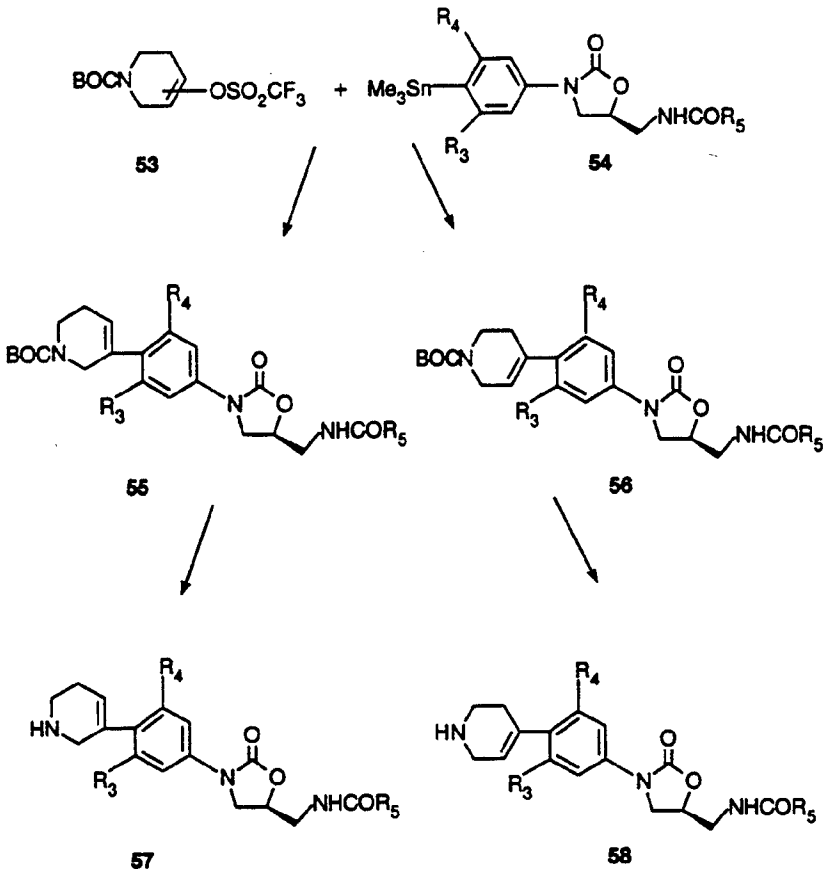
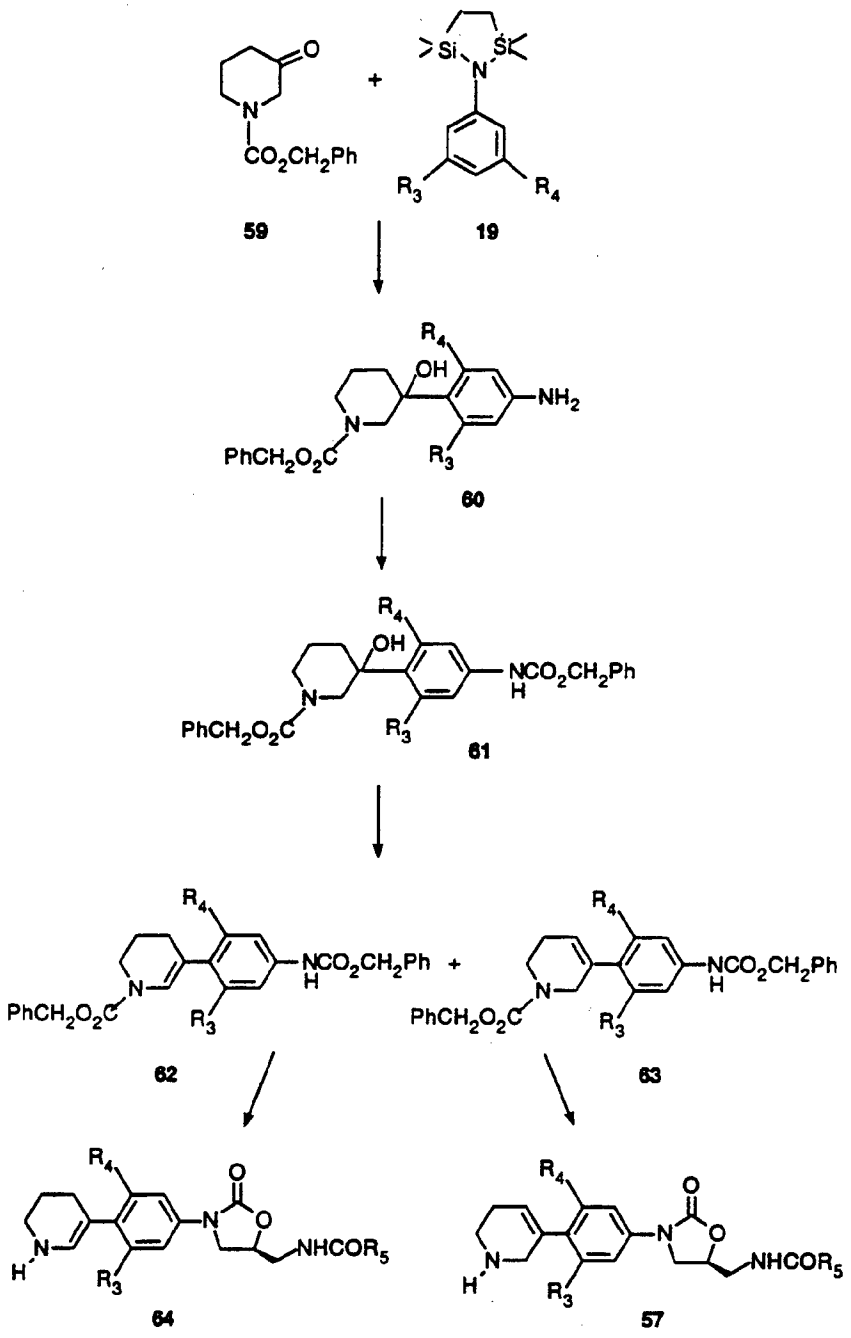
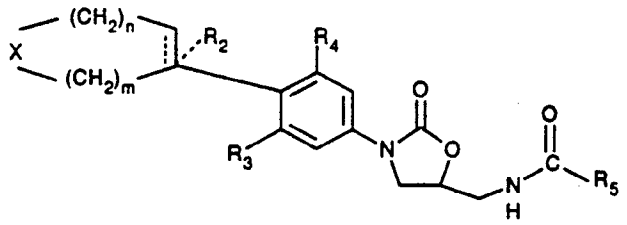


CHART J



We claim:

1. A compound of the formula I:



(I)

or pharmaceutical acceptable salts thereof wherein:

X is

a) NR_1,

b) $S(O)_g$, or

c) O;

R_1 is

a) H,

b) C_{1-6} alkyl, optionally substituted with one or more OH, CN, or halo,

c) $-(CH_2)_h$-aryl,

d) $-COR_{1-1}$,

e) $-COOR_{1-2}$,

f) $-CO-(CH_2)_h-COR_{1-1}$,

g) $-SO_2-C_{1-6}$ alkyl,

h) $-SO_2-(CH_2)_h$-aryl, or

i) $-(CO)_i$-Het;

R_{1-1} is

a) H,

b) C_{1-6} alkyl, optionally substituted with one or more OH, CN, or halo,

c) $-(CH_2)_h$-aryl, or

d) $-(CH_2)_h-OR_{1-3}$;

R_{1-2} is

a) C_{1-6} alkyl, optionally substituted with one or more OH, CN, or halo,

b) $-(CH_2)_h$-aryl, or

c) $-(CH_2)_h-OR_{1-3}$;

R_{1-3} is

a) H,

b) C_{1-6} alkyl,

c) -$(CH_2)_h$-aryl, or

d) -$CO(C_{1-6}$ alkyl);

R_2 is

a) H,

b) C_{1-6} alkyl,

c) -$(CH_2)_h$-aryl, or

d) halo;

R_3 and R_4 are the same or different and are

a) H, or

b) halo;

R_5 is

a) H,

b) C_{1-12} alkyl, optionally substituted with one or more halo,

c) C_{3-12} cycloalkyl,

d) C_{1-6} alkoxy;

g is 0, 1, or 2;

h is 1, 2, 3, or 4;

i is 0 or 1;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1, 2, 3, 4, or 5;

and with the provisio that m and n taken together are 1, 2, 3, 4, or 5.

2. A compound of Claim 1 wherein R_1 is selected from the group consisting of H, fluoroethyl, cyanomethyl, methyl sulfonyl, formyl, hydroxyacetyl, acetyl, methoxyacetyl, benzyloxyacetyl, acetoxyacetyl, dichloroacetyl, methoxy carbonyl, tert-butoxy carbonyl, benzyloxy carbonyl, 3-hydroxypropionyl, 3-methoxypropionyl, 4-oxopentanoyl, 2-indole carbonyl, 5-isoxazole carbonyl, 5-nitro-2-thiazoyl, 4-oxo-2-thiazolinyl, and 5-methyl-1,3,4-thiadiazol-2-yl.

3. A compound of Claim 1 wherein R_2 is H, F, or CH_3.

4. A compound of Claim 1 wherein R_3 and R_4 are the same and different and are H or F.

5. A compound of Claim 1 wherein R_5 is methyl or methyl substituted with one or more F or Cl.

6. A compound of Claim 1 wherein m is 1 and n is 0.

7. A compound of Claim 1 wherein m and n taken together are 2.

8. A compound of Claim 1 wherein m and n taken together are 3.

9. A compound of Claim 1 wherein m and n taken together are 4.

10. A compound of Claim 1 which is an optically pure enantiomer having the S-configuration at C5 of the oxazolidinone ring.

11. A compound of Claim 1 which is

(S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-(3-methyl)-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[3-methyl-3-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(methoxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(dichloroacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(3-methoxypropionyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(3-hydroxypropionyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(4-oxopentanoyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-acetyl-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(2-fluoroethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(cyanomethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(5-nitro-2-thiazolyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(methanesulfonyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(benzyloxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(carbobenzyloxy)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2 fluorophenyl]-1-pyrrolidinecarboxylic acid methyl ester;

(S)-N-[[3-[3-Fluoro-4-(3,4-dihydro-2H-pyran-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[3-Fluoro-4-(dihydrothien-3-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1-oxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4,5dihydro-1-oxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid phenylmethyl ester;

(S)-(-)-N-[[2-Oxo-3-[4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-[(Benzyloxy)acetyl]-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Indole-2-carbonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Isoxazole-5-carbonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Methylsulfonyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid methyl ester;

(S)-(-)-N-[[3-[4-[1-(Cyanomethyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(2-Fluoroethyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[[(2,2-Dichloroacetyl)amino]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperidinecarboxylic acid 1,1-dimethylethyl ester;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-(4-piperidinyl)phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-(hydroxyacetyl)-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-4-piperidinyl]phenyl]-5-

oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide;

(S)-(-)-N-[[3-[4-(Tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-3,6-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)-3-fluorophenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-

yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester;

(S)-(-)-N-[[2-Oxo-3-[4-(3,6-dihydro-2H-pyridin-4-yl)phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-4-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester;

(S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-5,6-dihydro-2H-pyridin-3-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[4-[1-(Hydroxyacetyl)-5,6-dihydro-2H-pyridin-3-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,4,7-tetrahydro-1*H*-azepin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)hexahydro-1H-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,4-dihydro-2H-pyridin-5-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,4-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; or

(S)-(-)-N-[[3-[4-[1-Formyl-4-fluoro-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide.

12. A compound of Claim 11 which is:

(S)-N-[[3-[3-Fluoro-4-[1-(carboxymethyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-(3-methyl)-azetidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide;

(5S)-N-[[3-[3-Fluoro-4-[1-(hydroxyacetyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(5S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-pyrrolidinecarboxylic acid methyl ester;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Formyl)-4-piperidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-2,2-Dichloro-N-[[2-oxo-3-[3-fluoro-4-[1-(hydroxyacetyl)-4-piperidinyl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[2-Oxo-3-[3-fluoro-4-[1-[(acetoxy)acetyl]-3,6-dihydro-2H-pyridin-4-yl]phenyl]-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-3,6-dihydro-2H-pyridin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-pyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide;

(S)-(-)-N-[[3-[4-[Tetrahydro-2H-pyran-4-yl]phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-(3,6-Dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide;

(5S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1-oxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(2,5-dihydro-1,1-dioxido-3-thienyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(Hydroxyacetyl)-2,3,6,7-tetrahydro-1*H*-azepin-4-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(4-Oxo-2-thiazolinyl)-3,6-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-(-)-N-[[3-[4-[1-(5-Methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydro-2H-pyridin-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; or

(S)-N-[[3-[3-Fluoro-4-[1-(formyl)-3-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

13. A method for treating microbial infections in patients comprising: administering to a patient in need thereof an effective amount of a compound of Formula I as shown in Claim 1.

14. The method of Claim 13 wherein said compound of Formula I is administered orally, parenterally or topically in a pharmaceutical composition.

15. The method of Claim 13 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCI/US 96/12766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/10 A61K31/42 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 09103 (UPJOHN CO) 13 May 1993 cited in the application see claims ---	1,13-15
X	EP,A,0 352 781 (E.I.DU PONT DE NEMOURS AND COMPANY) 31 January 1990 cited in the application see claims -----	1,13-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"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 when the document is taken alone

"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

1

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 1996	29.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/US 96/12766

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 claim 13 is 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 96/12766

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9309103	13-05-93	AU-B-	667198	14-03-96
		AU-A-	2689892	07-06-93
		CA-A-	2119556	13-05-93
		EP-A-	0610265	17-08-94
		JP-T-	7500603	19-01-95
		US-A-	5565571	15-10-96
EP-A-0352781	31-01-90	US-A-	4948801	14-08-90
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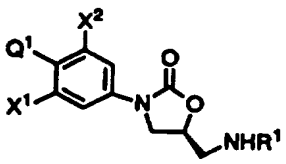
(54) Title: AMINOARYL OXAZOLIDINONE N-OXIDES

(57) Abstract

The present invention provides for aminoaryl oxazolidinone N-oxide compounds of formula (I), wherein the variables are as defined herein. These compounds are exceedingly water soluble which is useful in preparing pharmaceutical formulations of these compounds. They are also rapidly converted back to the parent amines *in vivo*, making them useful as prodrugs of the parent amines. They are effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms, such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*, and in organisms such as *Mycoplasma spp.*.



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AMINOARYL OXAZOLIDINONE N-OXIDES

FIELD OF THE INVENTION

The present invention provides for aminoaryl oxazolidinone N-oxide compounds. These compounds are exceedingly water soluble which is useful in preparing pharmaceutical formulations of these compounds. They are also rapidly converted back to the parent amines *in vivo*, making them useful as prodrugs of the parent amines.

These compounds have antibiotic activity comparable to the parent amines. They are effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms, such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis, Mycobacterium avium* and *Mycobacterium spp.*, and in organisms such as *Mycoplasma spp.*

BACKGROUND OF THE INVENTION

A variety of antibiotic oxazolidinone compounds are known in the art. For example, please see the following:

WO 95/07271, published 16 March 1995, "Substituted Oxazine and Thiazine Oxazolidinones Antimicrobials"; WO96/15130, published 23 May 1996, "Bicyclic Oxazine and Thiazine Oxazolidinone Antibacterials"; WO96/13502, published 9 May 1996, "Phenyloxazolidinone Antimicrobials"; WO 93/23384, published 25 November 1993, "Oxazolidinone Antimicrobials Containing Substituted Diazine Moieties"; WO 90/02744, published 22 March 1990; U.S. Patent No. 5,164,510; U.S. Patent No. 5,225,565; U.S. Patent No. 5,182,403; "5'-Indolinyl-5β-Amidomethyloxazolidin-2-ones"; WO 95/25106, published 21 September 1995, "Oxazolidinone Derivatives and Pharmaceutical Compositions Containing Them"; WO 93/09103, published 13 May 1993, "Substituted Aryl and Heteroaryl-Phenyloxazolidinones"; WO 95/14684, published 1 June 1995, "Esters of Substituted Hydroxyacetyl-Piperazine Phenyl Oxazolidinones"; PCT/US96/05202, filed 18 April 1996, "Spirocyclic and Bicyclic Diazinyl and Carbazinyl Oxazolidinones"; U.S. Patent Nos. 5,231,188 and 5,247,090, "Tricyclic [6,6,5]-Fused Oxazolidinone Antibacterial Agents;" WO 96/23788, published 8 August 1996, "Hetero-Aromatic Ring Substituted Phenyloxazolidinone Antimicrobials;" and WO 94/13649, published 23 June 1994, "Tropone-Substituted Phenyloxazolidinone Antibacterial Agents."

Nowhere do these patents, applications or publications teach or suggest N-

oxide oxazolidinone compounds.

INFORMATION DISCLOSURE

U.S. Patent No. 4,722,928 discloses N-oxide prodrug derivatives of 3-hydroxy morphinans and partial morphinans analgesics, agonist-antagonists, and narcotic antagonists, which are useful therapeutic entities providing enhanced bioavailability of these compounds from orally administered dosage forms. In contrast, there is no change in the bioavailability of the N-oxide compounds of the present invention.

This patent further states that there is no way to accurately predict which prodrug structure will be suitable for a particular drug. A derivative which may work well for one drug may not do so for another. Differences in the absorption, metabolism, distribution, and excretion among drugs do not permit generalizations to be made about prodrug design.

Chemical Abstracts 118:147331y (1993) discloses anti-cancer anthracene amine N-oxide prodrugs with low cytotoxicity which are bioreduced within anaerobic neoplastic tissue to the cytotoxic amine anticancer agents. There is no suggestion that N-oxide prodrugs can be bioreduced in normal tissue. These compounds are also potentially useful against anaerobic bacterial and protozoal infections.

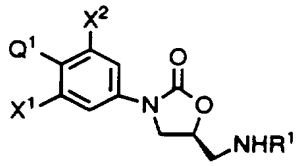
L.H. Patterson, "Rationale for the use of aliphatic N-oxides of cytotoxic anthraquinones as prodrug DNA binding agents: a new class of bioreductive agent," *Cancer and Metastasis Review 12:119-134 (1993)* discloses that such N-oxides are not intrinsically cytotoxic. It further states that investigations into the fate of N-oxide administration to animals show that, in general, aliphatic N-oxides are stable *in vivo* and are recovered quantitatively following intravenous dosing. Hence, the article concludes that it would appear that aliphatic N-oxides are not metabolised in oxygenated tissue to any significant extent. In contrast, the aliphatic N-oxide compounds of the present invention are surprisingly and unexpectedly reduced back to the parent amine very rapidly *in vivo*.

The problem in the art is difficulty in formulating the parent amine compounds for intravenous and injectable use. The N-oxide compounds of the present invention have high water solubility and are readily formulated in aqueous vehicles.

SUMMARY OF THE INVENTION

The present invention particularly provides:

A compound of the formula I



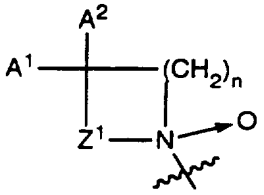
wherein X^1 and X^2 are independently

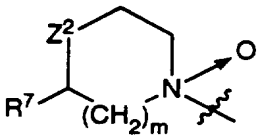
-H,

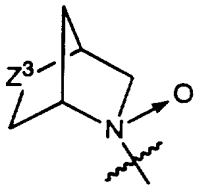
-F, or

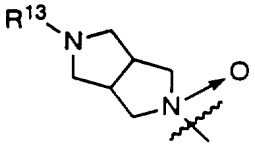
-Cl;

wherein Q^1 is:

a)  II

b)  III

c)  IV, or

d)  V;

wherein Z^1 is

a) $-CH_2-$, or

b) $-CH(R^5)-CH_2-$;

wherein Z^2 is

a) $-O_2S-$,

b) -O-, or

c) -N(R^8)-;

wherein Z^3 is

a) -O_2S-, or

b) -O-;

wherein A^1 is

a) H-, or

b) CH_3-;

wherein A^2 is

a) H-,

b) HO-,

c) CH_3CO_2-,

d) CH_3-,

e) CH_3O-,

f) R^2O-CH_2-C(O)-NH-

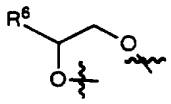
g) R^3O-C(O)-NH-,

h) R^4-C(O)-NH-,

i) (C_1-C_2)alkyl-O-C(O)-, or

j) HO-CH_2-; or

A^1 and A^2 taken together are:

a)  or

b) o= ;

wherein R^1 is

a) -CHO,

b) -$COCH_3$,

c) -$COCHCl_2$,

d) -$COCHF_2$,

e) -CO_2CH_3,

f) -SO_2CH_3, or

g) -$COCH_2OH$;

wherein R^2 is

a) H-,

b) CH_3-,

c) phenyl-CH_2-, or

d) $CH_3C(O)$-;

wherein R^3 is

a) $(C_1$-$C_3)$alkyl-, or

b) phenyl-;

wherein R^4 is

a) H-,

b) $(C_1$-$C_4)$alkyl,

c) aryl -$(CH_2)_p$,

d) ClH_2C-,

e) Cl_2HC-,

f) FH_2C-,

g) F_2HC-, or

h) $(C_3$-$C_6)$cycloalkyl;

wherein R^5 is

a) H-, or

b) $(C_1$-$C_3)$alkyl;

wherein R^6 is

a) H-, or

b) HOH_2C-;

wherein R^7 is

a) H-, or

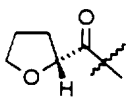
b) H_3C-;

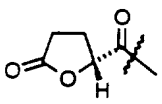
wherein R^8 is

a) R^2O-$C(R_{10})(R_{11})$-C(O)-,

b) R^3O-C(O)-,

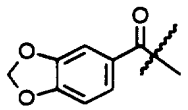
c) R^4-C(O)-,

d)  VI ,

e)  VII ,

f) H_3C-C(O)-$(CH_2)_2$-C(O)-,

g) R^9-SO_2-,

h)  VIII , or

i) R^{12}-NH-C(O)-;

wherein R^9 is

a) $-CH_3$,

b) $-CH_2Cl$

c) $-CH_2CH=CH_2$,

d) aryl, or

e) $-CH_2CN$;

wherein R^{10} and R^{11} are independently

a) H-,

b) CH_3-; or

R^{10} and R^{11} taken together are $-CH_2-CH_2-$;

wherein R^{12} is $-(CH_2)_p$-aryl;

wherein R^{13} is

a) R^2O-C(R_{10})(R_{11})-C(O)-,

b) R^3O-C(O)-,

c) R^4-C(O)-,

d) R^9-SO_2-, or

e) R^{12}-NH-C(O)-;

wherein m is zero (0) or one (1);

wherein n is one (1) to three (3), inclusive;

wherein p is zero (0) or one (1);

wherein aryl is phenyl substituted with zero (0) or one (1) of the following:

a) -F,

b) -Cl,

c) $-OCH_3$,

d) -OH,

e) $-NH_2$,

f) $-(C_1-C_4)$alkyl,

g) $-O-C(O)-OCH_3$,

h) $-NO_2$, or

i) -CN;

with the following provisos:

1) in the moiety of formula II, Z^1 is -CH(R^5)-CH_2- wherein R^5 is (C_1-C_3)alkyl, only when n is one (1), A^1 is H and A^2 is R^2O-CH_2-C(O)-NH-, R^3O-C(O)-NH-, or R^4-C(O)-NH-; and

2) in the moiety of formula II, when Z^1 is -CH_2-, n is one (1).

The present invention more particularly provides:

The compound of claim 1 wherein Q^1 is the moiety of formula II;

The compound of claim 1 wherein Q^1 is the moiety of formula III;

The compound of claim 1 wherein Q^1 is the moiety of formula IV;

The compound of claim 1 wherein Q^1 is the moiety of formula V;

The compound of claim 1 wherein one of X^1 and X^2 is -H and the other is -F or wherein X^1 is -F and X^2 is -F; and

The compound of claim 1 wherein R^1 is acetyl.

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, (C_1-C_3)alkyl refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl and isopropyl, straight and branched forms thereof.

Throughout this application, abbreviations which are well known to one of ordinary skill in the art may be used, such as "Ph" for phenyl, "Me" for methyl, and "Et" for ethyl.

The following Charts I-IX describe the preparation of the parent amine compounds, which are the starting compounds from which the N-oxide compounds of the present invention are prepared. All of the starting compounds are prepared by procedures described in these charts or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. The following applications and publications which further describe and exemplify these procedures are hereby incorporated by reference herein: WO 95/07271, published 16 March 1995; WO96/15130, published 23 May 1996; WO 95/25106, published 21 September 1995; WO96/13502, published 9 May 1996; WO 93/23384, published 25 November 1993; WO 95/4684, published 1 June 1995; and PCT/US96/05202, filed 18 April 1996.

In the text below corresponding to these charts, the formula at the left margin corresponds to a specific Q^2 moiety in the charts and the other variables are as defined with X^1 and X^2 most often being hydrogen or fluorine and R^1 most often being $-COCH_3$, for purposes of example only.

CHART I

I-A Using the procedures from WO 95/07271, published 16 March 1995, page 21, line 33, thru page 23, line 32 for preparation of the intermediate sulfide and then oxidation to the sulfone using the general procedures from WO 95/07271, published 16 March 1995, page 15, line 32 thru page 16, line 14.

I-B Using the procedures described in WO 95/07271, published 16 March 1995, page 21, line 33, thru page 23, line 32, but substituting oxazolidine for thiazolidine.

CHART II

II-A Using the general procedures from WO 95/07271, published 16 March 1995, page 12, line 31, thru page 16, line 14.

II-B Using the general procedures from WO 95/07271, published 16 March 1995, page 12, line 31 thru page 16, line 14, but substituting 2-methylthiomorpholine for thiomorpholine. 2-Methylthiomorpholine is prepared according to the procedure of Gallego, *et al, J. Org. Chem.*, 1993, *58*, 3905-11.

II-C Using the general procedures from WO96/15130, published 23 May 1996, Examples 2 and 3 at page 14, line 24, thru page 17, line 21.

CHART III

III-A Using the general procedures from WO 95/07271, published 16 March 1995, page 19, line 6, thru page 21, line 13; and page 23, line 33, thru page 24, line 35.

III-B Using the general procedures from WO96/15130, published 23 May 1996, Example 1 at page 12, line 1, thru page 14, line 22.

CHART IV

IV-A Using the general procedures from WO 95/25106, published 21 September 1995, page 20, line 27 thru page 22, line 5 but substituting azetidine for piperidine.

IV-B Using the general procedures of WO96/13502, published 9 May 1996, Example 11 at page 53, line 32 through page 56, line 3, but substituting 1-(diphenylmethyl)-3-azetidinone in place of 1-benzyl-3-pyrrolidinone. 1-(Diphenylmethyl)-3-azetidinone can be prepared by the procedure of

Chatterjee, et al, *Synthesis*, 1973, 153-4.

IV-C From IV-B using the general procedure from WO96/13502, published 9 May 1996, page 56, line 4 through line 17.

IV-D From IV-C using the general procedure from WO 95/25106, published 21 September 1995, page 28, line 26 through page 29, line 5.

IV-E Using the general procedures from WO96/13502, published 9 May 1996, Example 2 at page 33, line 4, thru page 36, line 22.

IV-F Starting with IV-E, and using procedures well known for acetylation; e.g., acetic anhydride and triethylamine in a suitable solvent.

IV-G Using the general procedures from WO96/13502, published 9 May 1996, Example 7 at page 43, line 36, thru page 47, line 28.

IV-H Using the general procedures from WO96/13502, published 9 May 1996, Example 6 at page 40, line 31, thru page 43, line 34.

IV-I Using the procedures of WO96/13502, published 9 May 1996, Example 1 at page 29, line 25 thru page 33, line 2.

IV-J Wherein R^2 is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13 at page 56, line 19 thru page 59, line 4, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride. 3-Acetylaminoazetidine hydrochloride is prepared by the procedure of Nisato, et al., J. Heterocycl. Chem. 1985, *22*, 961-3.

IV-J Wherein R^2 is methyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting methoxyacetyl chloride in place of benzyloxyacetyl chloride.

IV-J Wherein R^2 is benzyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride.

IV-J Wherein R^2 is acetyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting acetoxyacetyl chloride in place of benzyloxyacetyl chloride.

IV-K Wherein R^3 is methyl, ethyl, propyl, or phenyl; using the procedure

described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetyl-amino)pyrrolidine hydrochloride and substituting methyl, ethyl, propyl, or phenyl chloroformate in place of benzyloxyacetyl chloride.

IV-L Wherein R^4 is hydrogen; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting methyl formate in place of benzyloxyacetyl chloride.

IV-L Wherein R^4 is all others listed; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.

IV-M Using the general procedures of WO96/13502, published 9 May 1996, Example 1, Steps 2 thru 7, at page 30, line 14 thru page 33, line 2, but substituting methyl N-benzylazetidine-3-carboxylate in place of 1-(diphenyl-methyl)-3-methoxyazetidine. Methyl N-benzylazetidine-3-carboxylate can be prepared by the procedure of Mason, et al, EP 169602 A1.

IV-N Starting with IV-M and using the general procedures of WO 95/25106, published 21 September 1995, page 22, line 11 through line 20.

CHART V

V-A Using the procedure from WO 95/25106, published 21 September 1995, page 20, Example 1, but using pyrrolidine instead of piperidine.

V-B Using the procedures of WO96/13502, published 9 May 1996, Example 11 at page 53, line 32, thru page 56, line 3.

V-C From V-B, following the procedure of WO96/13502, published 9 May 1996, page 56, lines 4 through 17.

V-D From V-C, using the general procedure of WO 95/25106, published 21 September 1995, page 28, line 26, thru page 29, line 5.

V-E Using the procedures described in WO96/13502, published 9 May 1996, Example 10 at page 50, line 25, thru page 53, line 30. Or, from V-C by reduction using methods well known in the art such as sodium borohydride in methanol.

V-F From V-E using standard acetylation procedures; e.g., acetic anhydride in pyridine.

V-G As described in WO96/13502, published 9 May 1996, Example 7 at page 43, line 36, thru page 47, line 28 but substituting 1-benzyl-3-methyl-3-pyrrolidinol hydrochloride for 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride. 1-Benzyl-3-methyl-3-pyrrolidinol hydrochloride can be prepared from 1-benzyl-3-pyrrolidinone by methods known in the art, eg, reaction with methylmagnesium bromide and treatment of the product with one equivalent of hydrochloric acid. 1-Benzyl-3-pyrrolidinone is commercially available.

V-H Using the general procedures of WO96/13502, published 9 May 1996, Example 6 at page 40, line 31 through page 43, line 34, but substituting 1-benzyl-3-methyl-3-pyrrolidinol hydrochloride (prepared as described above) in place of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride.

V-I As described in WO96/13502, published 9 May 1996, Example 1 at page 29, line 25, thru page 33, line 2, but substituting commercially available 1-benzyl-3-pyrrolidinol for 1-(diphenylmethyl)-3-azetidinol.

V-J Wherein R^2 is H and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13 at page 56, line 19, thru page 59, line 4;

V-J Wherein R^2 is methyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methoxyacetyl chloride for benzyloxyacetyl chloride.

V-J Wherein R^2 is benzyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27.

V-J Wherein R^2 is acetyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting acetoxyacetyl chloride for benzyloxyacetyl chloride.

V-J Where R^2 is H and R^5 is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15 at page 62, lines 5-28.

V-J Wherein R^2 is benzyl and R^5 is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15, Step 1, at page 62, lines 5-19.

V-J Wherein R^2 is methyl or acetyl and R^5 is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15, Step 1, at page 62, lines 5-19, but substituting methoxyacetyl chloride or acetoxyacetyl chloride for benzyloxyacetyl chloride.

V-J Wherein R^5 is other alkyl; using the general procedures described above but subsituting other 4-alkyl-3-aminopyrrolidines in place of 3-amino-4-methylpyrrolidine.

V-K Wherein R^3 is methyl, ethyl, propyl or phenyl and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methyl chloroformate, ethyl choroformate, propylchloroformate, or phenylchloroformate for benzyloxyacetyl chloride.

V-K Wherein R^3 is methyl, ethyl, propyl, or phenyl and R^5 is methyl; by reaction of (*S*)-(N)-[[[3-fluoro-4-(3-amino-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide with the appropriate chloroformate. The above amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

V-K Wherein R^5 is other alkyl; From the appropriate amine and chloroformate. The amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29, but starting with other 3-alkyl-4-aminopyrrolidines in place of 4-amino-3-methylpyrrolidine.

V-L Where R^4 is H and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methyl formate in place of benzyloxyacetyl chloride.

V-L Where R^4 is all others listed and R^5 is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.

V-L Where R^4 is H and R^5 is methyl; by reaction of formic acid and dicyclohexylcarbodiimide. The required amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

V-L Where R^4 is all others and R^5 is methyl; by reaction of (*S*)-(N)-[[[3-fluoro-4-(3-amino-4-methylpyrrolidinyl)phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide with the appropriate acid chloride. The required amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

V-L Where R^5 is other alkyl; Using the above procedures, but starting with other 3-alkyl-4-aminopyrrolidines in place of 4-amino-3-methylpyrrolidine.

V-M Using the general procedure from WO 95/25106, published 21 September 1995, page 22, lines 6 through 12, 5, but using pyrrolidine-3-carboxylic acid methyl ester instead of piperidine-4-carboxylic acid ethyl ester. Pyrrolidine-3-carboxylic acid methyl ester is prepared by the procedure of Morgans, et al, *Tetrahedron Lett.*, 1979, 1959.

V-N From V-M, using the general procedure of WO 95/25106, published 21 September 1995, page 22, lines12 through 20.

CHART VI

VI-A Using the general procedures from WO 95/25106, published 21 September 1995, page 20, line 27, thru page 22, line 5.

VI-B Using the procedure of WO 95/25106, published 21 September 1995, WO 95/25106, published 21 September 1995, page 22, line 21 thru line 26.

VI-C From VI-B, using the procedure from WO 95/25106, published 21 September 1995, page 22, lines 27 through 35.

VI-D From VI-C, using the procedure from WO 95/25106, published 21 September 1995, page 28, line 26 thru page 29, line 5.

VI-E Prepared from VI-C by reduction via standard procedures known in the art; eg, sodium borohydride in methanol.

VI-F Prepared from VI-E by procedures known in the art; eg, acetic anhydride and triethylamine.

VI-G Using the procedures from WO96/13502, published 9 May 1996, Example 7, page 43, line 36 thru page 47, line 28 but substituting commercially available 4-hydroxy-4-methylpiperidine for 3-hydroxy-3-methylazetidine.

VI-H Using the procedures from WO 95/25106, published 21 September 1995, page 20, line 27 thru page 22, line 5, but substituting 4-methoxy-4-methylpiperidine in place of piperidine. 4-Methoxy-4-methylpiperidine can be prepared according to the procedure of McManus, et al, *J. Med. Chem.*, 1965, *8*, 766-776.

VI-I Using the procedures from WO 95/25106, published 21 September 1995, page 20 line 27 thru page 22, line 5, but substituting 4-methoxypiperidine

for piperidine. 4-Methoxypiperidine can be made by the procedure of McManus, et al, *J. Med. Chem.*, 1965, *8*, 766-776.

VI-J Wherein R^2 = H; Prepared by reaction of (S)-N-[[3-[4-(4-aminopiperidinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared according to the procedures of WO 95/25106, published 21 September 1995, page 22, line36 thru page 23, line 24) with acetoxyacetyl chloride and triethylamine followed by hydrolysis of the acetoxy group with methanolic potassium carbonate.

VI-J Wherein R^2 = methyl; prepared by reaction of the starting material of VI-J (R^2 = H) with methoxyacetyl chloride and triethylamine.

VI-J Wherein R^2 is benzyl; prepared by reaction of the starting material of VI-J (R^2 = H) with benzyloxyacetyl chloride and triethylamine.

VI-J Wherein R^2 is acetyl; prepared by reaction of the starting material of VI-J (R^2 = H) with acetoxyacetyl chloride and triethylamine.

VI-K Wherein R^3 is methyl, ethyl, propyl, or phenyl; prepared by reaction of the starting material of VI-J (R^2 = H) with methyl-, ethyl-, propyl-, or phenylchloroformate.

VI-L Wherein R^4=H; By reaction of the starting material of VI-J (R^2 = H) with methylformate.

VI-L Wherein R^4 = all others listed; By reaction of the starting material of VI-J (R^2 = H) with the appropriate acid chloride.

VI-M Using the procedure from WO 95/25106, published 21 September 1995, page 22, line 6 thru line 12.

VI-N Using the procedure from WO 95/25106, published 21 September 1995, page 22, lines 12 through 20.

CHART VII

VII-A Using the general procedures of WO 95/25106, published 21 September 1995, page 20, line 27 through page 22, line 5, but substituting commercially available azepine in place of piperidine.

VII-B Using the procedure of WO 95/25106, published 21 September 1995, page 22, line 21 thru line 26 but substituting 1,4-dioxo-8-aza-spiro[4.6]undecane for 1,4-dioxo-8-aza-spiro[4.5]decane. 1,4-Dioxo-8-aza-spiro[4.6]undecane can be prepared by the procedure of R. A. Johnson, et al, *J. Org. Chem.*, 1968, *33*, 3187-3195.

VII-C From VII-B, following the procedure of WO96/13502, published 9 May 1996, page 56, lines 4 through 17.

VII-D From VII-C using the general procedure of WO 95/25106, published 21 September 1995, page 28, line 26, thru page 29, line 5.

VII-E Prepared from VII-C by reduction via standard procedures known in the art; eg, sodium borohydride in methanol.

VII-F Prepared from VII-E by procedures known in the art; eg, acetic anhydride and triethylamine.

VII-G Using the procedures from WO96/13502, published 9 May 1996, Example 7, page 43, line 36 thru page 47, line 28 but substituting 4-hydroxy-4-methyl-azepine for 3-hydroxy-3-methylazetidine. 4-Hydroxy-4-methylazepine can be prepared by the procedure pf Grob, et al, *Helv. Chim.Acta*, 1962, *45*, 1823-1830.

VII-H Using the general procedures of WO96/13502, published 9 May 1996, Example 6, page 40, line 31 through page 43, line 34, but substituting 1-benzyl-4-methyl-4-azepinol in place of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride. 1-Benzyl-4-methyl-4-azepinol can be prepared by the reaction of methyl magnesium bromide with 1-benzyl-4-azepinone. 1-Benzyl-4-azepinone can be prepared by the procedure of Casy, et al, *J. Chem. Soc.* 1964, 5130-5132.

VII-I As described in WO96/13502, published 9 May 1996, Example 1, at page 29, line 25, thru page 33, line 2, but substituting 1-benzyl-4-azepinol for 1-(diphenylmethyl)-3-azetidinol. 1-Benzyl-4-azepinol can be prepared by the procedure of S. Sakanoue, et al, *Chem. Pharm. Bull.*, 1990 *38*, 2981-2985.

VII-J Wherein R^2 is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13, page 56, line 19, thru page 59, line 4 but substituting 4-(trifluoroacetylamino)azepine in place of 3-(trifluoroacetylamino)pyrrolidine. 4-(Trifluoroacetylamino)azepine can be prepared by reaction of 1-benzyl-4-azepinamine with trifluoroacetic anhydride in a suitable solvent such as chloroform, followed by removal of the benzyl protecting group via hydrogenolysis using palladium on carbon as a catalyst in a solvent such as ethyl acetate. 1-Benzyl-4-azepinamine can be prepared by the procedure of Morosawa, et al, *Bull. Chem. Soc. Jpn.*, 1958, *31*, 418-422.

VII-J Wherein R^2 is methyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetylamino)azepine for 4-(trifluoroacetylamino)pyrrolidine and substituting methoxyacetyl chloride in

place of benzyloxyacetyl chloride.

VII-J Wherein R^2 is benzyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetylamino)azepine for 4-(trifluoroacetylamino)pyrrolidine.

VII-J Wherein R^2 is acetyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetylamino)azepine for 4-(trifluoroacetylamino)pyrrolidine and substituting acetoxyacetyl chloride in place of benzyloxyacetyl chloride.

VII-K Wherein R^3 is methyl, ethyl, propyl, or phenyl; prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (prepared as an intermediate in the synthesis of VII-J) with the appropriate chloroformate and triethylamine in chloroform.

VII-L Wherein R^4 is H; Prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared as an intermediate in the synthesis of VII-J) with formic acid according to the general procedure of WO 93/23384, published 25 November 1993, page 23, lines 4-17.

VII-L Wherein R^4 is all others; Prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared as an intermediate in the synthesis of VII-J) with the appropriate acid chloride and triethylamine.

VII-M Using the procedure from WO 95/25106, published 21 September 1995, page 22, line 6 thru line 12, but substituting azepine-4-carboxylic acid ethyl ester in place of piperidine-4-carboxylic acid ethyl ester. Azepine-4-carboxylic acid ethyl ester can be prepared from azepine-4-carboxylic acid by normal procedures known in the art, eg, reaction with ethanol and hydrochloric acid. Azepine-4-carboxylic acid can be prepared by the procedure of Krogsgaard-Larsen, et al, *Eur. J. Med. Chem. Chim. Ther.*, 1979, *14*, 157-164.

VII-N From VII-M, using the general procedure of WO 95/25106, published 21 September 1995, page 22, lines12 through 20.

CHART VIII

VIII-A Wherein R^2 = H; According to the procedure of WO 95/14684, published 1 June 1995, page 9, lines 1-28.

VIII-A Wherein R^2 = methyl; According to the general procedures of WO 93/23384, published 25 November 1993, page 19, lines 26- 33.

VIII-A Wherein R^2 = benzyl; According to the procedure of WO 95/14684, published 1 June 1995, page 9, lines 1-14.

VIII-A Wherein R^2 = acetyl; According to the procedure of WO 95/14684, published 1 June 1995, page 28, lines 24-35.

VIII-B Wherein R^3 = Me, Et, Pr, or Ph; Using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28 and substituting methyl-, ethyl, propyl, or phenylchloroformate as appropriate.

VIII-C Wherein R^4 = H; Using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 4-17.

VIII-C Wherein R^4 = all others; Using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 19-28, and substituting the appropriate acid chloride for methylchloroformate.

VIII-D Prepared according to the general procedure found in WO 93/23384, published 25 November 1993, page 25, lines 13-25.

VIII-E Prepared according to the general procedure from WO 93/23384, published 25 November 1993, page 25, lines 13-25, but substituting commercially available 5-oxo-2-tetrahydrofurancarboxylic acid in place of (R)-2-tetrahydrofuranoic acid.

VIII-F Prepared according to the procedure of WO 93/23384, published 25 November 1993, page 18, lines 10-17.

VIII-G Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate sulfonyl chloride using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28. Methyl, chloromethyl, allyl, and substituted arylsulfonyl chlorides are commercially available. Cyanomethylsulfonyl chloride can be prepared according to the procedure of M. P. Sammes, et al, *J. Chem. Soc. (C).*, 1971, 2151-2155.

VIII-H Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and piperonyl chloride using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28. Piperonyl chloride is commercially available.

VIII-I Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate carboxylic acid using the general procedure of WO 95/14684, published 1 June 1995, page 10,

lines 4-17. The acids are commercially available.

VIII-J Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate isocyanate. The required isocyanates are commercially available.

CHART IX

IX-A Wherein R^2 is H; Prepared according to the procedures of PCT/US96/05202, filed 18 April 1996, Examples 1, 2 and 3, page 12, line 11 through page 15, line 7.

IX-A Wherein R^2 is methyl; Prepared according to the general procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting methoxyacetyl chloride for benzyloxyacetyl chloride.

IX-A Wherein R^2 is benzyl; Prepared accroding to the procedures of PCT/US96/05202, filed 18 April 1996. Example 2, page 14, lines 16-32.

IX-A Wherein R^2 is acetyl; Prepared according to the general procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting acetoxyacetyl chloride for benzyloxyacetyl chloride.

IX-B Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate chloroformate for benzyloxyacetyl chloride.

IX-C Wherein R^4 is H; Prepared from (*S*)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]-octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 4-16.

IX-C Wherein R^4 is all others listed; Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.

IX-D Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate sulfonyl chloride in place of benzyloxyacetyl chloride. The sulfonyl chlorides can be obtained as described for VIII-G.

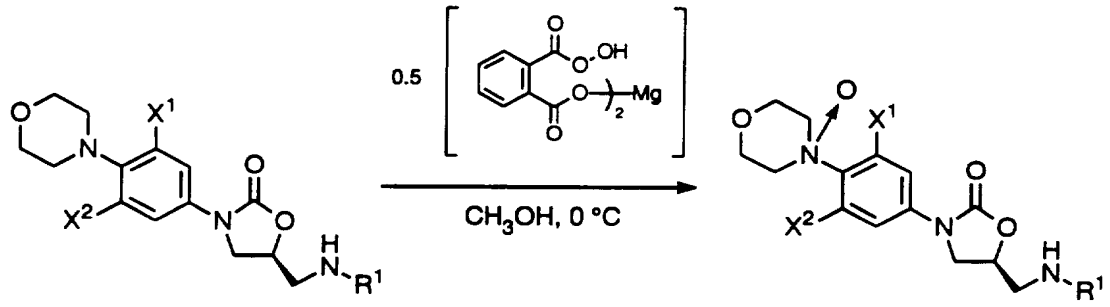
IX-E Prepared from (*S*)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) and the appropriate carboxylic acid using the general procedures of WO 93/23384, published 25 November 1993,

page 18, lines 10-17. The appropriate carboxylic acids are commercially available.

IX-F Prepared by combining (*S*)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) and the appropriate isocyanate. The required isocyanates are commercially available.

GENERAL PROCEDURE:

The compounds of this invention are prepared by oxidation of a suitable precursor amine with any of a variety of oxidizing agents. Suitable oxidants include pertrifluoroacetic acid, meta-chloroperbenzoic acid (MCPBA), and magnesium monoperoxyphthalate (MMPP). For example, the synthesis is shown below for the case wherein Q^1 is morpholine and the oxidant is MMPP.



Oxidation of any of the oxazolidinones of Charts I-IX in which Q^2 is any of the other groups previously described is carried out similarly.

Charts X-XVIII show the final N-oxide compounds of the present invention which are prepared from the parent amines of Charts I-IX, respectively, by using the above General Procedures.

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative synthetic processes are known to one of ordinary skill in organic chemistry.

The compounds of the present invention have an advantage over the parent amines in being exceedingly water soluble (see Table 1 below). For example, the compound of Example No. 2 has a solubility of 409 mg/ml. The parent amine has a water solubility of only 3.7 mg/ml. The N-oxide compounds of the present invention also retain all the *in vitro* and *in vivo* activities of the parent amines. The enhanced water solubility makes the N-oxide compounds of the present invention ideal for intravenous or injectable formulations.

Table 1. Solubility Data for the N-oxides and parent amines.

Example Number	Parent Amine Solubility (mg/mL)	N-Oxide Solubility (mg/mL)
1	4.2	348
2	3.7	534
3	0.28	12.9
6	0.031	1.1

Procedure for Measuring Solubility:

In all solubility studies, an excess of compound is added to 0.5 to 1 ml of pH 7, 50 mM phosphate buffer or other vehicle of interest. The samples are capped and stirred via magnetic stir bars for 24 to 48 hours at room temperature. Samples are filter centrifuged (800 x g) for 5-10 minutes through Millipore Ultrafree-MC 0.22 micron filter units. The supernate is analyzed by either UV or HPLC to quantitate the drug concentration. Results of the solubility testing of the compounds of the present invention are given above in Table 1.

The oxazolidinone compounds of the present invention have useful activity against a variety of microorganisms. The *in vitro* activity of compounds of the present invention are assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Methods for Dilution Antimicrobial Susceptiblity Tests for Bacteria That Grow Aerobically" (MFT) published January 1993 by the National Committee for Clinical Laboratory Standards (NCCLS), 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The activity of selected compounds of the present invention against *Staphylococcus aureus* and *Streptococcus pneumoniae* are shown in Table 2.

Table 2. Activity of the N-oxides against *S. Aureus* and *S. Pneumoniae*.

Example Number	MIC (μg/mL) *S. Aureus UC® 9213*	MIC (μg/mL) *S. Pneumoniae UC® 9912*
1	2	0.5
2	4	1
3	4	1
4	2	0.5
5	4	0.5
6	2	0.25

As such, the compounds of the present invention are useful for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I. The compound is administered in a pharmaceutical composition orally, parenterally (such as subcutaneously or intravenously), or topically. 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.

The following compounds of the present invention (with cross-references to the formulas in the charts below) are preferred:

X-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiazolidin-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

X-B $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(3-oxazolidinyl)]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide N-oxide.

XI-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothio-morpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XI-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide.

XII-A $R^1 = COCH_3$, X^1 = F, X^2 = H: (*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide N-oxide.

XII-A $R^1 = COCH_2OH$, X^1 = F, X^2 = H: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]hydroxyacetamide N-oxide.

XII-A R^1 = CHO, X^1 = F, X^2 = H: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]formamide N-oxide.

XII-A $R^1 = CO_2CH_3$, X^1 = F, X^2 = H: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]methylcarbamate N-oxide.

XII-A $R^1 = COCH_2Cl_2$, X^1 = F, X^2 = H: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]dichloroacetamide N-oxide.

XII-B $R^1 = COCH_3$, X^1 = F, X^2 = H: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-C $R^1 = COCH_3$, X^1 = F, X^2 = H: (*S*)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-H $R^1 = COCH_3$, X^1 = F, X^2 = H: (*S*)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-K $R^1 = COCH_3$, X^1 = F, X^2 = H, $R^3 = CH_3$: (*S*)-N-[[3-[3-fluoro-4-[3-[(methoxy-carbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-J $R^1 = COCH_3$, X^1 = F, X^2 = H, R^2 = H: (*S*)-N-[[3-[3-fluoro-4-[3-[(hydroxy-acetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIV-E $R^1 = COCH_3$, X^1 = F, X^2 = H: (S)-N-[[3-[3-Fluoro-4-(3-hydroxypyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIV-J $R^1 = COCH_3$, X^1 = F, X^2 = H, R^2 = H, $R^5 = CH_3$: (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(hydroxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide.

XIV-K $R^1 = COCH_3$, X^1 = F, X^2 = H, $R^3 = CH_3$, $R^5 = CH_3$: (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XV-B $R^1 = COCH_3$, X^1 = F, X^2 = H: (S)-N-[3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XV-D $R^1 = COCH_3$, X^1 = F, X^2 = H: (S)-N-[3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XV-M $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-1-[4-[5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-piperidine-4-carboxylic acid ethyl ester N-oxide.

XV-N $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[3-[3-fluoro-4-(4-hydroxymethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XVI-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[3-[3-fluoro-4-(4-oxoazepin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XVII-B $R^1 = COCH_3$, $X^1 = H$, $X^2 = H$, $R^3 = CH_3$: (S)-4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester N-oxide.

XVII-B $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^3 = CH_2CH_3$: (S)-4-(4-(5-((acetylamino)-methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester N-oxide.

XVIII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxy-acetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide N-oxide.

XVIII-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, R^4 = cyclopropyl: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVIII-D $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^9 = CH_3$: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7- yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxy-acetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[4-(hydroxy-acetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = X^2 = F$: (*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = F$, $X^2 = H$: (*S*)-4-[4-[5-[(acetylamino)-methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

The following compounds of the present invention (with cross references to the formulas in the charts below) are most preferred:

XII-A $R^1 = COCH_3$, $X^1 = X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

XII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide N-oxide;

XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

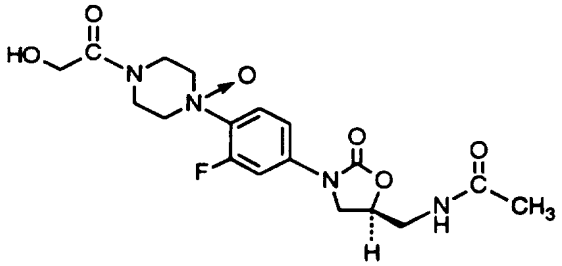
XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = X^2 = F$: (*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]- 1-piperazinecarboxylic acid, methyl ester N-oxide;

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = F$, $X^2 = H$: (*S*)-4-[4-[5-[(acetylamino)-methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1. (*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]- 2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide



(S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (VIII-A, $R^1 = COCH_3$, $R^2 = H$, $X^1 = F$, $X^2 = H$) (11.8 g) is dissolved in 200 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 18.5 g) is added and the resulting suspension is stirred at 25°C for two hours. The reaction is filtered and the filtrate is concentrated to afford a white solid. This solid is chromatographed on silica gel using 20% methanol in chloroform as eluent to afford the N-oxide. Lyophilization of this material affords the purified product as a hydrate (9.5 g).

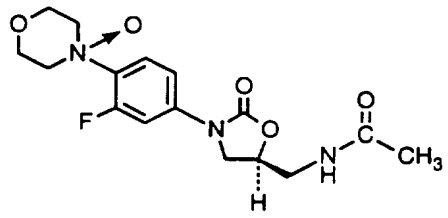
Physical characteristics are as follows:

Mp 158-160 °C;

IR (mull) 3276, 3071, 1754, 1658, 1622, 1502, 1444, 1410, 1286, 1255, 1224, 1204, 1135, 1095, 752 cm^{-1};

MS (FAB) *m/z* 411, 565, 412, 411, 396, 395, 394, 393, 392, 335, 56.

EXAMPLE 2. (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide



(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (III-A, R^1 = $COCH_3$, X^1 = F, X^2 = H) (12.5 g) is suspended in 200 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 11.5 g) is added and the resulting suspension is stirred at 25°C for two hours. The reaction mixture is filtered and the filtrate is concentrated to afford a light-yellow solid. This material is chromatographed on silica gel using 10% methanol (saturated with ammonia) in chloroform as eluent to afford 8.75 g of the N-oxide.

Physical characteristics are as follows:

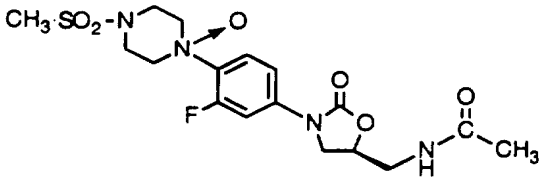
Mp 202-204 °C;

IR (mull) 1747, 1669, 1620, 1556, 1508, 1495, 1445, 1413, 1341, 1295, 1269, 1232, 1204, 1124, 755 cm^{-1};

MS (FAB) *m/z* 354, 708, 707, 355, 354, 339, 338, 337, 336, 86, 56.

Anal. Found: C, 53.99; H, 5.70; N, 11.76.

EXAMPLE 3. (*S*)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide



Pertrifluoroacetic acid is prepared in situ by the addition of 30% H_2O_2 solution (0.15 mL) to trifluoroacetic anhydride (0.45 mL) in 5 mL of methylene chloride at 0°C. This solution is stirred at 0°C for ten minutes, at 25°C for 30 minutes and then cooled back to 0 °C. (*S*)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide (VIII-G, R^1 = $COCH_3$, R^9 = CH_3, X^1 = F, X^2 =H) (0.207 g) is added and the reaction is stirred at 25°C for 30 minutes and then concentrated. The residue is chromatographed on silica gel using

10% methanol (saturated with ammonia) in chloroform as the eluent to afford 0.14 g of the N-oxide as a hydrate.

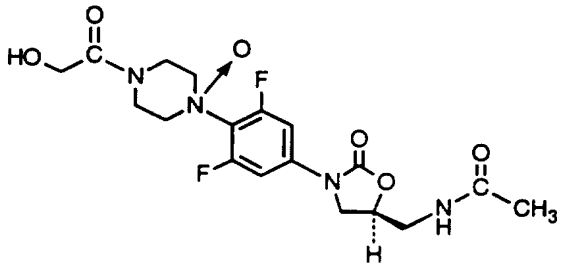
Physical characteristics are as follows:

Mp 168-170 °C;

IR (mull) 1751, 1668, 1658, 1503, 1443, 1408, 1340, 1328, 1277, 1260, 1226, 1157, 1130, 1081, 855 cm^{-1};

MS (FAB) *m/z* 431, 862, 861, 432, 431, 416, 415, 414, 413, 335, 56.

EXAMPLE 4. (*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide.



(S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]- acetamide (VIII-A, $R^1 = COCH_3$, $R^2 = H$, $X^1 = X^2 = F$) (0.13 g) is dissolved in 5 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.2 g) is added and the resulting suspension is stirred at 25°C for 72 hours. An additional 0.2 g of monoperoxyphthalic acid is added and the reaction is stirred an additional 48 hours. The reaction mixture is filtered and the filtrate is concentrated to afford a light-yellow oil. This material is chromatographed on silica gel using 20% methanol (saturated with ammonia) in chloroform as eluent to afford 55 mg of the N-oxide.

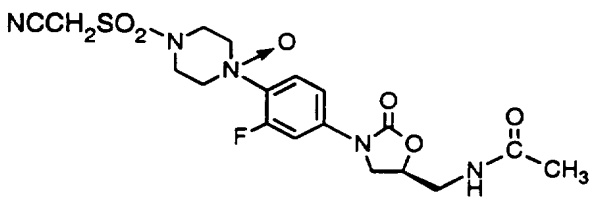
Physical characteristics are as follows:

Mp 100-105 °C;

IR (mull) 3292, 1757, 1658, 1636, 1584, 1557, 1497, 1413, 1287, 1245, 1213, 1098, 1054, 1043, 1020 cm^{-1};

MS (FAB) *m/z* 429 (M+H), 857, 429, 413, 412, 411, 353, 161, 145, 73, 56.

EXAMPLE 5. (S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.



(S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, R^1 = $COCH_3$, R^9 = $NCCH_2$, X^1 = F, X^2 = H) (0.550 g) is dissolved in 15 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.616 g) is added and the reaction is stirred at room temperature for 4 hours. The reaction is then filtered and the filtrate is concentrated to afford an oil. This oil is chromatographed on silica gel using 10% methanol (saturated with ammonia) in chloroform as eluent to afford 0.42 g of the N-oxide.

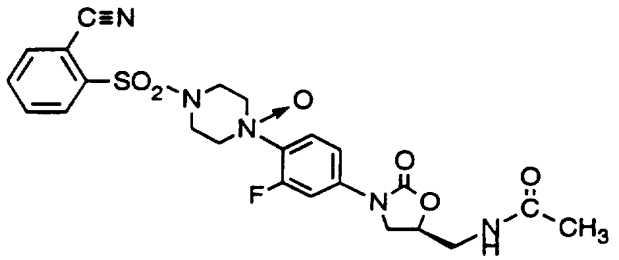
Physical characteristics are as follows:

Mp 153-156 °C.

IR (mull) 1748, 1656, 1625, 1503, 1443, 1406, 1357, 1342, 1257, 1224, 1161, 1148, 1137, 931, 756 cm^{-1};

MS (FAB) *m/z* 456 (M+H), 457, 456, 441, 440, 439, 438, 336, 335, 91, 56.

EXAMPLE 6. (S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.



(S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, R^1 = $COCH_3$, R^9 = 2-cyanophenyl, X^1 = F, X^2 = H) (0.5 g) is suspended in 10 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.616 g) is added and the reaction mixture is stirred at room temperature for 2 hours. The reaction is concentrated and the resulting oil is chromatographed on silica gel using 7% methanol (saturated with ammonia) in chloroform as eluent to afford 0.33 g of the N-oxide.

Physical characteristics are as follows:

Mp 190-192 °C.

IR (mull) 1756, 1678, 1661, 1620, 1500, 1486, 1408, 1280, 1256, 1222, 1181, 1168, 1129, 1082, 924 cm^{-1};

MS (FAB) *m/z* 518 (M+H), 520, 519, 518, 503, 502, 501, 500, 336, 335, 56.

EXAMPLE 7: Reduction of the N-oxide of Example 2 *in vivo* Following Intravenous and Oral Administration to Rats.

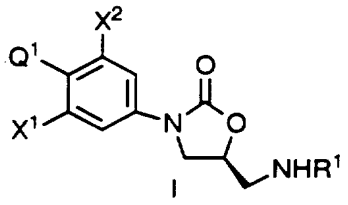
The rate and extent of reduction of the N-oxide of Example 2 was investigated *in vivo* using the following procedures: Six male Sprague-Dawley rats are used for this study. Three rats are given a single intravenous 10 mg/kg dose of the N-oxide and three rats are given a single oral 25 mg/kg dose of the N-oxide. Blood is collected pre-dose and up to 24 h post dose. The plasma is analyzed for the N-oxide and the parent amine by LC-MS.

Results:

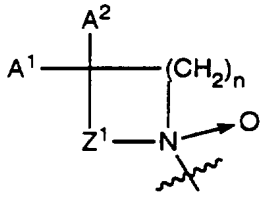
Only traces of the N-oxide were found in plasma in the first time point immediately post intravenous injection. The parent amine was detected in plasma up to 10 h post dosing. The lower limit of quantitation for the assay was ≈0.01 µg/mL. Because the N-oxide was reduced to the parent amine so rapidly, pharmacokinetic parameters were measured for the parent amine rather than for the N-oxide.

After both intravenous and oral dosing of the N-oxide, the Cmax, Tmax and AUC values for the parent amine were very similar to those found when the parent amine compound was administered directly to rats using the same doses and protocol. The relative bioavailability of the parent amine from the orally administered N-oxide was approximately 100% when compared to orally administered parent amine. The rapid and essentially quantitative conversion of the N-oxide to the parent amine *in vivo* demonstrates that the N-oxide is a suitable prodrug for the parent amine.

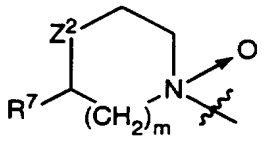
FORMULA CHART



I



II



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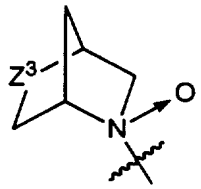

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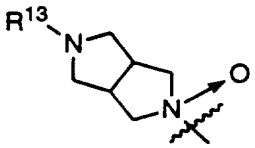

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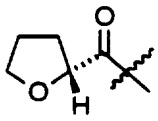

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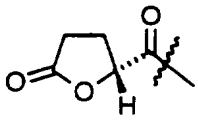

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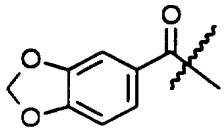
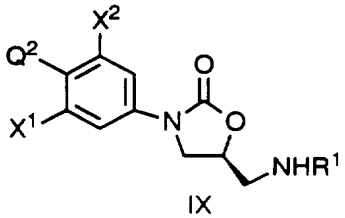
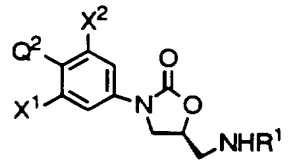


VIII



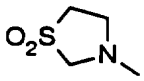
IX

CHART I - THIAZOLIDINES

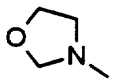


IX

wherein Q^2 is



I-A



I-B

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

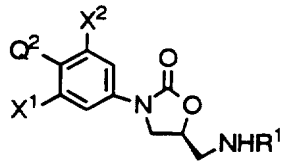
-$COCHF_2$,

-CO_2CH_3,

-SO_2CH_3, or

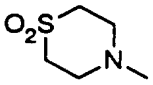
-$COCH_2OH$.

CHART II - THIOMORPHOLINES - BRIDGED THIOMORPHOLINES

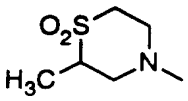


IX

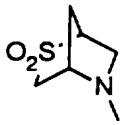
wherein Q^2 is



II-A



II-B



II-C

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

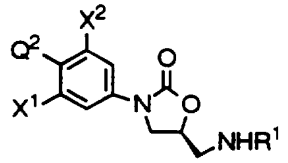
$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

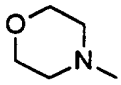
$-COCH_2OH$.

CHART III - MORPHOLINES - BRIDGED MORPHOLINES

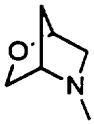


IX

wherein Q^2 is



III-A



III-B

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

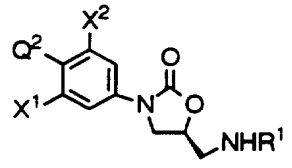
-$COCHF_2$,

-CO_2CH_3,

-SO_2CH_3, or

-$COCH_2OH$.

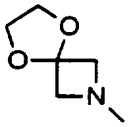
CHART IV - AZETIDINES



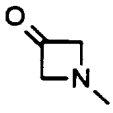
IX

wherein Q^2 is

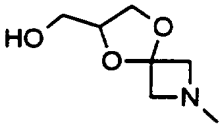
IV-A



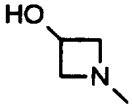
IV-B



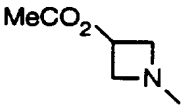
IV-C



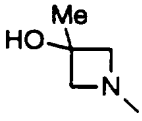
IV-D



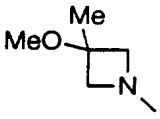
IV-E



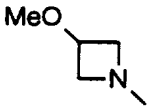
IV-F



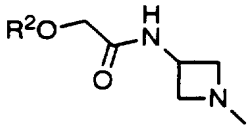
IV-G



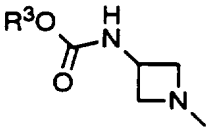
IV-H



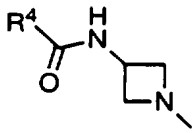
IV-I



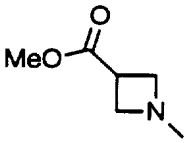
IV-J



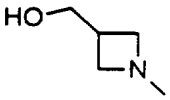
IV-K



IV-L



IV-M



IV-N

CHART IV - AZETIDINES (Continued)

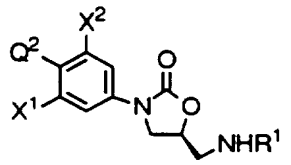
wherein X^1 and X^2 are independently
-H,
-F, or
-Cl;
wherein R^1 is
-CHO,
$-COCH_3$,
$-COCHCl_2$,
$-COCHF_2$,
$-CO_2CH_3$,
$-SO_2CH_3$, or
$-COCH_2OH$;
wherein R^2 is
-H,
$-CH_3$,
$-CH_2Ph$, or
$-COCH_3$;
wherein R^3 is
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$, or
-phenyl;
wherein R^4 is
-H,
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$,
$-CH_2CH_2CH_2CH_3$,
-phenyl,
$-CH_2Cl$,
$-CHCl_2$,
CH_2F,
$-CHF_2$,
-substituted aryl,

CHART IV- AZETIDINES (Continued)

-CH_2-(aryl), or

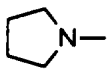
-cycloalkyl (rings of 3-6 carbons).

CHART V - PYRROLIDINES

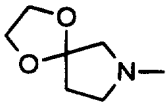


IX

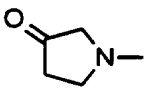
wherein Q^2 is



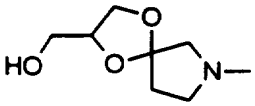
V-A



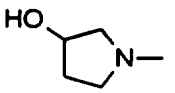
V-B



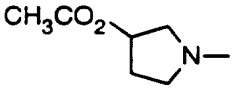
V-C



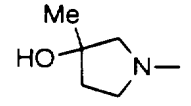
V-D



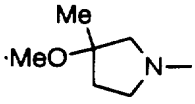
V-E



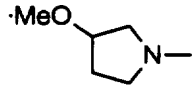
V-F



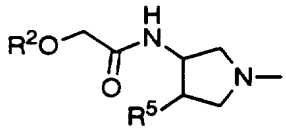
V-G



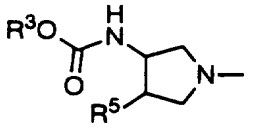
V-H



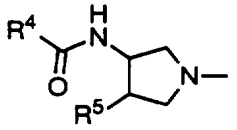
V-I



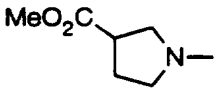
V-J



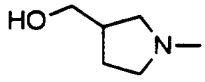
V-K



V-L



V-M



V-N

CHART V - PYRROLIDINES (Continued)

wherein X^1 and X^2 are independently
- -H,
- -F, or
- -Cl;

wherein R^1 is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein R^2 is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein R^3 is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

wherein R^4 is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- CH_2F,
- $-CHF_2$,
- -substituted aryl,

CHART V - PYRROLIDINES (Continued)

-CH_2-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein R^5 is

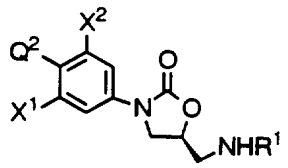
-H,

-CH_3,

-CH_2CH_3, or

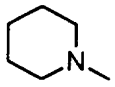
-$CH_2CH_2CH_3$.

CHART VI - PIPERIDINES

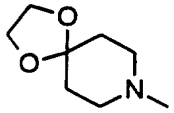


IX

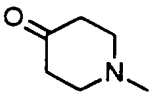
wherein Q^2 is



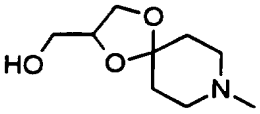
VI-A



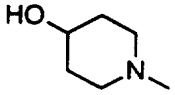
VI-B



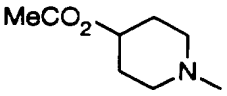
VI-C



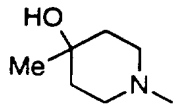
VI-D



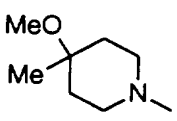
VI-E



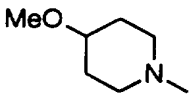
VI-F



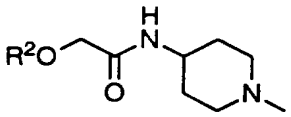
VI-G



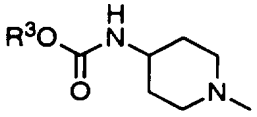
VI-H



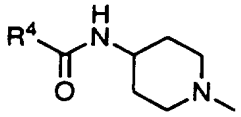
VI-I



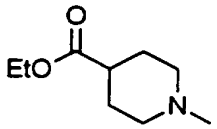
VI-J



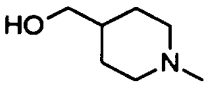
VI-K



VI-L



VI-M



VI-N

CHART VI - PIPERIDINES (Continued)

wherein X^1 and X^2 are independently
- -H,
- -F, or
- -Cl;

wherein R^1 is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $COCH_2OH$;

wherein R^2 is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein R^3 is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

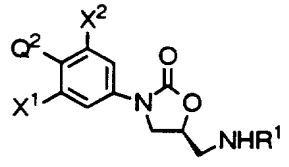
wherein R^4 is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- CH_2F,
- $-CHF_2$,
- -substituted aryl,

CHART VI - PIPERIDINES (continued)

-CH_2-(aryl), or

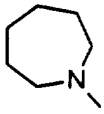
-cycloalkyl (rings of 3-6 carbons).

CHART VII - AZEPINES

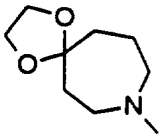


IX

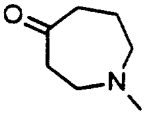
wherein Q^2 is



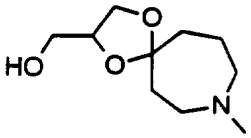
VII-A



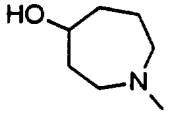
VII-B



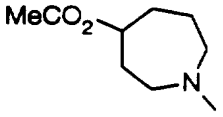
VII-C



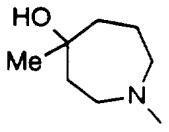
VII-D



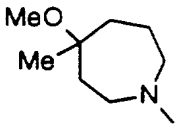
VII-E



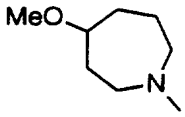
VII-F



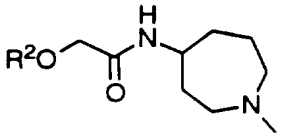
VII-G



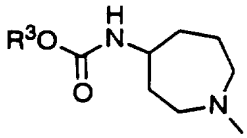
VII-H



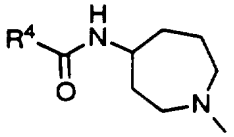
VII-I



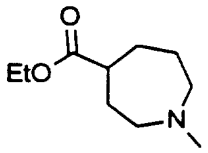
VII-J



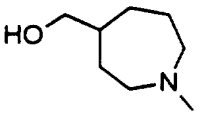
VII-K



VII-L



VII-M



VII-N

CHART VII - AZEPINES (Continued)

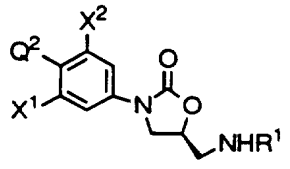
wherein X^1 and X^2 are independently
-H,
-F, or
-Cl;
wherein R^1 is
-CHO,
$-COCH_3$,
$-COCHCl_2$,
$-COCHF_2$,
$-CO_2CH_3$,
$-SO_2CH_3$, or
$-COCH_2OH$;
wherein R^2 is
-H,
$-CH_3$,
$-CH_2Ph$, or
$-COCH_3$;
wherein R^3 is
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$, or
-phenyl;
wherein R^4 is
-H,
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$,
$-CH_2CH_2CH_2CH_3$,
-phenyl,
$-CH_2Cl$,
$-CHCl_2$,
CH_2F,
$-CHF_2$,
-substituted aryl,

CHART VII - AZEPINES (Continued)

-CH_2-(aryl), or

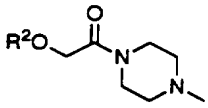
-cycloalkyl (rings of 3-6 carbons).

CHART VIII - PIPERAZINES

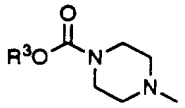


IX

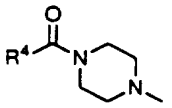
wherein Q^2 is



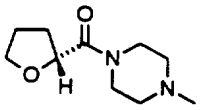
VIII-A



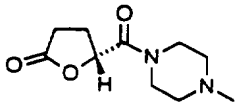
VIII-B



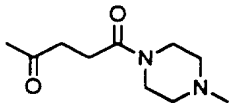
VIII-C



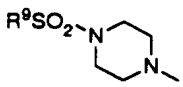
VIII-D



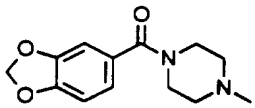
VIII-E



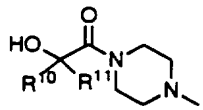
VIII-F



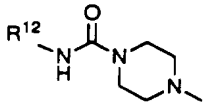
VIII-G



VIII-H



VIII-I



VIII-J

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$-COCH_2OH$;

CHART VIII - PIPERAZINES (Continued)

wherein R^2 is
-H,
-CH_3,
-CH_2Ph, or
-$COCH_3$;
wherein R^3 is
-CH_3,
-CH_2CH_3,
-$CH_2CH_2CH_3$, or
-phenyl;
wherein R^4 is
-H,
-CH_3,
-CH_2CH_3,
-$CH_2CH_2CH_3$,
-$CH_2CH_2CH_2CH_3$,
-phenyl,
-CH_2Cl,
-$CHCl_2$,
CH_2F,
-CHF_2,
-substituted aryl,
-CH_2-(aryl), or
-cycloalkyl (rings of 3-6 carbons);
wherein R^9 is
-CH_3,
-CH_2Cl,
-$CH_2CH=CH_2$,
substituted aryl, or
-CH_2CN;
wherein R^{10} and R^{11} are independently
-H,
-CH_3, or
-together form a cyclopropyl ring;

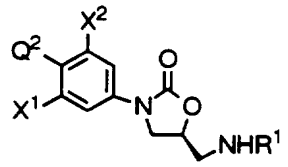
CHART VIII - PIPERAZINES (Continued)

wherein R^{12} is

-CH_2Ph, or

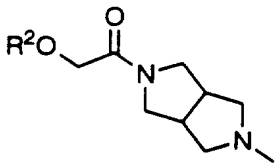
-substituted aryl.

CHART IX - PYRROLOPYRROLIDINES

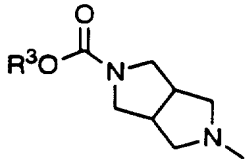


IX

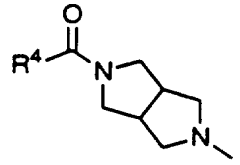
wherein Q^2 is



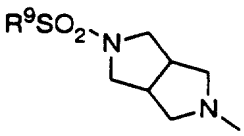
IX-A



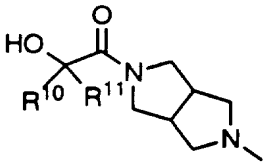
IX-B



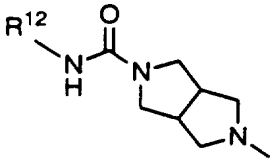
IX-C



IX-D



IX-E



IX-F

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

CHART IX - PYRROLOPYRROLIDINES (Continued)

wherein R^1 is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein R^2 is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein R^3 is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

wherein R^4 is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- $-CH_2F$,
- $-CHF_2$,
- -substituted aryl,
- $-CH_2$-(aryl), or
- -cycloalkyl (rings of 3-6 carbons);

wherein R^9 is
- $-CH_3$,

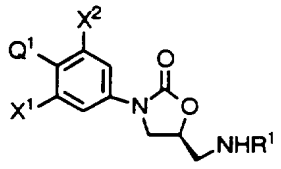
CHART IX - PYRROLOPYRROLIDINES (Continued)

-CH_2Cl,
-$CH_2CH{=}CH_2$,
substituted aryl, or
-CH_2CN;

wherein R^{10} and R^{11} are independently
-H,
-CH_3, or
-together form a cyclopropyl ring;

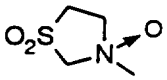
wherein R^{12} is
-CH_2Ph, or
-substituted aryl.

CHART X - THIAZOLIDINES

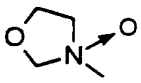


I

wherein Q^1 is



X-A



XI-B

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

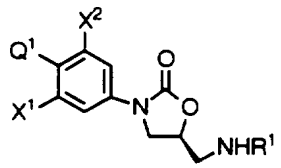
-$COCHF_2$,

-CO_2CH_3,

-SO_2CH_3, or

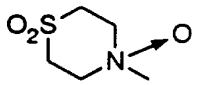
-$COCH_2OH$.

CHART XI - THIOMORPHOLINES - BRIDGED THIOMORPHOLINES

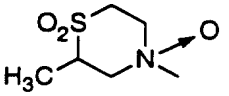


I

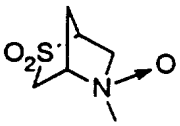
wherein Q^1 is



XI-A



XI-B



XI-C

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

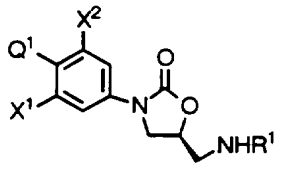
$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

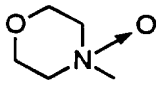
$-COCH_2OH$.

CHART XII - MORPHOLINES - BRIDGED MORPHOLINES

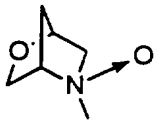


I

wherein Q^1 is



XII-A



XII-B

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

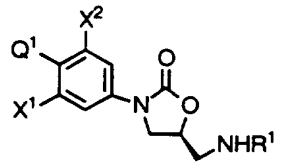
$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

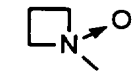
$-COCH_2OH$.

CHART XIII - AZETIDINES

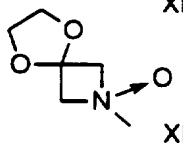


I

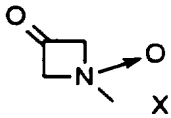
wherein Q^1 is



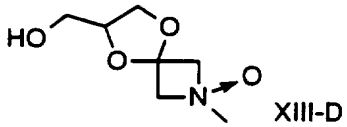
XIII-A



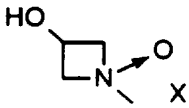
XIII-B



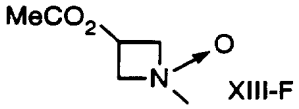
XIII-C



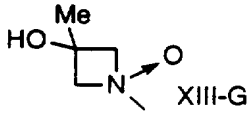
XIII-D



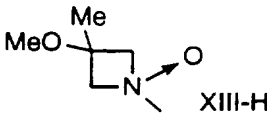
XIII-E



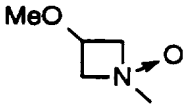
XIII-F



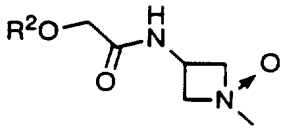
XIII-G



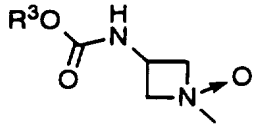
XIII-H



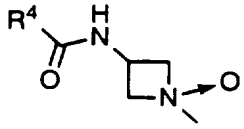
XIII-I



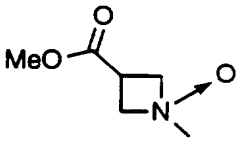
XIII-J



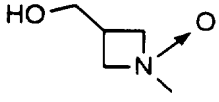
XIII-K



XIII-L



XIII-M



XIII-N

CHART XIII - AZETIDINES (Continued)

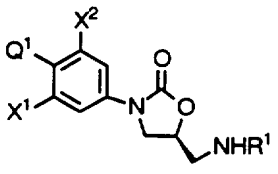
wherein X^1 and X^2 are independently
-H,
-F, or
-Cl;
wherein R^1 is
-CHO,
$-COCH_3$,
$-COCHCl_2$,
$-COCHF_2$,
$-CO_2CH_3$,
$-SO_2CH_3$, or
$-COCH_2OH$;
wherein R^2 is
-H,
$-CH_3$,
$-CH_2Ph$, or
$-COCH_3$;
wherein R^3 is
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$, or
-phenyl;
wherein R^4 is
-H,
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$,
$-CH_2CH_2CH_2CH_3$,
-phenyl,
$-CH_2Cl$,
$-CHCl_2$,
CH_2F,
$-CHF_2$,
-substituted aryl,

CHART XIII- AZETIDINES (Continued)

-CH_2-(aryl), or

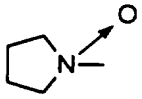
-cycloalkyl (rings of 3-6 carbons).

CHART XIV - PYRROLIDINES

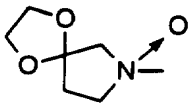


I

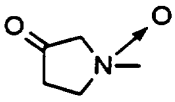
wherein Q^1 is



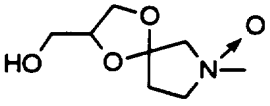
XIV-A



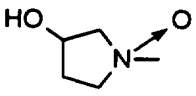
XIV-B



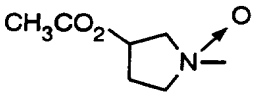
XIV-C



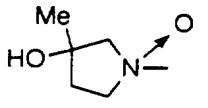
XIV-D



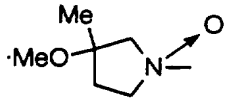
XIV-E



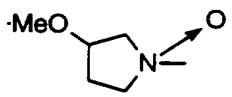
XIV-F



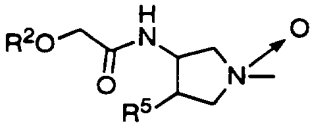
XIV-G



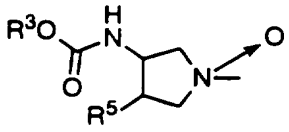
XIV-H



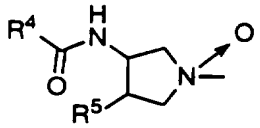
XIV-I



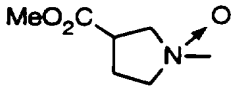
XIV-J



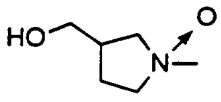
XIV-K



XIV-L



XIV-M



XIV-N

CHART XIV - PYRROLIDINES (Continued)

wherein X^1 and X^2 are independently
-H,
-F, or
-Cl;
wherein R^1 is
-CHO,
$-COCH_3$,
$-COCHCl_2$,
$-COCHF_2$,
$-CO_2CH_3$,
$-SO_2CH_3$, or
$-COCH_2OH$;
wherein R^2 is
-H,
$-CH_3$,
$-CH_2Ph$, or
$-COCH_3$;
wherein R^3 is
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$, or
-phenyl;
wherein R^4 is
-H,
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$,
$-CH_2CH_2CH_2CH_3$,
-phenyl,
$-CH_2Cl$,
$-CHCl_2$,
CH_2F,
$-CHF_2$,
-substituted aryl,

CHART XIV - PYRROLIDINES (Continued)

-CH_2-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein R^5 is

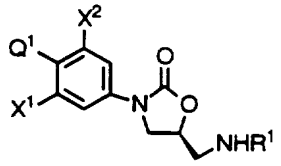
-H,

-CH_3,

-CH_2CH_3, or

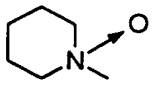
-$CH_2CH_2CH_3$.

CHART XV - PIPERIDINES

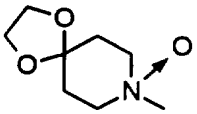


I

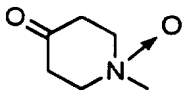
wherein Q^1 is



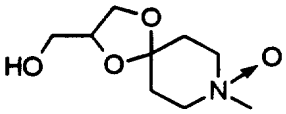
XV-A



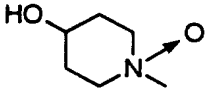
XV-B



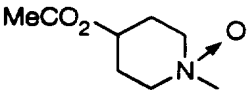
XV-C



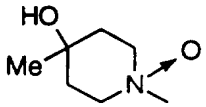
XV-D



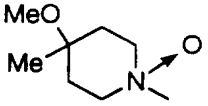
XV-E



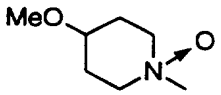
XV-F



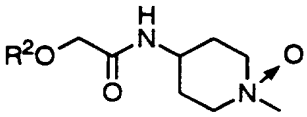
XV-G



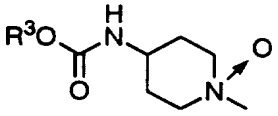
XV-H



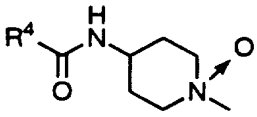
XV-I



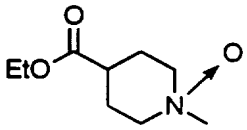
XV-J



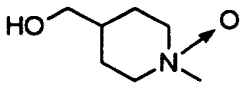
XV-K



XV-L



XV-M



XV-N

CHART XV - PIPERIDINES (Continued)

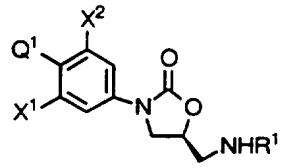
wherein X^1 and X^2 are independently
-H,
-F, or
-Cl;
wherein R^1 is
-CHO,
$-COCH_3$,
$-COCHCl_2$,
$-COCHF_2$,
$-CO_2CH_3$,
$-SO_2CH_3$, or
$COCH_2OH$;
wherein R^2 is
-H,
$-CH_3$,
$-CH_2Ph$, or
$-COCH_3$;
wherein R^3 is
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$, or
-phenyl;
wherein R^4 is
-H,
$-CH_3$,
$-CH_2CH_3$,
$-CH_2CH_2CH_3$,
$-CH_2CH_2CH_2CH_3$,
-phenyl,
$-CH_2Cl$,
$-CHCl_2$,
CH_2F,
$-CHF_2$,
-substituted aryl,

CHART XV - PIPERIDINES (continued)

-CH_2-(aryl), or

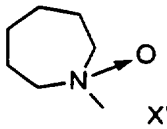
-cycloalkyl (rings of 3-6 carbons).

CHART XVI - AZEPINES

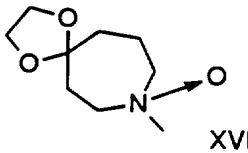


I

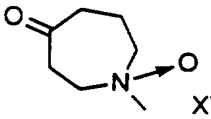
wherein Q^1 is



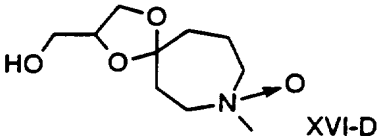
XVI-A



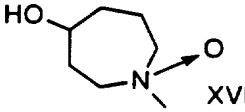
XVI-B



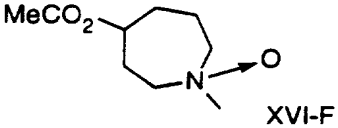
XVI-C



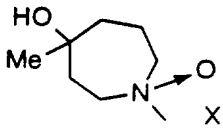
XVI-D



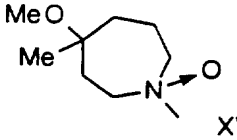
XVI-E



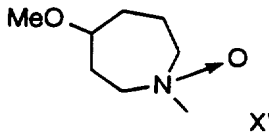
XVI-F



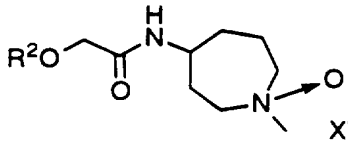
XVI-G



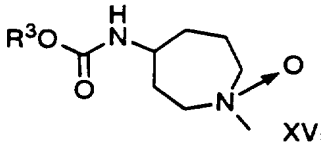
XVI-H



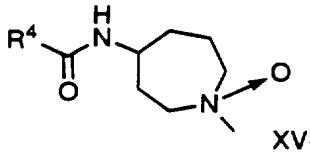
XVI-I



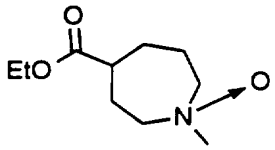
XVI-J



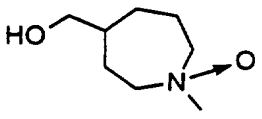
XVI-K



XVI-L



XVI-M



XVI-N

CHART XVI - AZEPINES (Continued)

wherein X^1 and X^2 are independently
- -H,
- -F, or
- -Cl;

wherein R^1 is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein R^2 is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein R^3 is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

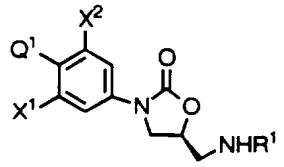
wherein R^4 is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- CH_2F,
- $-CHF_2$,
- -substituted aryl,

CHART XVI - AZEPINES (Continued)

-CH_2-(aryl), or

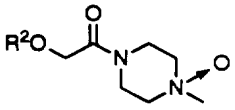
-cycloalkyl (rings of 3-6 carbons).

CHART XVII - PIPERAZINES

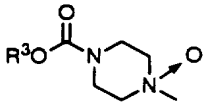


I

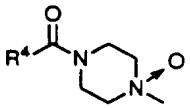
wherein Q^1 is



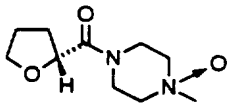
XVII-A



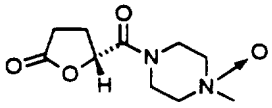
XVII-B



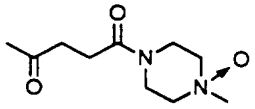
XVII-C



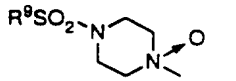
XVII-D



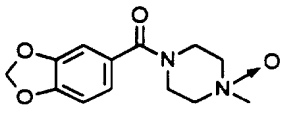
XVII-E



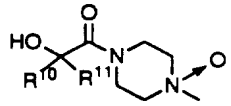
XVII-F



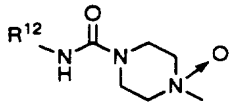
XVII-G



XVII-H



XVII-I



XVII-J

CHART XVII - PIPERAZINES (Continued)

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

wherein R^1 is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$-COCH_2OH$;

wherein R^2 is

-H,

$-CH_3$,

$-CH_2Ph$, or

$-COCH_3$;

wherein R^3 is

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$, or

-phenyl;

wherein R^4 is

-H,

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$,

$-CH_2CH_2CH_2CH_3$,

-phenyl,

$-CH_2Cl$,

$-CHCl_2$,

CH_2F,

$-CHF_2$,

-substituted aryl,

CHART XVII - PIPERAZINES (Continued)

-CH_2-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein R^9 is

-CH_3,

-CH_2Cl,

-$CH_2CH{=}CH_2$,

substituted aryl, or

-CH_2CN;

wherein R^{10} and R^{11} are independently

-H,

-CH_3, or

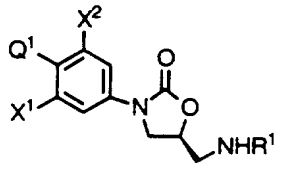
-together form a cyclopropyl ring;

wherein R^{12} is

-CH_2Ph, or

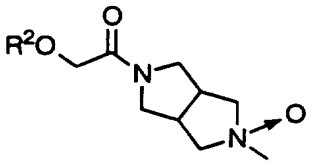
-substituted aryl.

CHART XVIII - PYRROLOPYRROLIDINES

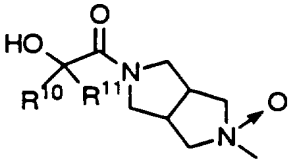


I

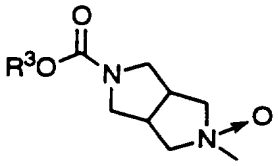
wherein Q^1 is



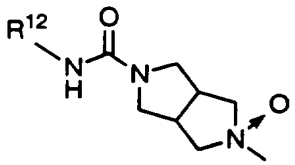
XVIII-A



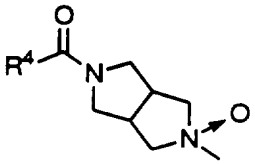
XVIII-E



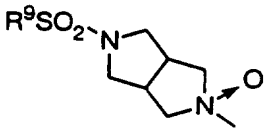
XVIII-B



XVIII-F



XVIII-C



XVIII-D

wherein X^1 and X^2 are independently

-H,

-F, or

-Cl;

CHART XVIII - PYRROLOPYRROLIDINES (Continued)

wherein R^1 is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein R^2 is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein R^3 is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

wherein R^4 is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- $-CH_2F$,
- $-CHF_2$,
- -substituted aryl,
- $-CH_2$-(aryl), or
- -cycloalkyl (rings of 3-6 carbons);

wherein R^9 is
- $-CH_3$,

CHART XVIII - PYRROLOPYRROLIDINES (Continued)

-CH_2Cl,

-$CH_2CH{=}CH_2$,

substituted aryl, or

-CH_2CN;

wherein R^{10} and R^{11} are independently

-H,

-CH_3, or

-together form a cyclopropyl ring;

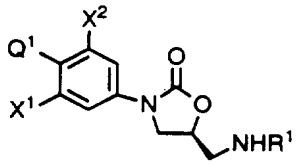
wherein R^{12} is

-CH_2Ph, or

-substituted aryl.

CLAIMS

1. A compound of the formula I



I

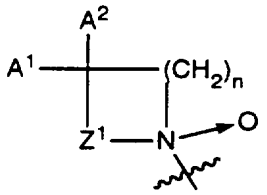
wherein X^1 and X^2 are independently

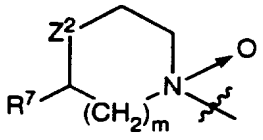
-H,

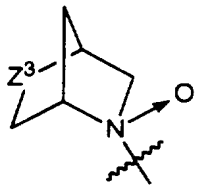
-F, or

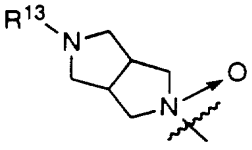
-Cl;

wherein Q^1 is:

a)  II

b)  III

c)  IV, or

d)  V;

wherein Z^1 is

a) $-CH_2-$, or

b) $-CH(R^5)-CH_2-$;

wherein Z^2 is

a) $-O_2S-$,
b) -O-, or
c) $-N(R^8)-$;

wherein Z^3 is

a) $-O_2S-$, or
b) -O-;

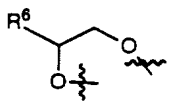
wherein A^1 is

a) H-, or
b) CH_3-;

wherein A^2 is

a) H-,
b) HO-,
c) CH_3CO_2-,
d) CH_3-,
e) CH_3O-,
f) $R^2O-CH_2-C(O)-NH-$
g) $R^3O-C(O)-NH-$,
h) $R^4-C(O)-NH-$,
i) (C_1-C_2)alkyl-O-C(O)-, or
j) $HO-CH_2-$; or

A^1 and A^2 taken together are:

a)  or

b) o= ;

wherein R^1 is

a) -CHO,
b) $-COCH_3$,
c) $-COCHCl_2$,
d) $-COCHF_2$,
e) $-CO_2CH_3$,
f) $-SO_2CH_3$, or
g) $-COCH_2OH$;

wherein R^2 is

a) H-,
b) CH_3-,
c) phenyl-CH_2-, or
d) $CH_3C(O)$-;

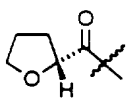
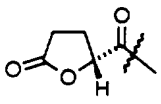
wherein R^3 is
a) $(C_1$-$C_3)$alkyl-, or
b) phenyl-;

wherein R^4 is
a) H-,
b) $(C_1$-$C_4)$alkyl,
c) aryl -$(CH_2)_p$,
d) ClH_2C-,
e) Cl_2HC-,
f) FH_2C-,
g) F_2HC-, or
h) $(C_3$-$C_6)$cycloalkyl;

wherein R^5 is
a) H-, or
b) $(C_1$-$C_3)$alkyl;

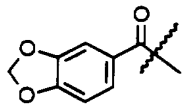
wherein R^6 is
a) H-, or
b) HOH_2C-;

wherein R^7 is
a) H-, or
b) H_3C-;

wherein R^8 is
a) R^2O-$C(R_{10})(R_{11})$-C(O)-,
b) R^3O-C(O)-,
c) R^4-C(O)-,
d)  VI ,
e)  VII ,

f) H_3C-C(O)-$(CH_2)_2$-C(O)-,

g) R^9-SO_2-,

h)  VIII , or

i) R^{12}-NH-C(O)-;

wherein R^9 is

a) $-CH_3$,

b) $-CH_2Cl$

c) $-CH_2CH=CH_2$,

d) aryl, or

e) $-CH_2CN$;

wherein R^{10} and R^{11} are independently

a) H-,

b) CH_3-; or

R^{10} and R^{11} taken together are $-CH_2-CH_2-$;

wherein R^{12} is $-(CH_2)_p$-aryl;

wherein R^{13} is

a) R^2O-C(R_{10})(R_{11})-C(O)-,

b) R^3O-C(O)-,

c) R^4-C(O)-,

d) R^9-SO_2-, or

e) R^{12}-NH-C(O)-;

wherein m is zero (0) or one (1);

wherein n is one (1) to three (3), inclusive;

wherein p is zero (0) or one (1);

wherein aryl is phenyl substituted with zero (0) or one (1) of the following:

a) -F,

b) -Cl,

c) $-OCH_3$,

d) -OH,

e) $-NH_2$,

f) $-(C_1-C_4)$alkyl,

g) $-O-C(O)-OCH_3$,

h) $-NO_2$, or

i) -CN;

with the following provisos:

1) in the moiety of formula II, Z^1 is -CH(R^5)-CH_2- wherein R^5 is (C_1-C_3)alkyl, only when n is one (1), A^1 is H and A^2 is R^2O-CH_2-C(O)-NH-, R^3O-C(O)-NH-, or R^4-C(O)-NH-; and

2) in the moiety of formula II, when Z^1 is -CH_2-, n is one (1).

2. The compound of claim 1 wherein Q^1 is the moiety of formula II.

3. The compound of claim 1 wherein Q^1 is the moiety of formula III.

4. The compound of claim 1 wherein Q^1 is the moiety of formula IV.

5. The compound of claim 1 wherein Q^1 is the moiety of formula V.

6. The compound of claim 1 wherein one of X^1 and X^2 is -H and the other is -F or wherein X^1 is -F and X^2 is -F.

7. The compound of claim 1 wherein R^1 is acetyl.

8. The compound of claim 1 selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiazolidin-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxazolidinyl)]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-hydroxyacetamide N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-

formamide N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-methylcarbamate N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-dichloroacetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[3-[(methoxycarbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[3-[(hydroxyacetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(S)-N-[[3-[3-Fluoro-4-(3-hydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

(S)-N-[[3-[3-Fluoro-4-(*cis*-3-(hydoxyacetylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(S)-N-[3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-N-[3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-1-[4-[5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-piperidine-4-carboxylic acid ethyl ester N-oxide;

(S)-N-[3-[3-fluoro-4-(4-hydroxymethylpiperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-N-[3-[3-fluoro-4-(4-oxoazepin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester N-oxide;

(S)-4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-

yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]-octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide; and

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

9. The compound of claim 8 selected from the group consisting of:

(*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide; and

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

10. The compound of claim 1 selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]- 2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]-2-oxo-5-

oxazolidinyl]-methyl]acetamide N-oxide;

(S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide; and

(S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 96/14135

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/20 A61K31/42 C07D417/10 C07D495/08 C07D491/08
C07D413/10 C07D471/04 C07D491/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 cited in the application see claims ---	1-10
Y	WO 93 23384 A (THE UPJOHN COMPANY) 25 November 1993 cited in the application see claims ---	1-10
Y	WO 92 18469 A (BRITISH TECHNOLOGY GROUP LTD) 29 October 1992 cited in the application see page 2,lines 8-21 and page 12,lines 16-31 see claims --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 722 928 A (GEORGE A.BOSWELL ET AL) 2 February 1988 cited in the application see the whole document	1-7
Y	WO 95 14684 A (THE UPJOHN COMPANY) 1 June 1995 cited in the application see claims	1-10
P,Y	WO 96 15130 A (THE UPJOHN COMPANY) 23 May 1996 cited in the application see claims	1-10
P,Y	WO 96 23788 A (PHARMACIA + UPJOHN COMPANY) 8 August 1996 cited in the application see claims	1-10
P,Y	WO 96 13502 A (THE UPJOHN COMPANY) 9 May 1996 cited in the application see claims	1-10
P,Y	WO 95 25106 A (THE UPJOHN COMPANY) 21 September 1995 cited in the application see claims	1-10
E	WO 96 35691 A (PHARMACIA + UPJOHN COMPANY) 14 November 1996 see claims	1-10

1

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Information on patent family members

International Application No
PCT/US 96/14135

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Information on patent family members

Inter nal Application No
PC1/US 96/14135

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		EP-A-	0730591	11-09-96
		ZA-A-	9407885	09-04-96
WO-A-9615130	23-05-96	AU-A-	3889095	06-06-96
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European Patent Office
Office européen des brevets

(11) EP 0 785 200 A2

(12) EUROPÄISCHE PATENTANMELDUNG

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  42115 Wuppertal (DE)
- **Ruppelt, Martin, Dr.**
  42115 Wuppertal (DE)
- **Bartel, Stephen, Dr**
  51465 Bergisch Gladbach (DE)
- **Guarnieri, Walter, Dr.**
  53909 Zülpich (DE)
- **Endermann, Rainer, Dr.**
  42113 Wuppertal (DE)
- **Kroll, Hein-Peter, Dr.**
  42115 Wuppertal (DE)

(54) Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone

(57) Die vorliegende Erfindung betrifft neue Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

EP 0 785 200 A2

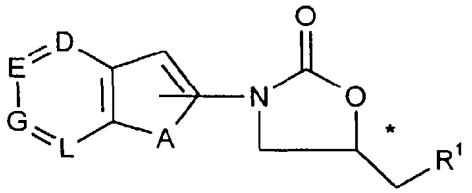
Beschreibung

Die vorliegende Erfindung betrifft neue Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

N-Aryloxazolidinone mit antibakterieller Wirkung sind beispielsweise aus den Publikationen EP 311 090 und US 4 705 799 bekannt. Außerdem sind 3-(Stickstoff-substituierte)phenyl-5-beta-amidomethyloxazolidin-2-one aus der EP 609 905 A1 bekannt.

Ferner sind unter anderem in der WO 93 08 179 A Oxazolidinonderivate mit einer Monoaminoxidase inhibitorischen Wirkung und in der EP 645 376 mit Wirkung als Adhäsionsrezeptor-Antagonisten publiziert.

Die vorliegende Erfindung betrifft Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone der allgemeinen Formel (I)



(I)

in welcher

A	für ein Sauerstoff- oder Schwefelatom oder für die SO_2-Gruppe steht, und
D, E, G und L	gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin
R^2	Wasserstoff, Cyano, Nitro, Carboxyl, geradkettiges oder verzweigtes Alkyl, Acyl oder Alkoxy mit jeweils bis zu 7 Kohlenstoffatomen, Halogen oder eine Gruppe der Formel $-NR^3R^4$, $-CO-NR^5R^6$, $-NR^7-CO-R^8$ oder $-S(O)_aR^9$ bedeutet, worin
R^3, R^4, R^5, R^6, R^7 und R^8	gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
a	eine Zahl 0, 1 oder 2 bedeutet,
R^9	Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet,
R^1	für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin
R^{10}	geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet,
R^{11}	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^{12} und R^{13}	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^{12} oder R^{13}	eine Gruppe der Formel -CO-R^{14}, -CS-$R^{14'}$, P(O)(OR^{15})(OR^{16}) oder -SO_2-R^{17} bedeutet, worin
R^{14} und $R^{14'}$	gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten, oder
R^{14} und $R^{14'}$	geradkettiges oder verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert ist, oder geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeuten, oder eine Gruppe der Formel -$NR^{18}R^{19}$ bedeuten,
	worin
R^{18} und R^{19}	gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder einen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeuten,
R^{15} und R^{16}	gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,
R^{17}	geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet

und deren Salze.

Physiologisch unbedenkliche Salze der neuen Pyrido-annellierten Thienyl- und Furanyl-Oxazolidinone 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 weiterhin 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, Dihydroabietylamin, 1-Ephenamin oder Methyl-piperidin.

Als Salze können außerdem Reaktionsprodukte mit C_1-C_4-Alkylhalogeniden, insbesondere C_1-C_4-Alkyljodiden fungieren.

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 und Tetrahydropyranyl.

Aminoschutzgruppen 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

A	für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2-$Gruppe steht, und
D, E, G und L	gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin
R^2	Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen, Fluor, Chlor oder Brom bedeutet,
R^1	für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin
R^{10}	geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,
R^{11}	geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Phenyl oder Tolyl bedeutet,
R^{12} und R^{13}	gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten, oder
R^{12} oder R^{13}	eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet, worin
R^{14} und $R^{14'}$	gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten, oder
R^{14} und $R^{14'}$	geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeuten, oder eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten, worin
R^{18} und R^{19}	gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, oder Isoxazolyl, Furyl, Thienyl, Pyrryl, Oxazolyl oder Imidazolyl bedeuten,
R^{15} und R^{16}	gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,
R^{17}	geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet

und deren Salze.

Besonders bevorzugt sind Verbindungen der allgemeinen Formel (I), in welcher

A	für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2-$Gruppe steht, und
D, E, G und L	gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin
R^2	Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Fluor bedeutet,

R^1 für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin

R^{10} geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet,

R^{11} Methyl, Ethyl, Phenyl oder Toluolyl bedeutet,

R^{12} und R^{13} gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 5 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten,
oder

R^{12} oder R^{13} eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2R^{17}$ bedeutet, worin

R^{14} und $R^{14'}$ gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluorethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten,
oder

R^{14} und $R^{14'}$ geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 4 Kohlenstoffatomen bedeuten, oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

R^{18} und R^{19} gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten, oder
Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeuten,

R^{15} und R^{16} gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

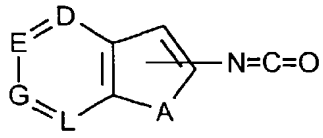
R^{17} Methyl oder Phenyl bedeutet

und deren Salze.

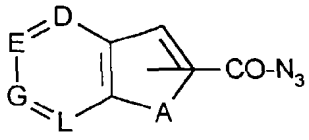
Ganz besonders bevorzugt sind die erfindungsgemäßen Verbindungen der allgemeinen Formel (I), in welcher
der Oxazolidinonrest in der Position 2 am 5-Ring-Heterocyclus angebunden ist.

Außerdem wurden Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) gefunden, dadurch gekennzeichnet, daß man

[A] Verbindungen der allgemeinen Formel (II) oder (III)



(II) oder

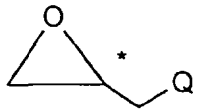


(III)

in welchen

A, D, E, G und L die oben angegebene Bedeutungen haben,

mit Lithiumbromid/$(C_4H_9)_3P(O)$ und Epoxiden der allgemeinen Formel (IV)



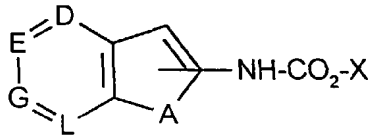
(IV)

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)



(V)

in welcher

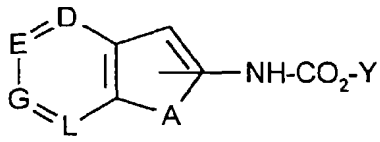
A, D, E, G und L die oben angegebene Bedeutung haben
und

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)



(Va)

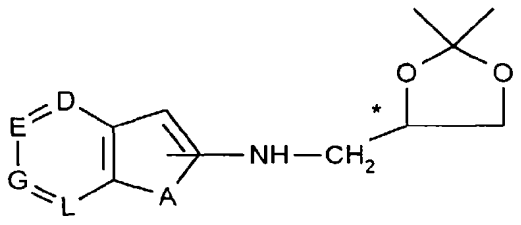
in welcher

A, D, E, G und L die oben angegebene Bedeutung haben
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 mit Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

[D] Verbindungen der allgemeinen Formel (VI)

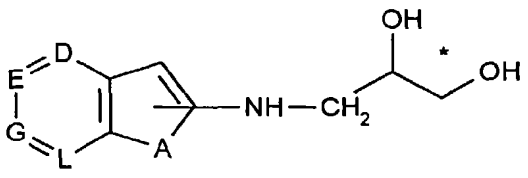


(VI)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

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)



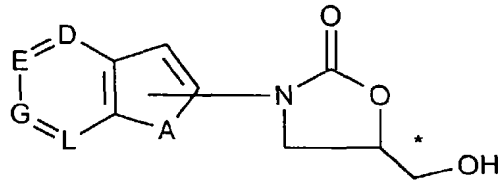
(VII)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert,
oder

[E] zunächst Verbindungen der allgemeinen Formel (Ia)

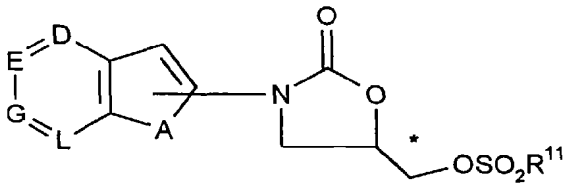


(Ia)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

durch Umsetzung mit (C_1-C_4)-Alkyl- oder Phenylsulfonsäurechloriden, die gegebenenfalls entsprechend substituiert sind, in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)

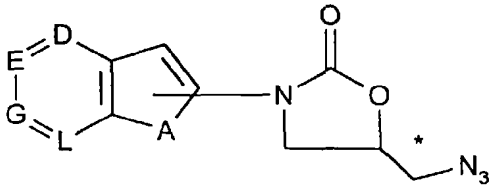


(Ib)

in welcher

A, D, E, G, L und R^{11} die oben angegebene Bedeutung haben,

überführt,
anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (Ic)



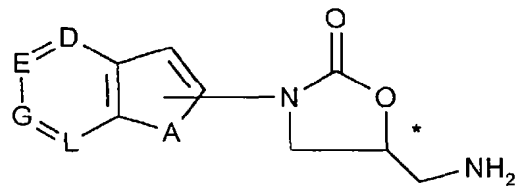
(Ic)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
in einem weiteren Schritt durch Umsetzung mit (C_1-C_4-O)$_3$-P oder PPh_3, vorzugsweise $(CH_3O)_3P$ in inerten Löse-

mitteln und mit Säuren in die Amine der allgemeinen Formel (Id)



(Id)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

überführt,
und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (VIII)

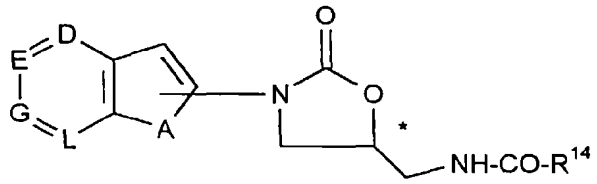
$$R^{20}\text{-}CO\text{-}R^{14} \qquad \text{(VIII)}$$

in welcher

R^{14} die oben angegebene Bedeutung hat
und

R^{20} für Halogen, vorzugsweise für Chlor oder für den Rest $-OCOR^{14}$ steht,

in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



(Ie)

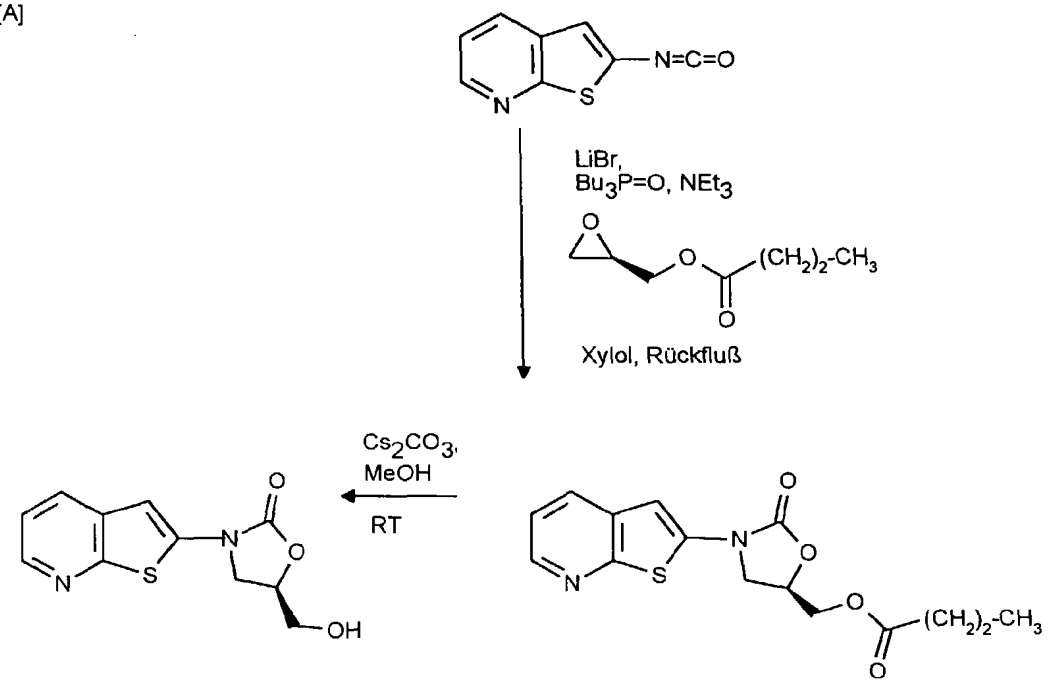
in welcher

A, D, E, G, L und R^{14} die oben angegebene Bedeutung haben,

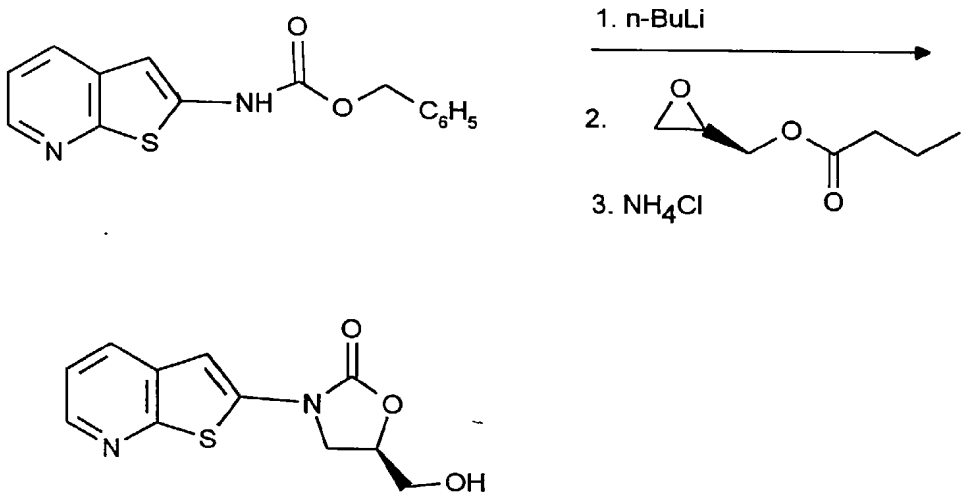
herstellt,
und im Fall $R^1 = NR^{12}\text{-}CS\text{-}R^{14'}$ Verbindungen der allgemeinen Formel (Id) mit Ethyldithiocarboxylaten und Triethylamin und im Fall $R^1 = NR^{12}\text{-}CS\text{-}NR^{18}R^{19}$ mit Thioisocyanaten umsetzt,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
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:

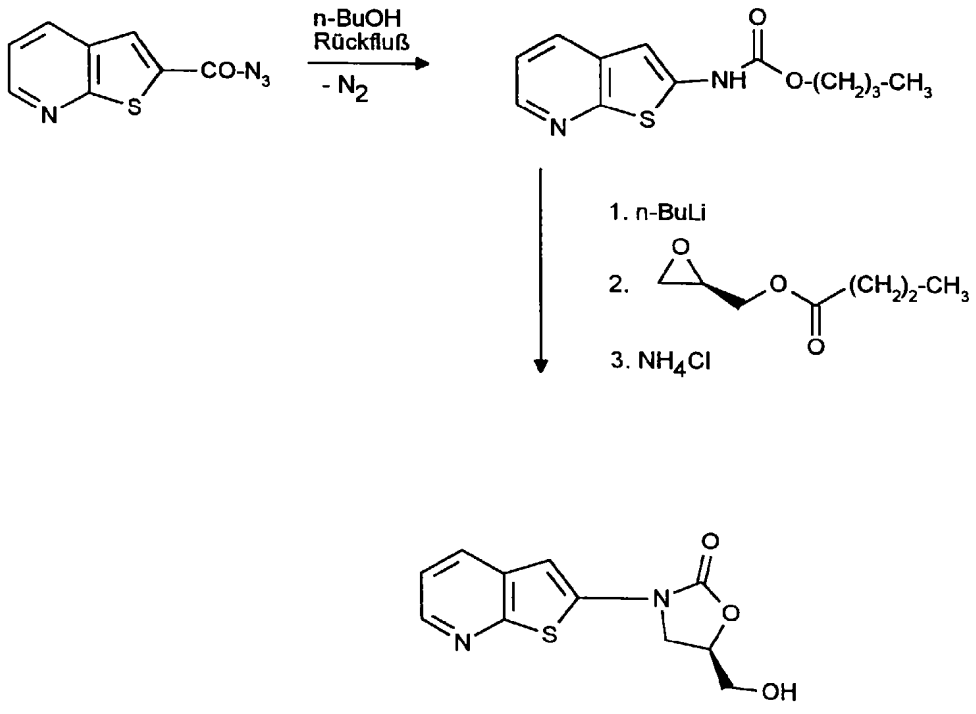
[A]


N=C=O
LiBr,
Bu3P=O, NEt3
(CH2)2-CH3
Xylol, Rückfluß
Cs2CO3,
MeOH
RT
OH

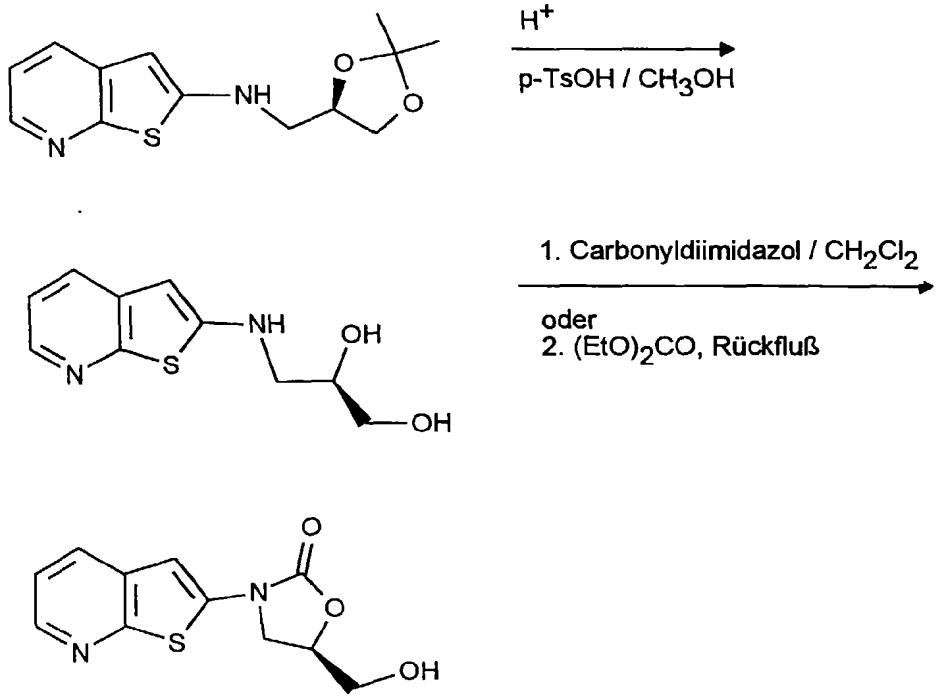
[B]



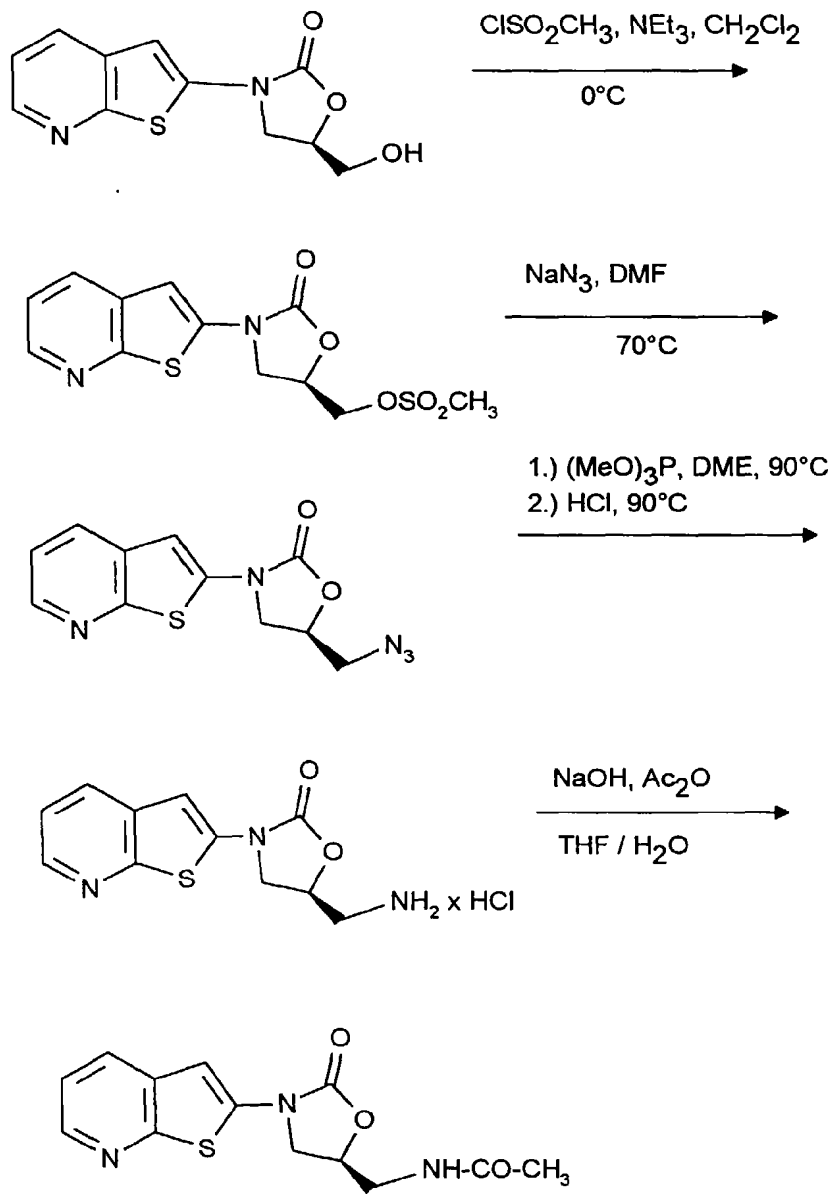
[C]



[D]


H+
p-TsOH / CH3OH
1. Carbonyldiimidazol / CH2Cl2
oder
2. (EtO)2CO, Rückfluß
NH
O
O
N
S
NH
OH
OH
O
N
O
N
S
OH

[E]



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 und 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, und zwar wird vorzugsweise Boc mit Salzsäure in Dioxan, Fmoc mit Piperidin und Z mit HBr/HOAc oder durch Hydrogenolyse abgespalten.

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, Glykoldimethylether, oder Kohlenwasserstoffe wie Benzol, Toluol, Xylol, Hexan, Cyclohexan oder Erdölfraktionen, oder Halogenkohlenwasserstoffe wie Dichlormethan, Trichlormethan, Tetrachlormethan, Dichlorethylen, Trichlorethylen oder Chlorbenzol, oder Essigester, oder Triethylamin, Pyridin, 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 Raumtemperatur 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-Dichlorethylen 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 Propanphosphonsäureanhydrid oder Isobutylchloroformat oder Benzotriazolyloxy-tris-(dimethylamino)phosphoniumhexafluorophosphat oder Phosphorsäurediphenylesteramid 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 Reak-

tanden.

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 Chlorameisensäuretrichlormethylester 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 Formel (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 Formeln (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 minimalen Hemmkonzentrationen (MHK) wurden per Reihenverdünnungsverfahren auf Iso-Sensitest Agar (Oxoid) bestimmt. Für jede Prüfungssubstanz wurde eine Reihe von Agarplatten hergestellt, die abfallende Konzentrationen des Wirkstoffes enthielten. Die Agarplatten wurden mit einem Multipoint-Inokulator (Denley) beimpft. Zum Beimpfen wurden Übernachtkulturen der Erreger verwandt, die zuvor so verdünnt wurden, daß jeder Impfpunkt ca. 10^4 koloniebildende Partikel enthielt. Die beimpften Agarplatten wurden bei 37°C bebrütet, und das Keimwachstum wurde nach ca. 20 Stunden abgelesen. Der MHK-Wert (µg/ml) gibt die niedrigste Wirkstoffkonzentration an, bei der mit bloßem Auge 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**
12	2	2	2	2	>64	>64	>64
13	8	8	8	8	>64	>64	>64
16	4	4	4	4	>64	>64	>64
18	4	4	2	2	>64	>64	>64
19	1	1	1	0,25	>64	>64	>64

Für schnellwachsende Mykobakterien wurde die MHK-Bestimmung in Anlehnung an die von Swenson beschriebene Methode der Bouillon-Mikrodilution durchgeführt [vgl. J.M. Swenson, C. Thornberry, U.A. Silcox, Rapidly growing mycobacteria. Testing of susceptibility to 34 antimicrobial agents by broth microdilution. Antimicrobial Agents and Chemotherapy Vol, 22, 186-192 (1982)]. Abweichend davon war das mit 0,1 Vol.% Tween 80 versetzte Hirn-Herzextrakt Medium.

Die verwendeten Mykobakterienstämme wurden von der DSM (Dt. Sammlung von Mikroorganismen, Braunschweig) bezogen. Sie wurden in einer feuchten Kammer bei 37°C bebrütet.

Die MHK-Werte wurden nach 2-4 Tagen abgelesen, wenn die präparatfreien Kontrollen durch Wachstum trüb waren. Der MHK-Wert definiert sich als die niedrigste Präparatkonzentration, die makroskopisch sichtbares Wachstum völlig inhibiert.

MHK Werte (µg/ml): Mycobacterium smegmatis		
Stamm:	**DSM 43061**	**DSM 43465**
Bsp.-Nr.		
13	16	8
19	32	16
Isoniazid	4	1
Streptomycin	4	4

Die erfindungsgemäßen Verbindungen der allgemeinen Formeln (I), (Ia), (Ib), (Ic), (Id) und (Ie) weisen bei geringer Toxizität ein breites antibakterielles Spektrum, speziell gegen gram-positive Bakterien, Haemophilus influenzae, anaerobe Keime und für schnellwachsende Mykobakterien auf. Diese Eigenschaften ermöglichen ihre Verwendung als chemotherapeutische Wirkstoffe in der Human- und Tiermedizin.

Besonders wirksam sind die erfindungsgemäßen Verbindungen gegen Bakterien und bakterienännliche Mikroorganismen wie Mycoplasmen. 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 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

Abkürzungen:

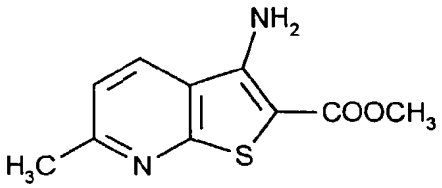
Z	Benzyloxycarbonyl
Boc	tert.Butyloxycarbonyl
DMF	Dimethylformamid

Ph	Phenyl
Me	Methyl
THF	Tetrahydrofuran
CDI	Carbonyldiimidazol
DCE	Dichlorethan

Ausgangsverbindungen

Beispiel I

3-Amino-6-methyl-thieno[2,3-b]pyridin-2-carbonsäuremethylester

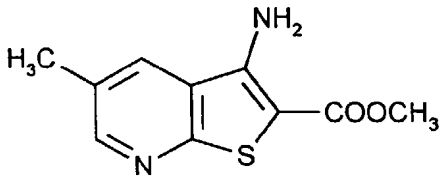


45 g (295 mmol)) 2-Chlor-6-methylpyridin-3-carbonitril werden in 180 ml DMSO gelöst, mit 90 ml (649 mmol) Triethylamin und 28 ml (310 mmol) Mercaptoessigsäuremethylester versetzt und 18 h bei 80°C verrührt. Man läßt auf Raumtemperatur kommen, kippt auf Eiswasser, saugt ab, wäscht den Rückstand mit Petrolether nach und trocknet 5 h im Umlufttrockenofen bei 60°C.

Ausbeute: 63 g (96%)
MS: 222 [M^+, 100%]
^{1}H-NMR (D_6-DMSO, TMS): 8,4 (d, J = 9 Hz, 1H); 7,83 (d, J = 9 Hz, 1H); 7,26 (s, 2H); 3,8 (s, 3H); 2,58 (s, 3H).

Beispiel II

3-Amino-5-methyl-thieno[2,3-b]pyridin-2-carbonsäuremethylester

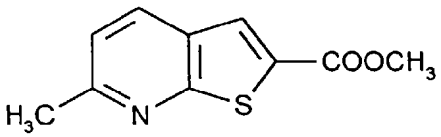


37,5 g (250 mmol) 2-Mercapto-3-cyano-5-methylpyridin werden in 175 ml DMSO gelöst und mit 76 ml (550 mmol) Triethylamin versetzt. Zu der so erhaltenen Lösung tropft man innerhalb von 5 min 22 ml (250 mmol) Chloressigsäuremethylester zu. Man verrührt 5 h bei 80°C, gibt auf Eiswasser, saugt vom ausgefallenen Feststoff ab, wäscht diesen mit Diethylether gut nach und trocknet im Umlufttrockenofen bei 50°C.

Ausbeute: 53,5 g (96%)
MS: 222 [M^+, 100%]
^{1}H-NMR (D_6-DMSO): 8,55 (s, 1H); 8,35 (s, 1H); 7,25 (s, 2H); 3,7 (s, 3H); 2,4 (s, 3H).

Beispiel III

6-Methyl-thieno[2,3-b]pyridin-2-carbonsäuremethylester

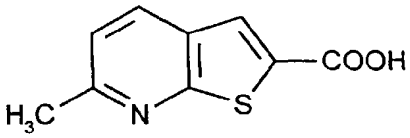


209 ml Wasser werden vorsichtig mit 628 ml H_2SO_4 konz. versetzt, auf 0°C gekühlt und mit 62 g (279 mmol) der Verbindung aus Beispiel I versetzt. Nun wird eine Lösung von 61,5 g (894 mmol) Natriumnitrit in 280 ml Wasser so zugetropft, daß die Innentemperatur der Reaktionslösung +5°C nicht übersteigt. Nach beendeter Zugabe wird 1 h bei 0°C nachgerührt. Die so erhaltene Reaktionslösung wird so in 1,675 l 50%ige Hypophosphorsäure eingetragen, daß die Innentemperatur nicht über +7°C ansteigt. Nach beendeter Zugabe läßt man 30 min bei 0°C nachrühren und hält über Nacht bei +4°C. Nun wird mit festem $NaHCO_3$ neutral gestellt (schäumt heftig) und vom ausgefallenen Feststoff abgesaugt. Der Rückstand wird in 2 l Aceton 10 min verrührt, abgesaugt und im Umlufttrockenofen bei 50°C getrocknet.

Ausbeute: 24,3 g (42%)
MS: 207 [M^+, 90%]
^{1}H-NMR (D_6-DMSO, TMS): 8,3 (d, J = 9 Hz, 1H); 8,15 (s, 1H); 7,4 (d, J = 9 Hz, 1H); 3,9 (d, 3H); 2,63 (s, 3H).

Beispiel IV

6-Methyl-thieno[2,3-b]pyridin-2-carbonsäure

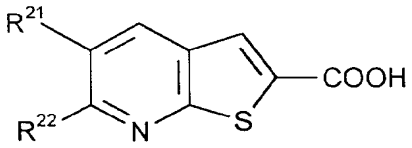


23 g (111 mmol) der Verbindung aus Beispiel III werden in 660 ml Ethanol gelöst, mit 93,5 g (1,66 mol) Kaliumhydroxid versetzt und 30 min am Rückfluß gekocht. Nach Abkühlen auf Raumtemperatur wird vom Niederschlag abgesaugt und dieser gut mit Ethanol nachgewaschen. Der Niederschlag wird in Wasser gelöst und mit Essigsäure auf pH 4 angesäuert. Von der ausgefallenen Säure wird abgesaugt, mit 2 l Petrolether nachgewaschen und im Umlufttrockenschrank bei 50°C getrocknet.

Ausbeute: 18,6 g (87%)
^{1}H-NMR (D_6-DMSO, TMS): 12,1 (s, 1H); 8,28 (d, J = 9 Hz, 1H); 8,05 (s, 1H); 7,39 (d, J = 9 Hz, 1H); 2,62 (s, 3H).

Analog den Vorschriften der Verbindungen I - IV werden die in der Tabelle I aufgeführten Verbindungen dargestellt:

Tabelle I

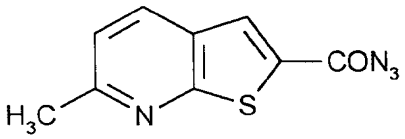


Bsp.-Nr.	R^{21}	R^{22}	Ausbeute (%d.Th.)	MS	Smp. (°C)
V	CH_3	H	91	-	263 u.Z.
VI *	H	H	86	180 $[M+H]^+$	312 u.Z.

* S.W. Schneller, F.W. Clough, I.E. Hardee, J. Heterocycl. Chem. (1976) 273-5

Beispiel VII

6-Methyl-thieno[2,3-b]pyridin-2-carbonsäureazid

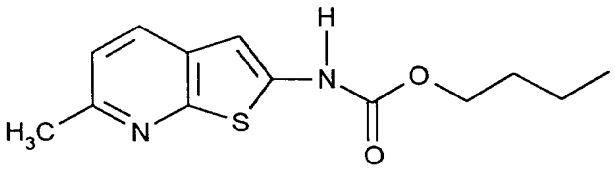


18 g (93,2 mmol) der Verbindung aus Beispiel IV werden in 180 ml Aceton gelöst und mit 15,4 ml (110 mmol) Triethylamin versetzt. Diese Reaktionsmischung wird auf -15°C gekühlt und langsam mit einer Lösung von 15,4 ml (121 mmol) Chlorameisensäureisobutylester in 77 ml Aceton versetzt, so daß die Innentemperatur -5°C nicht übersteigt. Man rührt 2 h bei -10°C nach und tropft eine Lösung von 9 g (140 mmol) Natriumazid in Wasser zu, rührt 2 h bei 0°C nach, kippt auf 2,5 l Eiswasser, saugt vom ausgefallenen Niederschlag ab, wäscht diesen mit Wasser gut nach und trocknet an der Luft.

Ausbeute: 18 g (89% d.Th.)

Beispiel VIII

2-Butyloxycarbonylamino-6-methyl-thieno[2,3-b]pyridin

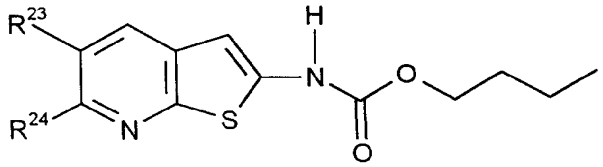


18 g (82 mmol) der Verbindung aus Beispiel VII werden portionsweise in 390 ml siedendes Butanol eingetragen. Nach beendeter Zugabe wird 10 min unter Rückfluß nachgerührt, auf Raumtemperatur abgekühlt, eingeengt, in Diethylether verrührt, abgesaugt und im Umlufttrockenofen bei 50°C getrocknet.

Ausbeute: 20,3 g (93%)
Smp.: 162°C
^{1}H-NMR (D_6-DMSO, TMS): 7,88 (d, J = 9 Hz, 1H); 7,24 (d, J = 9 Hz, 1H); 6,75 (s, 1H); 4,18 (t, J = 7 Hz, 2H); 2,53 (s, 3H); 1,65 (q, J = 7 Hz, 2H); 1,39 (h, J = 7 Hz, 2H); 0,93 (t, J = 7 Hz, 3H).

Analog den Vorschriften der Verbindungen VII und VIII werden die in der Tabelle II aufgeführten Verbindungen dargestellt:

Tabelle II

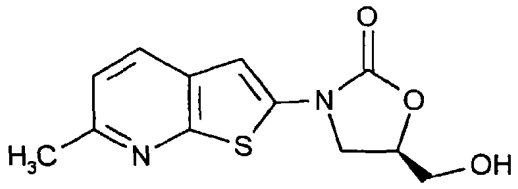


Bsp.-Nr.	R^{23}	R^{24}	Ausbeute (% d.Th.)	Smp. (°C)
IX	CH_3	H	84	180
X	H	H	68	204

Herstellungsbeispiele

Beispiel 1

(5R)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-hydroxymethyl-oxazolidin-2-on

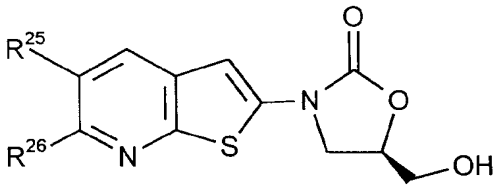


20,3 g (76,8 mmol) der Verbindung aus Beispiel VIII werden in 150 ml THF gelöst, mit 10 mg Benzylidenbenzylimin versetzt und auf -70°C gekühlt. Nun werden langsam ca. 31 ml 2,5 n-Butyllithium.-Lösung in Hexan bis zum Farbumschlag nach rot zugetropft. Anschließend werden 10,9 ml (76,8 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf Raumtemperatur kommen, versetzt mit gesättigter Ammoniumchlorid-Lösung, rührt 30 min bei Raumtemperatur nach und saugt vom ausgefallenen Niederschlag ab. Der Rückstand wird mit wenig Wasser und mit viel Diethylether gewaschen und im Umluftttrockenofen bei 50°C getrocknet.

Ausbeute: 19,7 g (97% d.Th.)
Smp.: 245°C u.Z.
R_f: 0,24 (I, 100:5)
MS: 265 [$(M+H)^+$, 100%]
^{1}H-NMR (D_6-DMSO, TMS): 7,95 (d, J = 9 Hz, 1H); 7,25 (d, J= 9 Hz, 1H); 6,69 (s, 1H); 5,3 (s, 1H); 4,8 - 4,96 (m, 1H); 4,18 (t, J = 9,5 Hz, 1H); 3,93 (dd, J = 9,5 Hz, 6,5 Hz, 1H); 3,55 - 3,8 (m, 2H); 2,55 (s, 3H).

Analog Verbindung 1 wurden die in der Tabelle 1 aufgeführten Verbindungen dargestellt:

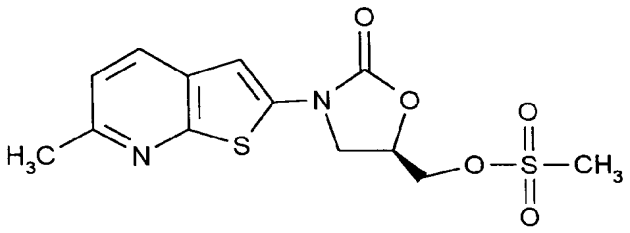
Tabelle 1



Bsp.-Nr.	R^{25}	R^{26}	Ausbeute (% d.Th.)	MS	Smp. (°C)
2	CH_3	H	88	-	245 u.Z.
3	H	H	98	251 $[M+H]^+$; 100%	235 u.Z.

Beispiel 4

(5R)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-methansulfonyloxymethyl-oxazolidin-2-on

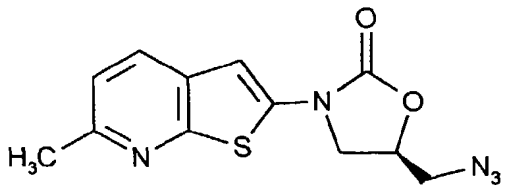


Eine Lösung von 18,8 g (71 mmol) der Verbindung aus Beispiel 1 in 290 ml Pyridin wird auf 0°C gekühlt und langsam mit 11 ml (142 mmol) Methansulfonsäurechlorid versetzt. Es wird 16 h bei 4°C gehalten und eingeengt. Der Rückstand wird in 5%iger Natriumhydrogencarbonatlösung verrührt, abgesaugt und mit Wasser und Diethylether nachgewaschen und im Umlufttrockenofen bei 50°C getrocknet.

Ausbeute: 23 g (95% d.Th.)
R_f = 0,47 (I, 100:5)

Beispiel 5

(5R)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-azido-methyl-oxazolidin-2-on

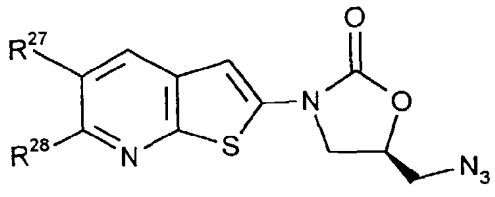


23 g (67,1 mmol) der Verbindung aus Beispiel 4 werden in 160 ml DMF gelöst und mit 4,8 g (74 mmol) Natriumazid versetzt. Die so erhaltene Reaktionsmischung wird 16 h bei 70°C verrührt. Man läßt auf Raumtemperatur abkühlen und kippt auf 2 l Eiswasser. Man saugt vom ausgefallenen Feststoff ab, wäscht mit Wasser und Petrolether nach und trocknet an der Luft.

Ausbeute: 17,9 g (92% d.Th.)
R_f: 0,31 (I, 100:2)
Smp.: 181°C u.Z.
MS: 290 [$(M+H)^+$; 100%]
^{1}H-NMR (D_6-DMSO, TMS): 7,96 (d, J) 9 Hz, 1H); 7,75 (d, J = 9 Hz, 1H); 6,72 (s, 1H); 4,98 - 5,12 (m, 1H); 4,24 (t, J = 9,5 Hz, 1H); 3,78 - 3,9 (m, 3H); 2,55 (s, 3H).

Analog den Vorschriften der Beispiele 4 und 5 werden die in der Tabelle 2 aufgeführten Verbindungen dargestellt:

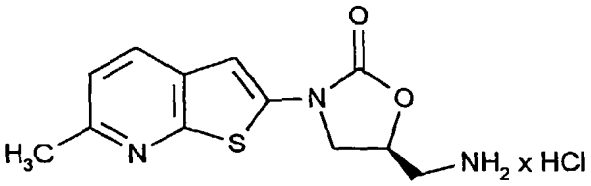
Tabelle 2



Bsp.-Nr.	R^{27}	R^{28}	Ausbeute (% d.Th.)	MS	Smp. (°C)
6	CH_3	H	95	289 [M^+]	204 u.Z.
7	H	H	54	-	197 u.Z.

Beispiel 8

(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-aminomethyl-oxazolidin-2-on Hydrochlorid

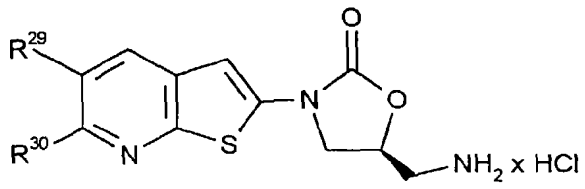


5 g (17,3 mmol) der Verbindung aus Beispiel 5 werden in 400 ml Ethanol gelöst, mit 500 mg 5%igem Palladium auf Aktivkohle versetzt und 16 h unter 3 bar Wasserstoffdruck hydriert. Man filtriert vom Katalysator ab, engt ein, nimmt in Methylenchlorid auf und versetzt langsam mit 5 ml 4,5 N HCl in Ether. Man rührt 1 h bei Raumtemperatur nach, saugt ab und wäscht mit Ether nach. Der Rückstand wird bei 40°C im Umlufttrockenofen getrocknet.

Ausbeute: 5,74 g (98% d.Th.)
^{1}H-NMR (D_2O): 8,3 (d, J = 9 Hz, 1H); 7,5 (d, J = 9 Hz, 1H); 6,78 (s, 1H); 5,11 - 5,27 (m, 1H); 4,37 (t, J = 9,5 Hz, 1H); 3,95 (dd, J = 9,5 Hz, J = 6,5 Hz, 1H); 3,30 - 3,5 (m, 2H); 2,65 (s, 3H).

Analog der Verbindung 8 werden die in der Tabelle 3 aufgeführten Verbindungen dargestellt:

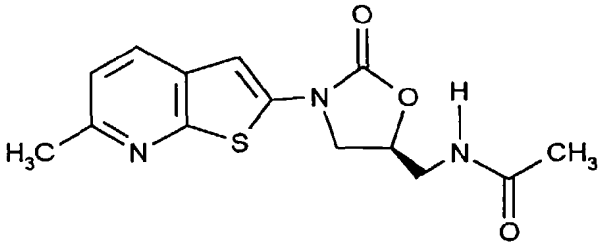
Tabelle 3



Bsp.-Nr.	R^{29}	R^{30}	Ausbeute (% d.Th.)	MS	Smp. (°C)
9	CH_3	H	68	363 ($[M+H]^+$; 40%)	-
10	H	H	81	249 ($[M^+]$; 60%)	257 u.Z.

Beispiel 11

(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-acetylaminomethyl-oxazolidin-2-on

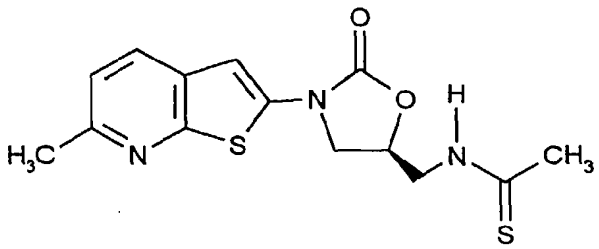


1,5 g (4,1 mmol) der Verbindung aus Beispiel 8 werden mit 1,14 ml (8,2 mmol) Triethylamin versetzt und in 8 ml Pyridin gelöst. Man kühlt die Reaktionslösung auf 0°C ab und tropft 0,73 ml (10,2 mmol) Acetylchlorid zu. Nach 4 Stunden bei 0°C wird mit 1 ml Methanol versetzt, eingeengt und an Kieselgel (Methlyenchlorid : Methanol = 100:3) chromatographiert.

Ausbeute: 0,84 g (67%)
Smp.: 215°C u.Z.
R_f: 0,44 (I; 10:1)
MS: 306 $[(M+H)^+$; 100%]
^{1}H-NMR (D_6-DMSO, TMS) 8,3 (t, J = 6,5 Hz, 1H); 7,95 (d, J= 9 H, 1H); 7,25 (d, J = 9 Hz, 1H); 6,68 (s, 1H); 4,83 - 4,98 (m, 1H); 4,2 (t, J = 9,5 Hz, 1H); 3,83 (dd, J = 9,5 Hz, J = 6,5 Hz, 1H); 3,47 (t, J = 6 Hz, 2H); 2,55 (s, 3H); 1,85 (s, 3H).

Beispiel 12

(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-thioacetylaminomethyl-oxazolidin-2-on

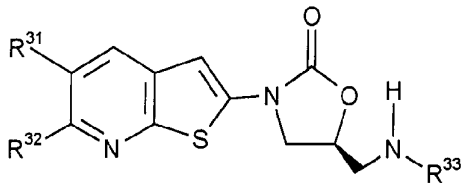


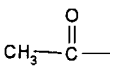
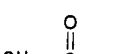
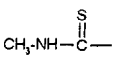
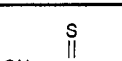
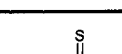
673 mg (2 mmol) der Verbindung aus Beispiel 8 werden in 4 ml THF gelöst, mit 0,61 ml (4,4 mmol) Triethylamin und 0,26 ml (2,2 mmol) Ethyldithioacetat versetzt und 18 h bei Raumtemperatur gerührt. Man engt ein und chromatographiert an Kieselgel (Methylenchlorid : Methanol = 100:1).

Ausbeute: 475 mg (74%)
Smp.: 202 u.Z.
R_f: 0,3 (I; 100:5)
MS: 321 (M^+, 20%)
^{1}H-NMR (D_6-DMSO, TMS): 10,45 (s, 1H); 7,95 (d, J = 9 Hz, 1H); 7,25 (d, J = 9 Hz, 1H); 6,68 (s, 1H); 5,05 - 5,2 (m, 1H); 4,25 (t, J = 9,5 Hz, 1H); 3,98 (t, J = 6,5 Hz, 2H); 3,9 (dd, J = 9,5 Hz, J = 6,5 Hz, 1H); 2,55 (s 3H); 2,43 (s, 3H).

Analog den Vorschriften der Beispiele 11 und 12 wurden die in Tabelle 4 aufgeführten Verbindungen dargestellt:

Tabelle 4

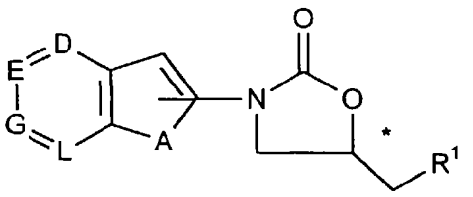


Bsp.-Nr.	R^{31}	R^{32}	Acetylierungsmittel	R^{33}	Equivalente Et_3N	Ausbeute (% d.Th.)	MS	Smp. (°C)	R_f (Laufmittelgemisch; Verhältnis)
13	CH_3	H	CH_3COCl		2,3	46	306 $[M+H]^+$; 100%	221 u.Z.	0,23 [I; 100:5]
14	H	H	CH_3COCl		2,3	45	291 $[M]^+$; 100%	220 u.Z.	0,25 [I; 100:5]
15	H	H	CH_3NCS		3	54	323 $[M+H]^+$; 10%	148 u.Z.	0,25 [I; 100:5]
16	H	H	$CH_3CSSCH_2CH_3$		2	66	308 $M+H]^+$; 50%	190 u.Z.	0,30 [I; 100:5]
17	H	CH_3	CH_3NCS		3	70	337 $[M+H]^+$; 10%	178 u.Z.	0,14 [I: 100:5]

Bsp.-Nr.	R^{31}	R^{32}	Acetylierungsmittel	R^{33}	Equivalente Et_3N	Ausbeute (% d.Th.)	MS	Smp. (°C)	R_f (Laufmittelgemisch; Verhältnis)
18	CH_3	H	CH_3NCS		3	40	337 $[M+H]^+$; 30%	167 u.Z.	0,27 [I; 100:5]
19	CH_3	H	$CH_3CSSCH_2CH_3$		2	39	321 $[M]^+$, 10%	186 u.Z.	0,37 [I; 100:5]
20	H	CH_3	CH_2CH_2COCl		3	25	320 $[M+H]^+$ 100%	222 u.Z.	0,26 (I; 100:5)
21	H	CH_3			3	46	322 $[M+H]^+$ 100%	228 u.Z.	0,26 (I; 100:5)
22	H	CH_3			3	47	322 $[M+H]^+$ 100%	227 u.Z.	0,34 (I; 100:5)

Patentansprüche

1. Verbindungen der allgemeinen Formel (I)



(I)

in welcher

A	für ein Sauerstoff- oder Schwefelatom oder für die SO_2-Gruppe steht, und
D, E, G und L	gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin
R^2	Wasserstoff, Cyano, Nitro, Carboxyl, geradkettiges oder verzweigtes Alkyl, Acyl oder Alkoxy mit jeweils bis zu 7 Kohlenstoffatomen, Halogen oder eine Gruppe der Formel $-NR^3R^4$, $-CO-NR^5R^6$, $-NR^7-CO-R^8$ oder $-S(O)_aR^9$ bedeutet, worin
R^3, R^4, R^5, R^6, R^7 und R^8	gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
a	eine Zahl 0, 1 oder 2 bedeutet,
R^9	Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet,
R^1	für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin
R^{10}	geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet,
R^{11}	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^{12} und R^{13}	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^{12} oder R^{13}	eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet, worin
R^{14} und $R^{14'}$	gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl,

Benzyloxy oder Wasserstoff bedeuten, oder

R^{14} und $R^{14'}$	geradkettiges oder verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert ist, oder geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeuten, oder eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten, worin
R^{18} und R^{19}	gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder einen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeuten,
R^{15} und R^{16}	gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,
R^{17}	geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet

als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

2. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher

A	für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2$-Gruppe steht, und
D, E, G und L	gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin
R^2	Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen, Fluor, Chlor oder Brom bedeutet,
R^1	für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin
R^{10}	geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,
R^{11}	geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Phenyl oder Tolyl bedeutet,
R^{12} und R^{13}	gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten, oder
R^{12} oder R^{13}	eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet, worin
R^{14} und $R^{14'}$	gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten, oder
R^{14} und $R^{14'}$	geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder

geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeuten, oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

R^{18} und R^{19} gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, oder
oder
Isoxazolyl, Furyl, Thienyl, Pyrryl, Oxazolyl oder Imidazolyl bedeuten,

R^{15} und R^{16} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

R^{17} geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet

als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

3. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher

A für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2-$Gruppe steht,
und

D, E, G und L gleich oder verschieden sind und für mindestens ein Stickstoffatom oder für den Rest der Formel $-CR^2$ stehen,
worin

R^2 Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Fluor bedeutet,

R^1 für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht,
worin

R^{10} geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet,

R^{11} Methyl, Ethyl, Phenyl oder Tolyl bedeutet,

R^{12} und R^{13} gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 5 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten,
oder

R^{12} oder R^{13} eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2R^{17}$ bedeutet,
worin

R^{14} und $R^{14'}$ gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluorethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten,
oder

R^{14} und $R^{14'}$ geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 4 Kohlenstoffatomen bedeuten, oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

R^{18} und R^{19} gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten, oder Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeu-

ten,

R^{15} und R^{16} gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

R^{17} Methyl oder Phenyl bedeutet

als reine Stereoisomeren oder als Stereoisomerengemisch,
und deren Salze.

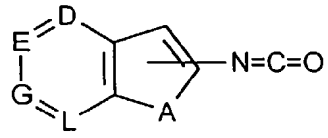
4. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher der Oxazolidinonrest in der Position 2 am 5-Ring-Heterocyclus angebunden ist, als reine Stereoisomere oder als Stereoisomerengemisch, und deren Salze.

5. Verbindungen gemäß Anspruch 1, ausgewählt aus der Gruppe

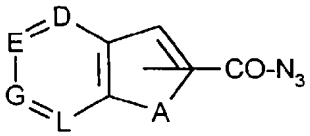
(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-thioacetylaminomethyl-oxazolidin-2-on,
(5S)-3-[5-Methyl-pyrido[2,3-b]thienyl]-5-acetylaminomethyl-oxazolidin-2-on,
(5S)-3-[Pyrido[2,3-b]thien-2-yl]-5-thioacetyl-aminomethyl-oxazolidin-2-on, 1-Methyl-3-(2-oxo-3-[5-(5S)-methyl-thieno-[2,3-b]pyridin-2-yl]-oxazolidin-5-ylmethyl)-thioharnstoff und
(5S)-3-[5-Methyl-pyrido[2,3-b]-thienyl]-5-thioacetylaminomethyl-oxazolidin-2-on.

6. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, dadurch gekennzeichnet, daß man

[A] Verbindungen der allgemeinen Formel (II) oder (III)



(II) oder

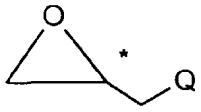


(III)

in welchen

A, D, E, G und L die in Anspruch 1 angegebenen Bedeutungen haben,

mit Lithiumbromid/$(C_4H_9)_3$ P(O) und Epoxiden der allgemeinen Formel (IV)



(IV)

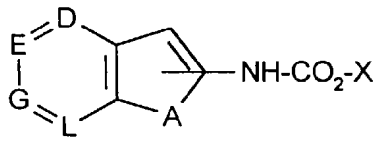
in welcher

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)



(V)

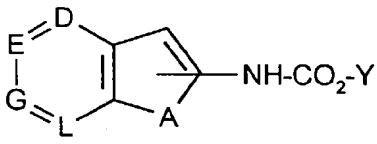
in welcher

A, D, E, G und L die oben angegebene Bedeutung haben
und

X für eine typische Schutzgruppe steht,

in inerten Lösemitteln und in Anwesenheit einer Base 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)



(Va)

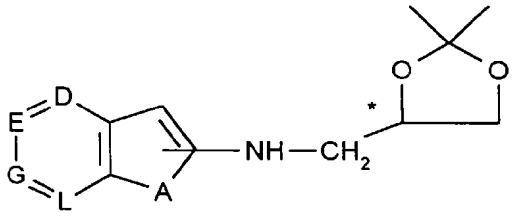
in welcher

A, D, E, G und L die oben angegebene Bedeutung haben
und

Y für geradkettiges oder verzweigtes C_2-C_6-Alkyl steht,

überführt,
und in einem zweiten Schritt wie unter [A] beschrieben in inerten Lösemitteln und in Anwesenheit einer Base mit Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

[D] Verbindungen der allgemeinen Formel (VI)

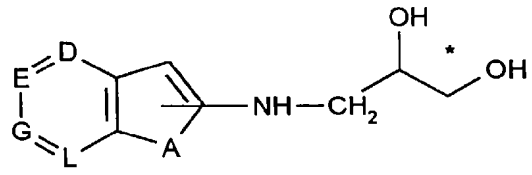


(VI)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

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)



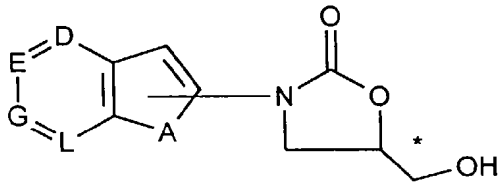
(VII)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert,
oder

[E] zunächst Verbindungen der allgemeinen Formel (Ia)

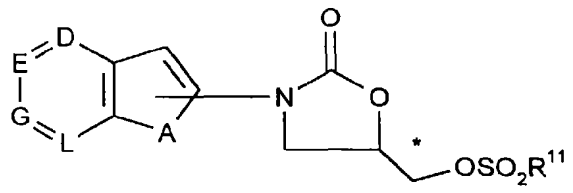


(Ia)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

durch Umsetzung mit (C_1-C_4)-Alkyl- oder Phenylsulfonsäurechloriden, die gegebenenfalls entsprechend substituiert sind, in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)



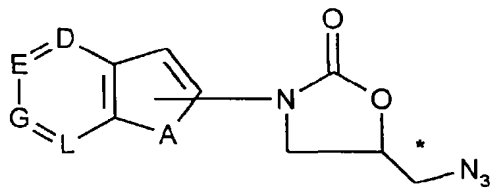
(Ib)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben und

R^{11} die in Anspruch 1 angegebene Bedeutung hat,

überführt,
anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (Ic)

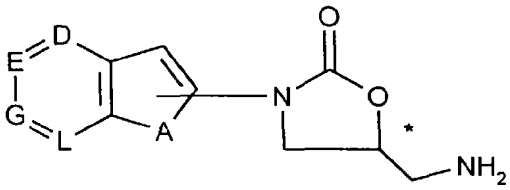


(Ic)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
in einem weiteren Schritt durch Umsetzung mit $(C_1\text{-}C_4\text{-}O)_3\text{-}P$ oder PPh_3 in inerten Lösemitteln und mit Säuren in die Amine der allgemeinen Formel (Id)



(Id)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

überführt,
und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (VIII)

$$R^{20}\text{-}CO\text{-}R^{14} \qquad \text{(VIII)}$$

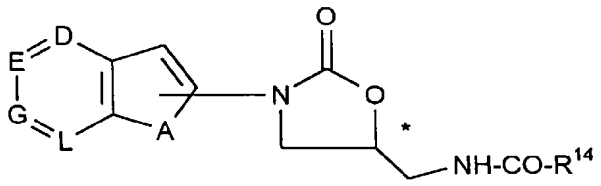
in welcher

R^{14} die in Anspruch 1 angegebene Bedeutung hat

und

R^{20} für Halogen oder für den Rest -$OCOR^{14}$ steht,

in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



(Ie)

in welcher

A, D, E, G, L und R^{14} die oben angegebene Bedeutung haben,

herstellt,
und im Fall R^1 = NR^{12}-CS-$R^{14'}$ Verbindungen der allgemeinen Formel (Id) mit Ethyldithiocarboxylaten und Triethylamin und im Fall R^1 = NR^{12}-CS-$NR^{18}R^{19}$ mit Thioisocyanaten umsetzt,
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,
und gegebenenfalls nach üblichen Methoden die Stereoisomeren trennt.

7. Verbindungen nach einem der Ansprüche 1 bis 5 zur Verwendung bei der Bekämpfung von Krankheiten.

8. Verwendung von Verbindungen nach einem der Ansprüche 1 bis 5 zur Herstellung von Arzneimitteln.

9. Arzneimittel enthaltend Verbindungen nach einem der Ansprüche 1 bis 5.

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

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A 61 K 31/425
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A 61 K 31/50

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// C07M 9:00 (C07D 413/14,263:20,213:24,333:36) (C07D 417/04,263:20,277:74)C07D 215/12,237/08,261/08,231/12, 235/24,307/79,521/00,471/04 (A61K 31/42,31:425,31:44,31:50)

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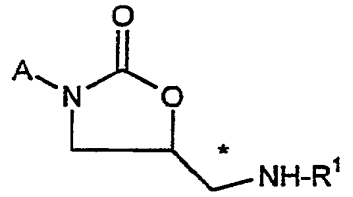
(54) Neue substituierte Oxazolidinone

(57) Die vorliegende Erfindung betrifft neue substituierte Oxazolidinone der allgemeinen Formel (I)



(I)

in welcher die Substituenten die in der Beschreibung angegebene Bedeutung haben, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

DE 196 04 223 A 1

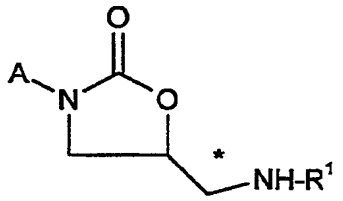
Beschreibung

Die vorliegende Erfindung betrifft neue substituierte Oxazolidinone, 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, 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 sind in der EP 609 491 und EP 657 440 Oxazolidinonderivate mit einer Monoaminoxidase inhibitorischen Wirkung und in der EP 645 376 mit Wirkung als Adhäsionsrezeptor-Antagonisten publiziert.

Die vorliegende Erfindung betrifft neue substituierte Oxazolidinone der allgemeinen Formel (I)



(I)

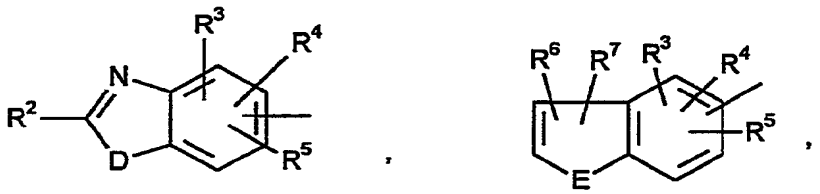
in welcher

A für einen über ein Kohlenstoffatom direkt gebundenen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der zusätzlich einen annellierten Benzol- oder Naphthylring besitzen kann, oder

für einen über ein Kohlenstoffatom direkt gebundenen 6-gliedrigen, aromatischen Heterocyclus mit mindestens einem Stickstoffatom steht, oder für einen über ein Kohlenstoffatom direkt gebundenen, jeweils 6-gliedrigen, bi- oder tricyclischen aromatischen Rest mit mindestens einem stickstoffhaltigen Ring steht, oder

für β-Carbolin-3-yl oder für über den 6-Ring direkt gebundenes Indolizinyl steht, wobei die Cyclen gegebenenfalls jeweils bis zu 3-fach gleich oder verschieden durch Carboxy, Halogen, Cyano, Mercapto, Formyl, Pyridyl, Phenyl, Trifluormethyl, Nitro, geradkettiges oder verzweigtes Alkoxy, Alkoxycarbonyl, Alkylthio oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen substituiert sind, die ihrerseits durch Phenyl substituiert sein können, oder

für einen Rest der Formel



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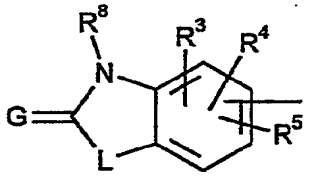

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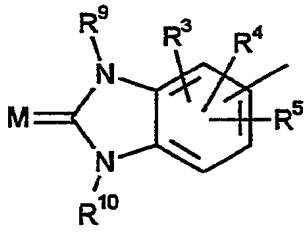

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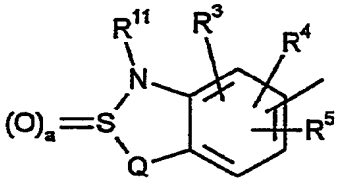
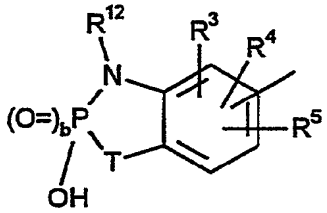


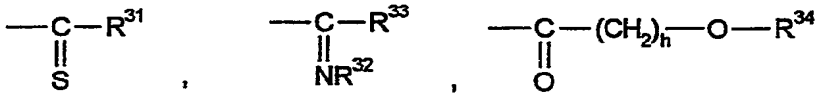
oder



steht, worin

R^3, R^4, R^5, R^6 und R^7 gleich oder verschieden sind und Wasserstoff oder Carboxy, Halogen, Cyano, Formyl, Trifluormethyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder für eine Gruppe der Formel $-CO-NR^{13}R^{14}$ stehen,

worin
R^{13} und R^{14} gleich oder verschieden sind und Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeuten,
R^2, R^8, R^9, R^{10}, R^{11} und R^{12} gleich oder verschieden sind und Wasserstoff, Cycloalkylcarbonyl oder Cycloalkyl mit jeweils 3 bis 6 Kohlenstoffatomen, oder geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder geradkettiges oder verzweigtes Alkyl mit bis zu 10 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Trifluormethyl, Halogen, Phenyl, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen, Aryl mit 6 bis 10 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen und/oder durch eine Gruppe der Formel $-(CO)_c-NR^{15}R^{16}$, $R^{17}-N-SO_2-R^{18}$, $R^{19}R^{20}-N-SO_2-$ oder $R^{21}-S(O)_d$ substituiert ist,
worin
c eine Zahl 0 oder 1 bedeutet,
R^{15}, R^{16} und R^{17} die oben angegebene Bedeutung von R^{13} und R^{14} 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^{19} und R^{20} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
d eine Zahl 0, 1 oder 2 bedeutet,
R^1 und R^{21} gleich oder verschieden sind und geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder
geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls Trifluormethyl, Trichlormethyl oder durch eine Gruppe der Formel $-OR^{22}$ substituiert ist,
worin
R^{22} Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Aryl mit bis zu 10 Kohlenstoffatomen substituiert ist,
oder
eine Gruppe der Formel $(CO)_e-NR^{23}R^{24}$, $-NR^{25}-SO_2R^{26}$, $R^{27}R^{28}-NSO_2-$ oder $R^{29}-S(O)_f$ bedeuten,
worin
e die oben angegebene Bedeutung von c hat und mit dieser gleich oder verschieden ist,
R^{23} und R^{24} und R^{25} jeweils die oben angegebene Bedeutung von R^{15}, R^{16} und R^{17} haben und mit dieser gleich oder verschieden sind,
R^{27} und R^{28} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
f die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist,
R^{26} und R^{29} die jeweils oben angegebene Bedeutungen von R^{18} und R^{21} haben und mit dieser gleich oder verschieden sind,
D ein Sauerstoffatom oder einen Rest der Formel $-S(O)_g$ bedeutet,
worin
g eine Zahl 0, 1 oder 2 bedeutet,
E und L gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom bedeuten,
G, M, T und Q gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom, oder eine Gruppe der Formel $-NR^{30}$ bedeuten,
worin
R^{30} Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
a und b gleich oder verschieden sind und eine Zahl 1 oder 2 bedeuten,
R^1 für einen Rest der Formel



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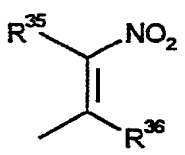


steht, worin
R^{31} geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
R^{38} und R^{39} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
R^{32} Wasserstoff, Cyano, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder geradkettiges oder verzweigtes

Alkyl mit bis zu 7 Kohlenstoffatomen bedeutet,
R^{33} Wasserstoff geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Phenyl, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
R^{40} und R^{41} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
R^{34} geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,
R^{35} und R^{36} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
oder
R^1 für Cyano oder für einen 5- bis 7-gliedrigen, gesättigten, partiell ungesättigten oder ungesättigten Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der gegebenenfalls auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Halogen oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen substituiert ist,
und deren Salze.

Physiologisch unbedenkliche Salze der substituierten Oxazolidinone 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-Alkylhalogeniden, insbesondere mit 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.

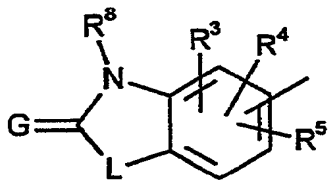
Hydroxyschutzgruppe im Rahmen der oben angegebenen Definition steht im allgemeinen für eine Schutzgruppe aus der Reihe: Trimethylsilyl, Triisopropylsilyl, tert.Butyl-dimethylsilyl, Benzyl, Benzyloxycarbonyl, 2-Nitrobenzyl, 4-Nitrobenzyl, tert. Butyloxycarbonyl, Allyloxycarbonyl, 4-Methoxybenzyl, 4-Methoxybenzyloxycarbonyl, 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.

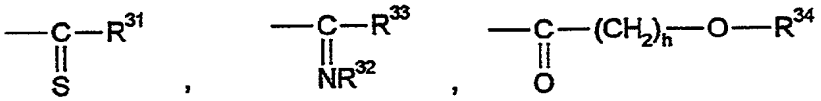
Hierzu gehören bevorzugt: Benzyloxycarbonyl, 2,4-Dimethoxybenzyloxycarbonyl, 4-Methoxybenzyloxycarbonyl, Methoxycarbonyl, Ethoxycarbonyl, tert.Butoxycarbonyl, Allyloxycarbonyl, Phthaloyl, 2,2,2-Trichlorethoxycarbonyl, Fluorenyl-9-methoxycarbonyl, Formyl, Acetyl, 2-Chloracetyl, 2,2,2-Trifluoracetyl, 2,2,2-Trichloracetyl, 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
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 3-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 4 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 4 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder
für einen Rest der Formel



steht, worin
G ein Sauerstoff- oder Schwefelatom bedeutet,
L ein Sauerstoff- oder Schwefelatom bedeutet,
R^8 geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet,
R^3, R^4 und R^5 gleich oder verschieden sind und Wasserstoff, Fluor, Chlor oder Brom bedeuten,
R^1 für einen Rest der Formel



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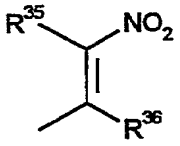
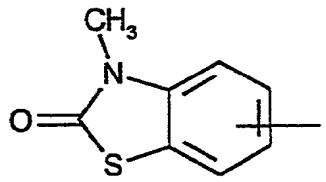
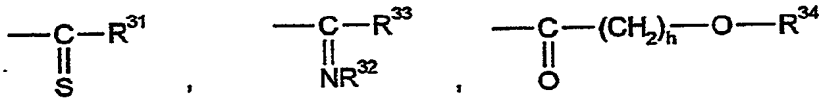


steht, worin
R^{31} geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{35}R^{39}$ bedeutet,
worin
R^{38} und R^{39} gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,
R^{32} Wasserstoff Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
R^{33} Wasserstoff geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
R^{40} und R^{41} die oben angegebene Bedeutung von R^{38} und R^{39} haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
R^{34} geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Benzyl bedeutet,
R^{35} und R^{36} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,
oder
R^1 für Cyano oder für Thienyl, Oxazolyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls, auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sind,
und deren Salze.

Besonders bevorzugt sind erfindungsgemäße Verbindungen der allgemeinen Formel (I),
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 2-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 3 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 3 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder
für einen Rest der Formel



steht,
R^1 für einen Rest der Formel



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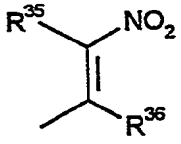
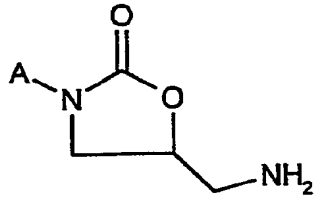


steht, worin
R^{31} geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
R^{38} und R^{39} gleich oder verschieden sind und Wasserstoff oder Methyl bedeuten,
R^{32} Wasserstoff, Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet,
R^{33} Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
R^{40} und R^{41} die oben angegebene Bedeutung von R^{38} und R^{39} haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
R^{34} geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Benzyl bedeutet,
R^{35} und R^{36} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,
oder
R^1 für Cyano oder für Thienyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls auch über eine N-Funktion bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,
und deren Salze.

Außerdem wurde ein Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) gefunden, dadurch gekennzeichnet, daß man
[A] Verbindungen der allgemeinen Formel (II)

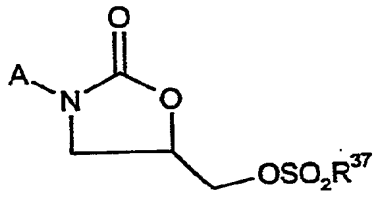


(II)

in welcher
A die oben angegebene Bedeutung hat,
mit Verbindungen der allgemeinen Formel (III)

R^1-Y (III)

in welcher
R^1 die oben angegebene Bedeutung hat, und
Y in Abhängigkeit von R^1 für Wasserstoff, Halogen oder für C_1-C_4 geradkettiges oder verzweigtes Alkoxy oder Oxyalkoxycarbonyl steht, oder
[B] Verbindungen der allgemeinen Formel (IV)



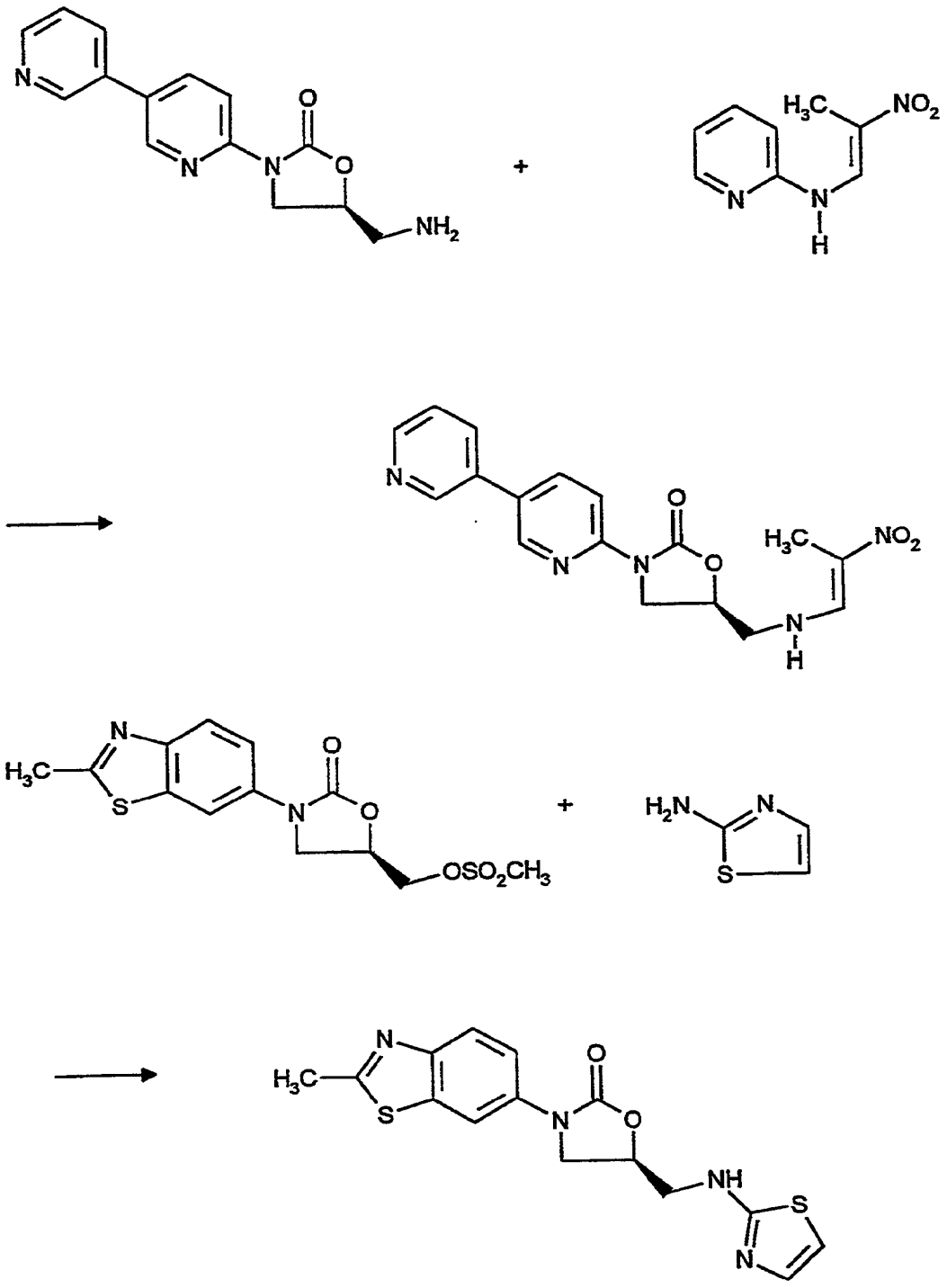
(IV)

in welcher
A die oben angegebene Bedeutung hat,
R^{37} für C_1-C_4-Alkyl steht,
mit Verbindungen der allgemeinen Formel (V)

$NH_2-R^{1'}$ (V)

in welcher
$R^{1'}$ für einen der oben unter R^1 aufgeführten Heterocyclen steht,
oder mit Ethyldithioacetat in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base umsetzt,
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:



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 Ethyldiisopropy-

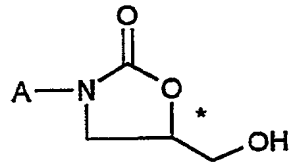
lamin, Triethylamin, Picolin, Pyridine oder N-Methylpiperidin, oder Amide wie Natriumamid oder Lithiumdiisopropylamid, oder Lithium-N-silylalkylamide, wie beispielsweise Lithium-N-(bis)triphenylsilylamid oder Lithiumalkyle wie n-Butyllithium.

Die Base wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 3 mol jeweils bezogen auf 1 mol der Verbindungen der allgemeinen Formeln (II) und (IV) 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.

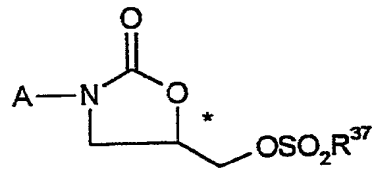
Die Verbindungen der allgemeinen Formeln (III) und (V) sind an sich bekannt oder nach üblichen Methoden herstellbar.

Die Verbindungen der allgemeinen Formel (II) sind teilweise neu und können hergestellt werden, indem man Verbindungen der allgemeinen Formel (VI)



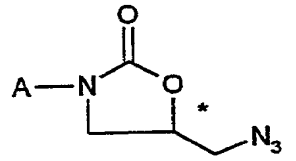
(VI)

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 (IV)



(IV)

in welcher
A und R^{37} die oben angegebene Bedeutung haben
überführt,
anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (VII)



(VII)

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 überführt.

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 1 mol der Verbindungen der allgemeinen Formel (VI) 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.

Die Reduktion der Azide 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 Verbindungen der allgemeinen Formeln (IV) und (VII) sind neu und können wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (VI) sind teilweise neu und können hergestellt werden, indem man

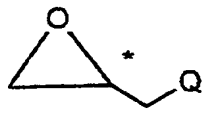
[D] Verbindungen der allgemeinen Formeln (VIII) oder (IX)

$$A-N=C=O \quad (VIII) \quad \text{oder} \quad A-CO-N_3 \quad (IX)$$

in welchen

A die oben angegebene Bedeutungen hat,

mit Lithiumbromid/$(C_4H_9)_3$ P(O) und Epoxiden der allgemeinen Formel (X)



(X)

in welcher

Q für C_1-C_6-Acyloxy steht,

in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base

umsetzt,

durch eine typische Esterverseifung oder durch eine typische Umesterung die Hydroxyfunktion freisetzt,

oder

[E] Verbindungen der allgemeinen Formel (XI)

$$A-NH-CO_2-X \quad (XI)$$

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 (X) umsetzt,

oder

zunächst Verbindungen der allgemeinen Formel (IX) durch Abspaltung von Stickstoff in Alkoholen in die Verbindungen der allgemeinen Formel (XIa)

$$A-NH-CO_2-Y \quad (XIa)$$

in welcher

A die oben angegebene Bedeutung hat

und

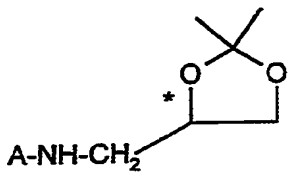
Y für geradkettiges oder verzweigtes C_2-C_6-Alkyl, vorzugsweise n-Butyl steht,

überführt,

und in einem zweiten Schritt wie unter [D] beschrieben in inerten Lösemitteln und in Anwesenheit einer Base, vorzugsweise Lithium-N-alkyl-oder N-Silylalkylamiden oder n-Butyllithium und Epoxiden der allgemeinen Formel (X) umsetzt,

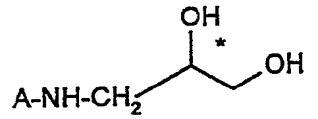
oder

[F] Verbindungen der allgemeinen Formel (XII)



(XII)

in welcher
A die oben angegebene Bedeutung hat,
entweder direkt mit Säuren und Kohlensäurediethylester
umsetzt,
oder zunächst durch Umsetzung der Verbindungen der allgemeinen Formel (XII) mit Säuren die Verbindungen der allgemeinen Formel (XIII)



(XIII)

in welcher A die oben angegebene Bedeutung hat,
herstellt,
und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert.

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 1 mol der Verbindungen der allgemeinen Formeln (X) und (XI) 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 [D] 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 Cäsiumcarbonat. Bevorzugt ist Cäsiumcarbonat.

Das Verfahren [E] 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 [F] 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 [F] 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 (XII) 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 Verbindungen der allgemeinen Formel (IX) sind bekannt oder können nach üblichen Methoden hergestellt werden.

Die Verbindungen der allgemeinen Formel (XIII) sind größtenteils neu und können beispielsweise wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (VIII) sind teilweise bekannt oder neu und können dann beispiels-

weise 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 (IX) 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 (XI) und (XIa) 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 minimalen Hemmkonzentrationen (MHK) wurden per Reihenverdünnungsverfahren auf Iso-Sensitest Agar (Oxoid) bestimmt. Für jede Prüfungssubstanz wurde eine Reihe von Agarplatten hergestellt, die bei jeweils doppelter Verdünnung abfallende Konzentrationen des Wirkstoffes enthielten. Die Agarplatten wurden mit einem Multipoint-Inokulator (Denley) beimpft. Zum Beimpfen wurden Übernachtkulturen der Erreger verwandt, die zuvor so verdünnt wurden, daß jeder Impfpunkt ca. 10^4 koloniebildende Partikel enthielt. Die beimpften Agarplatten wurden bei 37°C bebrütet, und das Keimwachstum wurde nach ca. 20 Stunden abgelesen. Der MHK-Wert (µg/ml) gibt die niedrigste Wirkstoffkonzentration an, bei der mit bloßem Auge 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
11	0.5	0.5	0.25	0.25	>64	>64	>64
12	1	1	1	0.5	>64	>64	>64
13	0.25	0.25	0.25	≤ 0.125	>64	>64	>64
14	1	1	1	0.5	>64	>64	>64
15	0.25	0.5	0.25	≤ 0.125	>64	>64	>64
20	0.25	0.25	0.25	≤ 0.125	64	>64	>64
23	0.25	0.5	0.5	0.25	>64	>64	>64
26	< 0.125	0.25	0.25	≤ 0.125	>64	>64	>64
42	< 0.125	>0.125	>0.125	< 0.125	64	64	>64
43	0.5	0.5	0.5	0.5	>64	>64	>64

Für schnellwachsende Mykobakterien wurde die MHK-Bestimmung in Anlehnung an die von Swenson beschriebene Methode der Bouillon Mikrodilution durchgeführt [vgl. J.M. Swenson, C. Thornberry, U.A. Silcox, Rapidly growing mycobacteria. Testing of susceptibility to 34 antimicrobial agents by broth microdilution. Antimicrobial Agents and Chemotherapy Vol, 22, 186—192 (1982)].

Abweichend davon war das mit 0,1 Vol.% Tween 80 versetzte Hirn-Herzextrakt Medium.

Die verwendeten Mykobakterienstämme wurden von der DSM (Dt. Sammlung von Mikroorganismen, Braunschweig) bezogen. Sie wurden in einer feuchten Kammer bei 37°C bebrütet.

Die MHK-Werte wurden nach 2—4 Tagen abgelesen, wenn die präparatfreien Kontrollen durch Wachstum trüb waren. Der MHK-Wert definiert sich als die niedrigste Präparatkonzentration, die makroskopisch sichtbares Wachstum völlig inhibiert.

MHK-Werte: Mycotbacterium smegmatis

Stamm:	DSM 43061	DSM 43078
Inoculum [/ml]	2,20E+04	4,20E+04
Bsp.-Nr.		
12	8	4
13	2	1
14	8	4
15	1	0.5
20	0.25	0.25
Isoniazid	4	2
Strepto-mycin	4	4

MHK-Bestimmung mit Mycoplasma pneumoniae

Mycoplasma pneumoniae Stamm PI 1428 wurde unter aeroben Bedingungen in PPLO-Medium, dem 1% Glukose, 2,5% Hefeextrakt, 20% Pferdeserum (donor horse serum) und 0,002% Phenolrot zugegeben wurde gezüchtet. MHK-Bestimmungen wurden in Anlehnung an die von ter Laak u. Mitarbeitern beschriebene Methode der Reihenmikrodilution in Flüssigmedium durchgeführt (E. A. ter Laak, A. Pijpers, J.H. Noordergraaf, E. Schoevers, J.H.M. Verheijden: Comparison of Methods for in vitro Testing of Susceptibility of Porcine Mycoplasma Species to Antimicrobial Agents; Antimicrobial Agents and Chemotherapy, Vol. 35, 228—233 (1991)). Zum Zeitpunkt des beginnenden Farbumschlags des Mediums der präparatfreien Kontrolle von rot nach gelb wurden 10 Vol% Alamar Blau zugegeben. Die Inkubation bei 37°C wurde für ca. 10 Stunden fortgesetzt und die MHK als der Wert definiert, bei dem das Medium mit der kleinsten Präparatkonzentration unverändert blau blieb.

Bsp.-Nr.	MHK (µg / ml)
12	2
13	2
14	8
23	4

Die erfindungsgemäßen Verbindungen der allgemeinen Formel (I) weisen bei geringer Toxizität ein breites antibakterielles Spektrum, speziell gegen gram-positive Bakterien sowie Mycobacterien, Haemophilus Influenzae, anaerobe Keime für schnellwachsende Mykobakteren auf. Diese Eigenschaften ermöglichen ihre Verwendung als chemotherapeutische Wirkstoffe in der Human- und Tiermedizin.

Besonders wirksam sind die erfindungsgemäßen Verbindungen gegen Bakterien und bakterienahnliche Mikroorganismen wie Mycoplasmen. 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 30 mg/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 in Acetonitril : Wasser
IV Ethylacetat
V Petrolether : Ethylacetat
VI CH_2Cl_2 : MeOH : $NH_{3(aq)}$
VII CH_2Cl_2 : MeOH

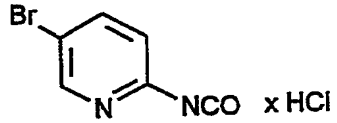
Abkürzungen

Z Benzyloxycarbonyl
Boc tert.Butoxycarbonyl
DMF Dimethylformamid
Ph Phenyl
Me Methyl
THF Tetrahydrofuran
CDI Carbonyldiimidazol
DCE Dichlorethan

Ausgangsverbindungen

Beispiel I

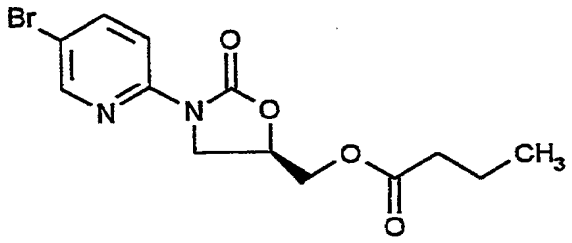
5-Brom-2-isocyanato-pyridin Hydrochlorid



Zu einer gerührten Lösung von 100 g (0,58 mol) 2-Amino-5-brompyridin in 400 ml 1,2-Dichlorethan tropft man in der Siedehitze 78,0 ml (0,64 mol) Chlorameisensäuretrichlorethylester. Nach der Zugabe wird 2h im Rückfluß gekocht, dann darf sich das Gemisch auf Raumtemperatur abkühlen. Der entstandene Niederschlag wird durch Filtration abgetrennt, mit 100 ml 1,2-Dichlorethan gut gewaschen und im Hochvakuum über Natriumhydroxid getrocknet. Man erhält 98,3 g (72%) der Titelverbindung als gelben Feststoff.
Schmp.: 248—254° C (Zers.)
R_f = 0,23 (Ethylacetat)
MS (EI) m/z = 198 $(M)^+$

Beispiel II

(5R)-3-(5-Brom-pyridin-2-yl)-5-butyryloxy-methyl-oxazolidin-2-on



Eine Suspension von 2,17 g (25 mmol) Lithiumbromid und 5,46 g (25 mmol) Tributylphophinoxid in 73 ml Xylol wird 1 h am Wasserabscheider gekocht. Dazu wird in der Siedehitze ein Gemisch von 58,-5 ml (0,42 mol) Triethylamin und 66,6 g (0,42 mol) (R)-Glycidylbutyrat getropft. Gleichzeitig werden innerhalb von 20 min 98,2 g (0,42 mol) der Verbindung aus Beispiel I portionsweise zugegeben. Nach beendeter Zugabe wird noch 1 h unter Rückfluß nachgerührt. Man läßt auf Raumtemperatur abkühlen und dampft das Lösemittel im Vakuum ab. Nach Chromatographie des Rückstands an 1 kg Kieselgel (Toluol : Ethylacetat 95 : 5) erhält man 37,9 g (26%) der Titelverbindung als Öl.

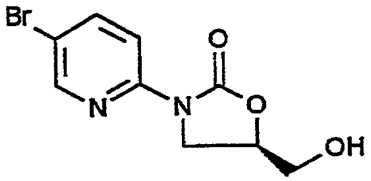
R_f = 0,43 (Toluol : Ethylacetat 4 : 1)

MS (FAB) m/z = 343 $(M+H)^+$

^{1}H-NMR (250 MHz, D_6—DMSO): δ = 0,81 (t, J = 7 Hz, 3H, CH_3CH_2); 1,5 (m, 2H, $CH_3\underline{CH_2}CH_2CO$); 2,29 (t, J = 7 Hz, 2H, $CH_3CH_2\underline{CH_2}CO$); 3,91 (dd, J = 7 Hz, 10 Hz, 1H, H-4 trans); 4,25 (dd, J = 9 Hz, 10 Hz, 1H, H-4 cis); 4,36 (m, 2H, CH_2O); 4,97 (m, 1H, H-5); 8,08 (d, J = 1 Hz, 2H, Pyridyl H-3,4); 8,50 (d, J = 1 Hz, pyridyl H-6).

Beispiel III

(5R)-3-(5-Brom-pyridin-2-yl)-5-hydroxymethyl-oxazolidin-2-on



Eine Lösung von 19,6 g (57,3 mmol) der Verbindung aus Beispiel 1 in 125 ml wasserfreiem Methanol wird mit 185 mg (0,57 mmol) Cäsiumcarbonat versetzt und 5 h bei Raumtemperatur gerührt. Das Lösemittel wird im Vakuum abgedampft und der Rückstand wird mit 30 ml Ether verrührt. Der Niederschlag wird durch Filtration abgetrennt, mit 25 ml Wasser und 5 ml Ether gewaschen und im Hochvakuum getrocknet. Man erhält 10,73 g (69%) der Titelverbindung als helle Kristalle.

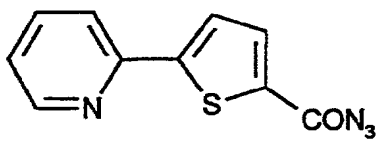
Schmp.: 0,09 (Toluol : Ethylacetat 4 : 1)

MS (DCI, NH_3) m/z = 273 $(M+H)^+$

^{1}H-NMR (200 MHz, CD_3OD) δ = 3,68 (d, J = 5,9 Hz, 1 H, CH_2O); 3,87 (dd, J = 4, 9 Hz, 1H, CH_2O); 4,06 (dd, J = 7, 10 Hz, 1H, H-4 trans); 4,26 (dd, J = 9, 10 Hz, 1H, H-4 cis); 4,75 (m, 1H, H-5); 7,92 (dd, J = 1,5 Hz, 10 Hz, 1H, Pyridyl H-3); 8,12 (d, J = 10 Hz, 1H, Pyridyl H-4); 8,40 (d, J = 1,5 Hz, 1H, Pyridyl H-6).

Beispiel IV

5-(2-Pyridyl)-thiophen-2-carbonsäureazid

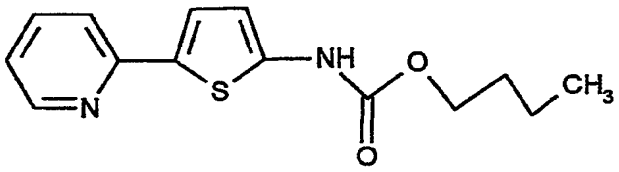


20 g (97,45 mmol) 5-(2-Pyridyl)-thiophen-2-carbonsäure werden in 200 ml Aceton gelöst, mit 15,94 ml (115 mmol) Et_3N versetzt und auf 0° C gekühlt. Zu der so erhaltenen Reaktionslösung tropft man langsam unter

Rühren eine Lösung von 14,85 ml (115 mmol) Chlorameisensäureisobutylester in 88 ml Aceton. Nach 1 h bei 0°C tropft man eine Lösung von 9,5 g (146 mmol) Natriumazid in 44 ml Wasser zu, rührt 1 h bei 0°C nach und läßt auf Raumtemperatur kommen. Die Reaktionsmischung wird auf Eiswasser gekippt und abgesaugt und so weiter umgesetzt.
Ausbeute: 21 g wasserfeuchtes Pulver.

Beispiel V

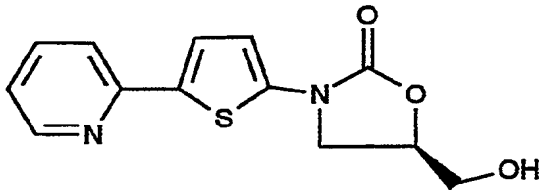
5-(2-Pyridyl)-butyloxycarbonylamino-thiophen



21 g der Verbindung aus Beispiel IV werden portionsweise in 400 ml siedendes n-Butanol eingetragen. Nach beendeter Gasentwicklung wird 15 min unter Rückfluß nachgerührt. Nach Abkühlen auf Raumtemperatur wird eingeengt, der Rückstand mit Ether verrührt, abgesaugt und bei 50°C im Umlufttrockenschrank getrocknet.
Ausbeute: 18,8 g (75% d.Th.)
^{1}H-NMR (200 MHz, D_6—DMSO): δ = 10,8 (s, 1H); 8,45 (d, J = 5 Hz, IH); 7,68 — 7,85 (m, 2H); 7,5 (d, J = 5 Hz, IH); 7,1—7,2 (m, 1H); 6,57 (d, J = 5 Hz, 1H); 4,14 (t, J = 7 Hz,, 2H); 1,62 (q, J = 7 Hz, 2H); 1,39 (h, J = 7 Hz, 2H); 0,92 (t, J = 7 Hz, 3H).

Beispiel VI

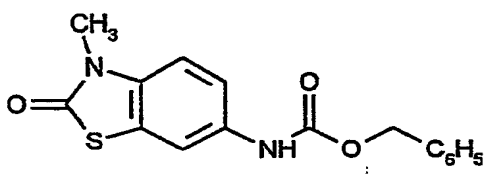
(5R)-3-(5-(2-Pyridyl)-thien-2-yl)-5-hydroxymethyl-oxazolidin-2-on



18,8 g (68 mmol) der Verbindung aus Beispiel V werden in 190 ml absolutem THF gelöst, mit 10 mg 1,10-Phenanthrolin-Hydrat versetzt und auf —70°C gekühlt. Nun werden langsam ca. 27 ml 2,5 N n-Butyllithium-Lösung in Hexan bis zum Farbumschlag nach rot zugetropft. Anschließend werden 9,6 ml (68 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf Raumtemperatur kommen, versetzt mit gesättigter Ammoniumchloridlösung, trennt die organische Phase ab und extrahiert die wäßrige Phase zweimal mit Methylenchlorid. Die vereinigten organischen Phasen werden getrocknet (Na_2SO_4) und eingeengt. Der Rückstand wird mit Ether verrührt und abgesaugt.
Ausbeute: 15,3 g (81,5% d.Th.)
R_f = 0,06 (CH_2Cl_2 : CH_3OH = 100 : 3)
Smp.: 191°C
^{1}H-NMR (200 MHz, D_6—DMSO): δ = 8,45 (d, J = 5 Hz, 1H); 7,7—7,9 (m, 2H); 7,6 (d, J = 5 Hz, 1H); 7,15—7,25 (m, 1H); 6,58 (d, J = 5 Hz, 1H); 5,28 (t, J = 7 Hz, 1H); 4,77 — 4,9 (m, 1H); 4,13 (dd, J = 10 Hz, 9 Hz, 1H); 3,86 (dd, J = 10 Hz, 6 Hz, 1H); 3,55—3,78 (m, 2H).

Beispiel VII

6-(Benzyloxycarbonylamino)-3-methyl-2-benzothiazolinon



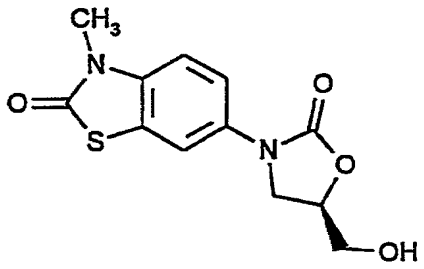
1,76 g (8,12 mmol) 6-Amino-3-methyl-2(3H)-benzothiazolon-hydrochlorid in 17 ml Wasser, 14 ml THF und 17 ml ges. $NaHCO_3$-Lösung werden bei 0°C tropfenweise mit 1,3 ml (9,10 mmol) Chlor-ameisensäurebenzylester versetzt.

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): δ = 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).

Beispiel VIII

(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 VII 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.

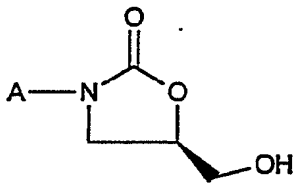
Ausbeute: 17,93 g (75%)
Smp.: 166°C
R_f (II, 1:1) = 0,09
MS (EI): m/z = 280 (M^+)
^{1}H-NMR ([D$_6$]DMSO): δ = 7,80 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,60 (dd, J = 6, J = 1 Hz, 1H, Benzothiazolinon 5-H); 7,32 (d, J = 6 Hz, 1H, Benzthiazolinon 4-H); 5,23 (t, J = 6 Hz, 1H, OH); 4,62 — 4,80 (m, 1H, 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).

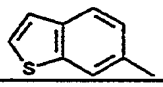
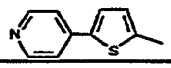
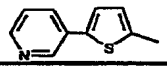
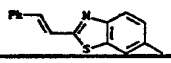
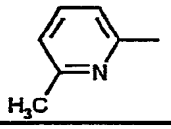
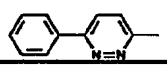
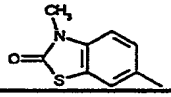
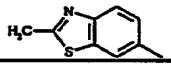
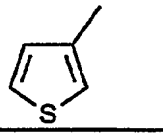
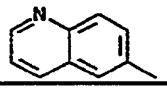
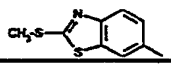
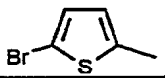
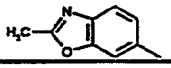
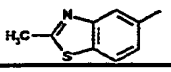
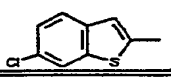
Methode B

9,3 g (0,03 mol) der Verbindung aus Beispiel VII 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%).

Analog den Vorschriften der Beispiele I bis VIII werden die in Tabelle I aufgeführten Verbindungen dargestellt:

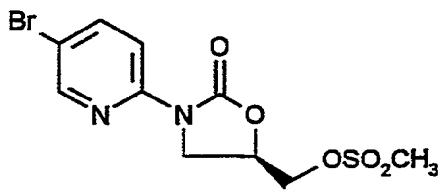
Tabelle I



Bsp.-Nr.	A	Smp. (°C)	R_f / Laufmittel (Verhältnis)	Ausbeute (% d.Th.)
IX		162	-	63
X		209 u.Z.	-	61
XI		185	-	71
XII		188	0,52, I (9:1)	76
XIII		144	0,32, I (95:5)	78
XIV		158	0,29, II (1:1)	28
XV		166	0,09, II (1:1)	82
XVI		-	0,05, II (1:1)	57
XVI		132	-	79
XVII		165	0,1, V (1:4)	45
XVIII		156	0,24, V (4:1)	67
XIX		109	-	24
XX		-	0,47, II (1:1)	68
XXI		-	0,05, II (1:1)	57
XXII		200 u.Z.	-	98

Beispiel XXIII

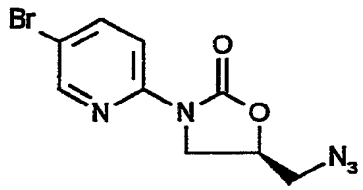
(5R)-3-(5-Brom-pyridin-2-yl)-5-methansulfonyloxy-methyl-oxazolidin-2-on



Eine auf 0°C gekühlte, gerührte Lösung von 10,5 g (38,44 mmol) der Verbindung aus Beispiel III und 6,40 ml (46,14 mmol) Triethylamin in 36 ml wasserfreiem Dichlormethan wird langsam mit 3,27 ml (42,28 mmol) Methansulfonsäurechlorid versetzt. Man rührt 10 min. bei 0—5°C nach und rührt das Gemisch in 50 ml Eiswasser ein. Die organische Phase wird abgetrennt, mit 20 ml gesättigter $NaHCO_3$-Lösung und 20 ml Eiswasser gewaschen und über $MgSO_4$ getrocknet. Das Lösemittel wird im Vakuum eingedampft und der Rückstand mit 50 ml Ether verrührt, abgesaugt und im Hochvakuum getrocknet. Man erhält 12,8 g (95%) der Titelverbindung als farblose Kristalle.
Schmp.: 138—138,5°C
R_f = 0,65 (Dichlormethan : Methanol 95 : 5)
MS (DCI, NH_3) m/z = 351 $(M+H)^+$
^{1}H-NMR (250 MHz, D_6-DMSO) δ = 3,25 (s, 3H, OSO_2CH_3); 3,91 (dd, J = 7, 10 Hz, 1H, H-4 trans); 4,27 (dd, J = 10, 10 Hz, 1H, H-4 cis); 4,52 (m, 2H, CH_2O); 5,02 (m, 1H, H-5); 8,09 (s, 2H, Pyridyl H-3,4); 8,52 (s, 1H, Pyridyl H-6).

Beispiel XXIV

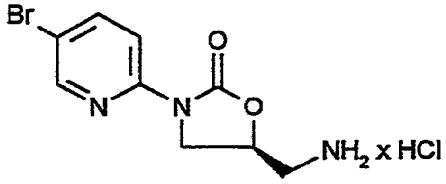
(5R)-3-1-(5-Brom-pyridin-2-yl)-5-azidomethyl-oxazolidin-2-on



Eine gerührte Lösung von 12,5 g (35,6 mmol) der Verbindung aus Beispiel XXIII in 48 ml wasserfreiem DMF wird mit 3,01 g (46,28 mmol) Natriumazid versetzt und 3 h bei 70°C gerührt. Man läßt auf Raumtemperatur abkühlen und rührt in 100 ml Eiswasser ein. Der entstandene Niederschlag wird durch Filtration abgetrennt, mit 50 ml Wasser und 20 ml Petrolether gewaschen und an der Luft getrocknet. Man erhält 10,1 g (95%) der Titelverbindung als helle Kristalle.
Schmp.: 64—67°C
R_f = 0,63 (Toluol : Ethylacetat 2 : 3)
MS (DCI, NH_3) m/z = 298 $(M+H)^+$
^{1}H-NMR (250 MHz, D_6—DMSO) δ = 3,73 (m, 2H, CH_2N_3); 3,87 (dd, J = 6, 8 Hz, 1H, H-4 trans); 4,22 (dd, J = 8, 8 Hz, 1H, H-4 cis); 4,92 (m, 1H, H-5); 8,08 (s, 2H, Pyridyl H-3,4); 8,51 (s, 1H, Pyridyl H-6).

Beispiel XXV

(5S)-3-(5-Brom-pyridin-2-yl)-5-aminomethyl-oxazolidin-2-on Hydrochlorid

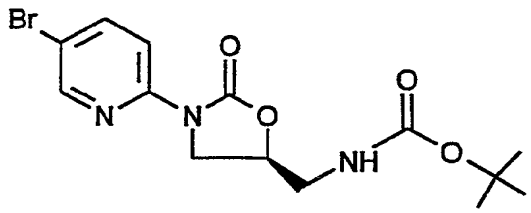


Eine gerührte Lösung von 10,1 g (33,9 mmol) der Verbindung aus Beispiel XXIV in 16,5 ml 1,2-Dimethoxyethan wird auf 50° C erwärmt. Man tropft langsam 4,68 ml (4,70 mmol) Trimethylphosphit zu (Gasentwicklung) und

rührt nach beendeter Zugabe nach 2 h bei 90°C nach. Nun tropft man 6,6 ml 6 N HCl zu und rührt nochmals 2 h bei 90°C nach. Man läßt auf Raumtemperatur abkühlen, trennt den Niederschlag durch Filtration ab, wäscht mit 2 × 10 ml 1,2-Dimethoxyethan und trocknet im Hochvakuum über NaOH. Man erhält 8,9 g (85%) der Titelverbindung als farblose Kristalle.
Schmp.: 260—262°C
R_f = 0,53 (Acetonitril : Wasser 4 : 1)
MS (EI) m/z = 271 (M^+)
^{1}H-NMR (250 MHz, D_6—DMSO) δ = 3,28 (m, 2H, CH_2NH_2); 3,93 (dd, J 7, 9 Hz, 1H, H-4 trans); 4,28 (dd, J = 9, 9 Hz, 1H, H-4 cis); 5,00 (m, 1H, H-5); 8,05 (s, 2H, Pyridyl H-3,4); 8,5 (m, 3H, NH2, Pyridyl H-6).

Beispiel XXVI

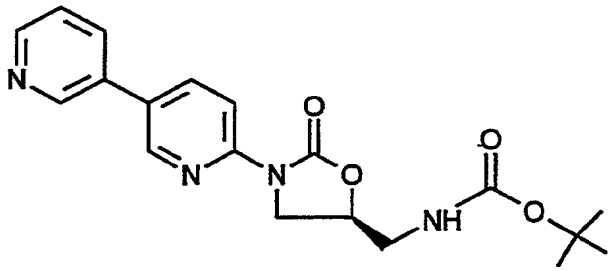
(5S)-3-(5-Brom-pyridin-2-yl)-5-((tert.butyloxy)carbonyl)aminomethyl-oxazolidin-2-on



Man suspendiert 4,7 g (15 mmol) der Verbindung aus Beispiel XXV in 100 ml CH_2Cl_2. Anschließend fügt man 2,2 ml (16 mmol) Triethylamin zu, wobei eine Lösung entsteht. Man kühlt auf 0°C ab. Nun addiert man 3,5 g (16 mmol) Boc-Anhydrid so zu, daß die Temperatur +5°C nicht übersteigt und läßt bei Raumtemperatur über Nacht nachrühren. Man wäscht die organische Phase mit ges. NaCl-Lösung, trocknet über $MgSO_4$ und engt ein. Man erhält 5,4 g (97% d.Th.) des Produktes als weißen Feststoff.
Fp.: 184°C
R_f-Wert (Petrolether : Essigester = 10 : 4) = 0,30

Beispiel XXVII

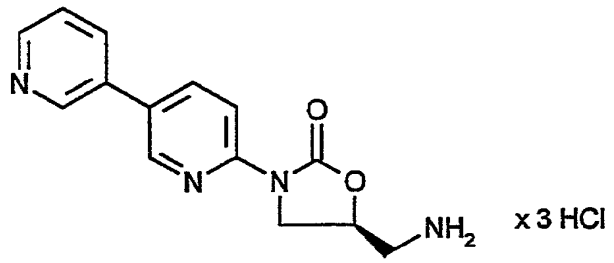
((5S)-3-(5-[3-Pyridyl]-pyridin-2-yl)-5-((tert.butyloxy)carbonyl)aminomethyloxazolidin-2-on



Unter Argon legt man 5,3 g (14,24 mmol) der Verbindung aus Beispiel XXVI und 2,81 g Diethyl-(3-pyridyl)-boran in 100 ml abs. THF vor. Man addiert eine Lösung von 0,5 g (0,43 mmol) [$(PPh_3)_4Pd$] in 90 ml THF und 4,9 ml (9,83 mmol) 2 M Natriumcarbonatlösung. Man läßt den Ansatz 5 Tage bei Rückfluß rühren. Nach dem Abkühlen auf RT gibt man 10 g Kieselgur zu und engt ein. Der Rückstand wird auf eine mit Kieselgel gefüllte Säule aufgetragen und mit Essigester eluiert.
Man erhält 4 g (76% d.Th.) der Titelverbindung
Fp.: 163°C
R_f-Wert = 0,36 (CH_2Cl_2 : MeOH = 100 : 5)

Beispiel XXVIII

(5S)-3-(5-[3-Pyridyl]-pyridin-2-yl)-5-aminomethyl-oxazolidin-2-on Trihydrochlorid



3,8 g (10,3 mmol) der Verbindung aus Beispiel XXVII werden in 25 ml Dioxan suspendiert. Man addiert 32,1 ml einer 4 M HCl-Lösung in Dioxan und läßt über Nacht bei Raumtemperatur rühren. Man engt ein und rührt den Rückstand mit Ether aus. Anschließend wird der Feststoff durch eine Fritte abgesaugt und mit Ether nachgewaschen. Man trocknet am Hochvakuum und erhält 3,7 g (95% d.Th.) der Titelverbindung.

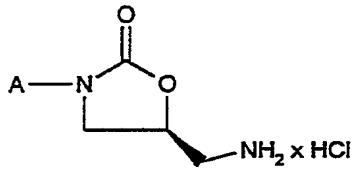
Fp.: >250°C

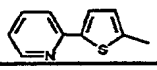
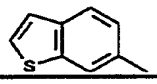
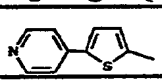
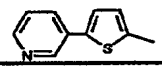
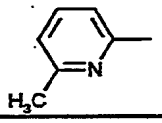
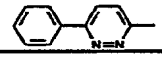
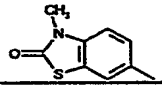
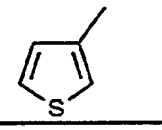
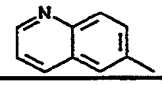
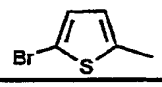
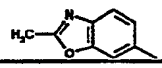
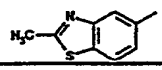
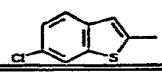
MS (EI): 271 (M^+), 172

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 9,35 (sb, 1H); 8,93 (m, 3H); 8,6 (breit, 3H); 8,42 (dd, J = 9, J = 3, 1H); 8,24 (d, J = 9, 1H); 8,11 (dd, J = 7,5, J = 6,5, 1H); 6,7 – 5,3 (breit, 2H); 5,06 (m, 1H); 4,38 (tr, J = 10,1H); 4,03 (dd, J = 10, J = 7,5, 1H); 3,29 (m, 2H).

Analog den Vorschriften der Beispiele XXIII bis XXVIII wurden die in Tabelle II aufgeführten Verbindungen dargestellt:

Tabelle II

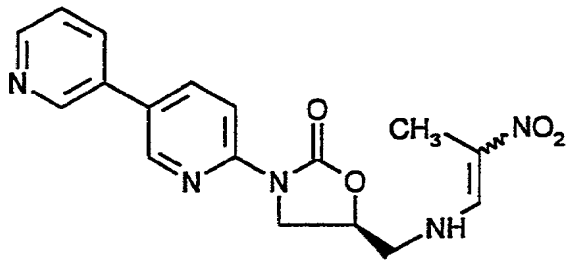


Bsp.-Nr.	A	Smp. (°C)	R_f / Laufmittel (Verhältnis)	Ausbeute (% d.Th.)
XXIX		-	-	95
XXX		-	-	87
XXXI		-	-	94
XXXII		-	-	94
XXXIII		303	0,19, III (9:1)	94
XXXIV		-	0,21, III (9:1)	75
XXXV		273	0,24, III (4:1)	75
XXXVI		259 u.Z.	0,09, III (9:1)	75
XXXVII		264 u.Z.	0,16, III (9:1)	94
XXXVIII		272 u.Z.	0,13, III (9:1)	61
XXXIX		80	0,12, II (4:1)	87
XL		-	0,27, VI (100:10:4)	26
XLI		258 u.Z.	-	58
XLII		188	0,13, II (1:4)	80
XLIII		-	0,05, II (1:1)	57
XLIV		-	0,5, I (100:3)	79

Herstellungsbeispiele

Beispiel 1

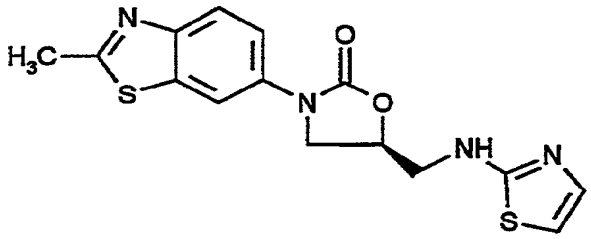
(5S)-3-(5-[3-Pyridyl]-pyridin-2-yl)-5-(2-nitro-prop-1-en-1-yl-aminomethyl)-oxazolidin-2-on



Unter Argon läßt man 100 mg (0,37 mmol) der Verbindung aus Beispiel XXVIII (freie Base; hergestellt durch Lösen in Wasser, $NH_{3(aq)}$-Zugabe bis pH 11, Extraktion mit CH_2Cl_2, Trocknen über $MgSO_4$ und Einengen) in 1 ml DMF und gibt 200 mg (1,11 mmol) 2-(2-Nitro-prop-1-en-1-yl-amino)-pyridin zu und läßt über Nacht rühren. Man versetzt mit Wasser, extrahiert 3 × mit Essigester, wäscht die organische Phase mit ges. NaCl-Lösung und trocknet über $MgSO_4$. Man engt ein und reinigt durch Säulenchromatographie an Kieselgel (Laufmittel CH_2Cl_2: MeOH = 100 : 5). Man erhält 126 mg (96% d.Th.) der Titelverbindung.
Fp.: 207°C
R_f-Wert: (CH_2Cl_2 : MeOH = 10 : 1) 0,57
MS (DCI): 356 $(M+H)^+$
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 8,95 (d, J = 2, 1H); 8,79 (d, J = 2, 1H); 8,60 (dd, J = 5, J = 2, 1H); 8,4 — 7,9 und 7,6 — 7,4 (m, insgesamt 6H); 4,9 (m, 1H); 4,3 (m, 1H); 4,05 (m, 1H); 3,7 (m, 2H); 1,95 und 1,93 (s; insgesamt 3H).

Beispiel 2

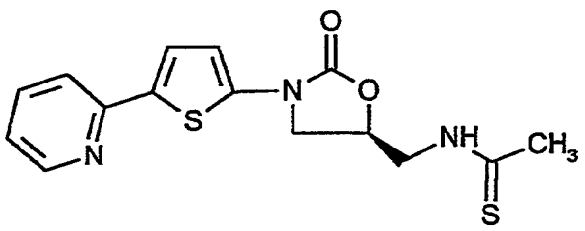
(5R)-3-(2-Methyl-benzo[4,5-d]thiazol-6-yl)-5-(2-thiazolyl-aminomethyi)-oxazolidin-2-on



Unter Argon werden 292 mg (2,92 mmol) 2-Aminothiazol in 5 ml abs. THF vorgelegt und bei —78°C mit 1,33 ml (2,92 mmol) 2,2 M n-BuLi-Lösung versetzt. Man läßt 30 Minuten bei —78°C rühren. Man addiert 0,5 g (1,46 mmol) (5R)-3-(2-Methyl-benzo[4, 5-d]thiazol-6-yl)-5-methoxysulfonyloxymethyl-oxazolidin-2-on, gelöst in 5 ml abs. THF, und läßt 1 h bei —78°C rühren. Man entfernt das Kühlbad und läßt über Nacht rühren. Man addiert NH_4Cl-Lösung und HCl-Lösung (auf pH 3), extrahiert mit Chloroform, trocknet über $MgSO_4$ und engt ein. Die Substanz wird säulenchromatographisch an Kieselgel gereinigt (Laufmittel CH_2Cl_2 : MeOH = 100 : 1 bis 100 : 3). Man erhält 193 mg (38% d.Th.) der Titelverbindung.
Fp.: 207°C
R_f = 0,47 (CH_2Cl_2 : MeOH = 10 : 1)

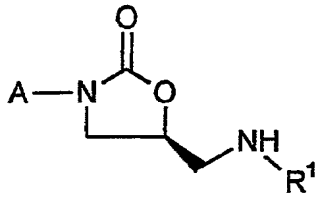
Beispiel 3

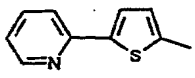
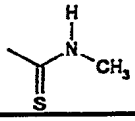
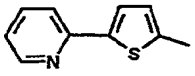
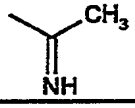
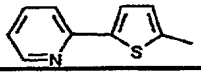
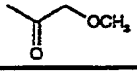
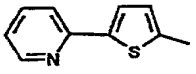
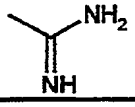
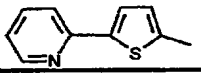
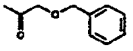
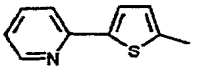
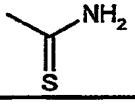
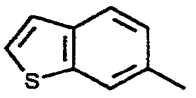
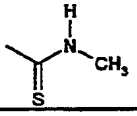
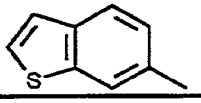
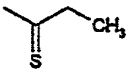
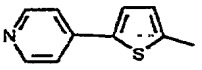
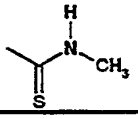
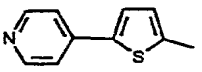
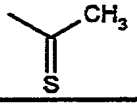
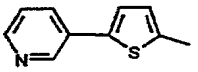
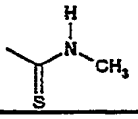
(5R)-3-(5-(2-Pyridyl)-thien-2-yl)-5-thioacetylamino-methyl-oxazolidi-n-2-on

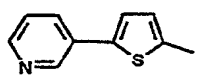
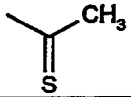
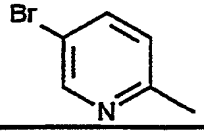
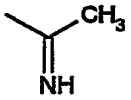
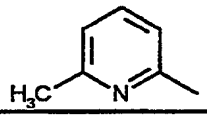
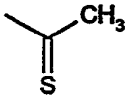
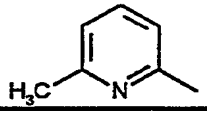
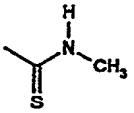
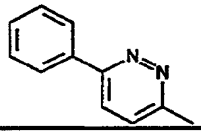
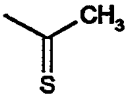
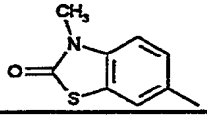
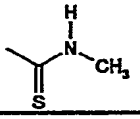
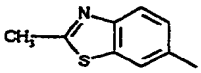
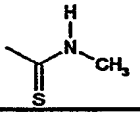
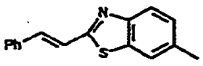
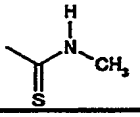
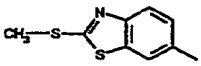
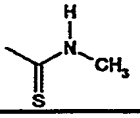
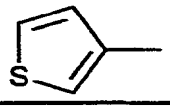
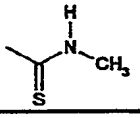
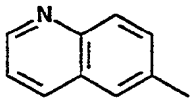
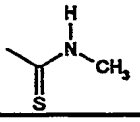
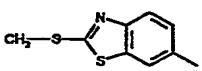
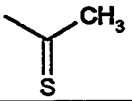


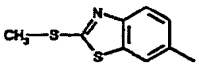
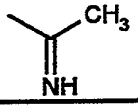
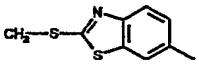
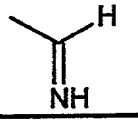
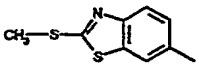
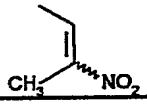
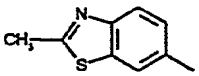
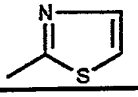
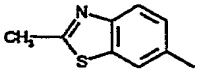
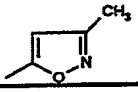
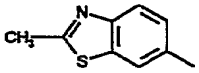
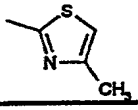
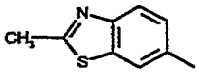
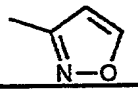
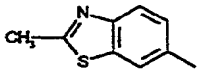
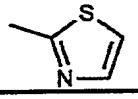
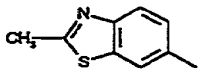
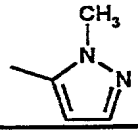
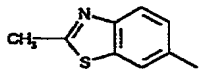
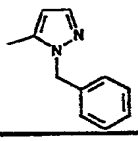
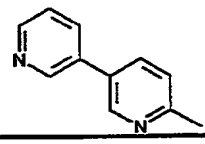
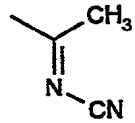
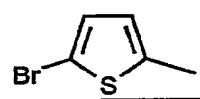
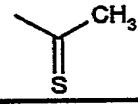
3,48 mg (1 mmol) der Verbindung aus Beispiel XXIX werden mit 4 ml THF und 0,24 ml (1,7 mmol) Triethylamin versetzt. Zu der so erhaltenen Reaktionsmischung gibt man unter Rühren 152 µl (1,1 mmol) Dithioessigsäureethylester und hält 24 h bei Raumtemperatur. Nach Einengen wird mit Methylenchlorid/Methanol (100 : 2) an Kieselgel chromatographiert.
Ausbeute: 100 mg (36% d.Th.)
Smp.: 181°C n.Z.
R_f: 0,36 (I; 100 : 5)
^{1}H-NMR (D_6—DMSO, 300 MHz): δ = 10,37 (br, 1H); 8,47 (d, J = 5 Hz, 1H); 7,75 —7,88 (m, 2H); 7,62 (d, J = 5 Hz, 1H); 7,2 (m, 1H); 6,58 (d, J = 5 Hz, 1H); 5,03— 5,13 (m, 1H); 4,21 (dd, J = 10 Hz, 9 Hz, 1H); 3,95 (t, J = 6 Hz, 2H); 3,85 (dd, J = 10 Hz, 6 HZ, 1H); 2,45 (s, 3H).
Analog den Vorschriften der Beispiele 1 bis 3 werden die in Tabelle 1 aufgeführten Verbindungen dargestellt:

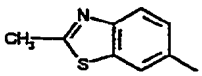
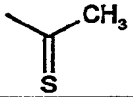
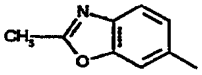
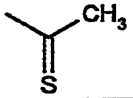
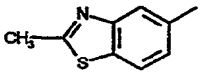
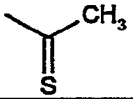
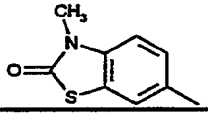
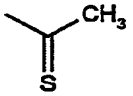
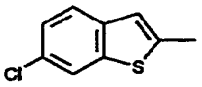
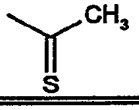
Tabelle 1



Bsp.-Nr.	A	R^1	Smp. (°C)	R_f	Ausbeute (% d.Th.)
4			160 u.Z.	0,23, I (100:5)	50
5			214 u.Z.	0,02, I (100:5)	40
6			127	0,29, I (100:5)	80
7			212 u.Z.		13
8			152	0,32, I (100:5)	79
9			137 u.Z.		25
10			143 u.Z.		99
11			142 u.Z.	0,48, I (100:5)	76
12			153	0,52, I (10:1)	24
13			159	0,57, I (10:1)	30
14				0,48, I (10:1)	5

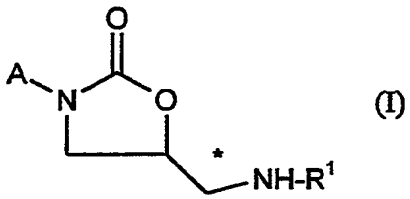
Bsp.-Nr.	A	R^1	Smp. (°C)	R_f	Ausbeute (% d.Th.)
15			160 u.Z.	0,58, I (10:1)	28
16			160	0,11, I (85:15)	54
17			-	0,11, I (97:3)	58
18			91	0,59, I (9:1)	39
19			189	0,53, I (9:1)	48
20			190	0,44, I (9:1)	63
21			160	0,48, I (9:1)	72
22			182	0,12, I (95:5)	75
23			152	0,31, I (9:1)	52
24			77	0,55, I (9:1)	70
25			115	0,51, I (9:1)	71
26			163 u.Z.	0,32, II (100:3)	38

Bsp.-Nr.	A	R^1	Smp. (°C)	R_f	Ausbeute (% d.Th.)
27			184	-	27
28			203	0,08, VI (100:5:2)	32
29			206	0,58 VII (10:1)	68
30			207	0,47, I (10:1)	38
31			211	0,34, I (100:5)	35
32			201	0,49, I (100:5)	29
33			184	0,42, I (100:5)	39
34			223	0,39, I (100:5)	18
35			214	0,29, I (100:5)	25
36			218	0,39, I (100:5)	39
37			229	0,28, I (100:5)	37
38			133 u.Z.	0,58, I (100:3)	58

Bsp.-Nr.	A	R^1	Smp. (°C)	R_f	Ausbeute (% d.Th.)
39			224		5
40			183		33
41			180 u.Z.	0,31, I (100:3)	45
42			203 u.Z.	0,31, I (100:3)	53
43			176 u.Z.	0,45, I (100:3)	22

Patentansprüche

1. Substituierte Oxazolidinone der allgemeinen Formel (I)



(I)

in welcher

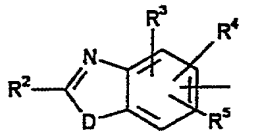
A für einen über ein Kohlenstoffatom direkt gebundenen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der zusätzlich einen annellierten Benzol- oder Naphthylring besitzen kann, oder

für einen über ein Kohlenstoffatom direkt gebundenen 6-gliedrigen, aromatischen Heterocyclus mit mindestens einem Stickstoffatom steht, oder

für einen über ein Kohlenstoffatom direkt gebundenen, jeweils 6-gliedrigen, bi- oder tricyclischen aromatischen Rest mit mindestens einem stickstoffhaltigen Ring steht, oder

für β-Carbolin-3-yl oder für über den 6-Ring direkt gebundenes Indolizinyl steht, wobei die Cyclen gegebenenfalls jeweils bis zu 3-fach gleich oder verschieden durch Carboxy, Halogen, Cyano, Mercapto, Formyl, Pyridyl, Phenyl, Trifluormethyl, Nitro, geradkettiges oder verzweigtes Alkoxy, Alkoxycarbonyl, Alkylthio oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen substituiert sind, die ihrerseits durch Phenyl substituiert sein können, oder

für einen Rest der Formel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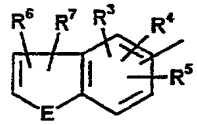
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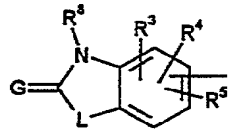
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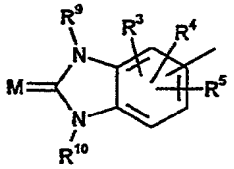
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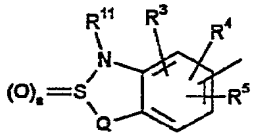
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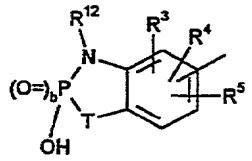
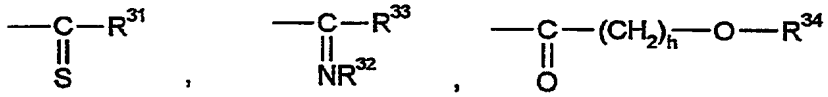
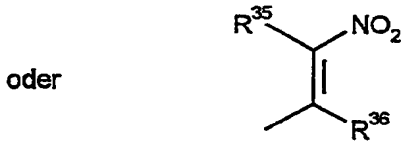


steht, worin
R^3, R^4, R^5, R^6 und R^7 gleich oder verschieden sind und Wasserstoff oder Carboxy, Halogen, Cyano, Formyl, Trifluormethyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder für eine Gruppe der Formel $-CO-NR^{13}R^{14}$ stehen,
worin
R^{13} und R^{14} gleich oder verschieden sind und Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeuten,
R^2, R^8, R^9, R^{10}, R^{11} und R^{12} gleich oder verschieden sind und Wasserstoff, Cycloalkylcarbonyl oder Cycloalkyl mit jeweils 3 bis 6 Kohlenstoffatomen, oder geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder geradkettiges oder verzweigtes Alkyl mit bis zu 10 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Trifluormethyl, Halogen, Phenyl, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen, Aryl mit 6 bis 10 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen und/oder durch eine Gruppe der Formel $-(CO)_c-NR^{15}R^{16}$, $R^{17}-N-SO_2-R^{18}$, $R^{19}R^{20}-N-SO_2-$ oder $R^{21}-S(O)_d$ substituiert ist,
worin
c eine Zahl 0 oder 1 bedeutet,
R^{15}, R^1 und R^{17} die oben angegebene Bedeutung von R^{13} und R^{14} 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^1 und R^{20} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
d eine Zahl 0, 1 oder 2 bedeutet,
R^1 und R^{21} gleich oder verschieden sind und geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder
geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls Trifluormethyl, Trichlormethyl oder durch eine Gruppe der Formel $-OR^{22}$ substituiert ist,
worin
R^{22} Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Aryl mit bis zu 10 Kohlenstoffatomen substituiert ist,
oder
eine Gruppe der Formel $-(CO)_e-NR^{23}R^{24}$, $-NR^{25}-SO_2R^{26}$, $R^{27}R^{28}-NSO_2-$ oder $R^{29}-S(O)_f$ bedeuten,
worin
e die oben angegebene Bedeutung von c hat und mit dieser gleich oder verschieden ist,
R^{23} und R^{24} und R^{25} jeweils die oben angegebene Bedeutung von R^{15}, R^{16} und R^{17} haben und mit dieser gleich oder verschieden sind,
R^{27} und R^{28} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
f die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist,
R^{26} und R^{29} die jeweils oben angegebene Bedeutungen von R^{18} und R^{21} haben und mit dieser gleich oder verschieden sind,
D ein Sauerstoffatom oder einen Rest der Formel $-S(O)_g$ bedeutet,
worin

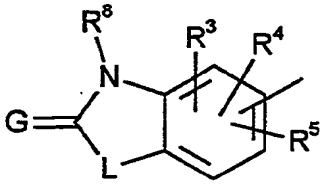
g eine Zahl 0, 1 oder 2 bedeutet,
E und L gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom bedeuten,
G, M, T und Q gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom, oder eine Gruppe der Formel $-NR^{30}$ bedeuten,
worin
R^{30} Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
a und b gleich oder verschieden sind und eine Zahl 1 oder 2 bedeuten,
R^1 für einen Rest der Formel





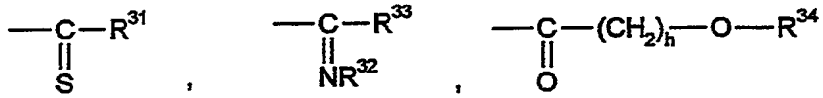
steht, worin
R^{31} geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
R^{38} und R^{39} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
R^{32} Wasserstoff, Cyano, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen bedeutet,
R^{33} Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Phenyl, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
R^{40} und R^{41} die oben angegebene Bedeutung von R^{13} und R^{14} haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
R^{34} geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,
R^{35} und R^{36} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
oder
R^1 für Cyano oder für einen 5- bis 7-gliedrigen, gesättigten, partiell ungesättigten oder ungesättigten Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der gegebenenfalls auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Halogen oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen substituiert ist,
als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

2. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1,
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 3-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 4 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 4 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder für einen Rest der Formel

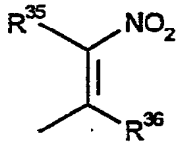


steht, worin
G ein Sauerstoff- oder Schwefelatom bedeutet,
L ein Sauerstoff- oder Schwefelatom bedeutet,
R^8 geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet,

R^3, R^4 und R^5 gleich oder verschieden sind und Wasserstoff, Fluor, Chlor oder Brom bedeuten,
R^1 für einen Rest der Formel

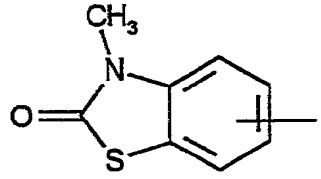


oder

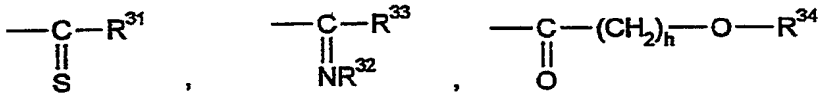


steht, worin
R^{31} geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
R^{38} und R^{39} gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,
R^{32} Wasserstoff, Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
R^{33} Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
R^{40} und R^{41} die oben angegebene Bedeutung von R^{38} und R^{39} haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
R^{34} geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Benzyl bedeutet,
R^{35} und R^{36} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,
oder
R^1 für Cyano oder für Thienyl, Oxazolyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls, auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sind,
als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

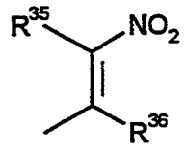
3. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1,
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 2-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 3 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 3 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder
für einen Rest der Formel



steht,
R^1 für einen Rest der Formel

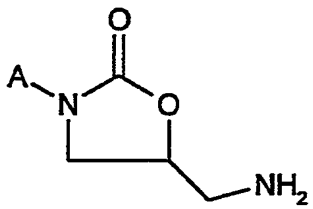


oder



steht, worin
R^{31} geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
R^{38} und R^{39} gleich oder verschieden sind und Wasserstoff oder Methyl bedeuten,
R^{32} Wasserstoff, Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet,
R^{33} Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
R^{40} und R^{41} die oben angegebene Bedeutung von R^{38} und R^{39} haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
R^{34} geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Benzyl bedeutet,
R^{35} und R^{36} gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,
oder
R^1 für Cyano oder für Thienyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls auch über eine N-Funktion bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,
als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

4. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, dadurch gekennzeichnet, daß man
[A] Verbindungen der allgemeinen Formel (II)

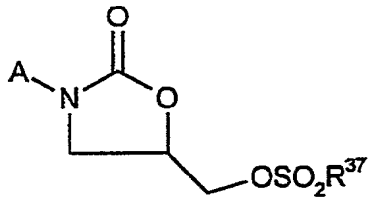


(II)

in welcher
A die in Anspruch 1 angegebene Bedeutung hat,
mit Verbindungen der allgemeinen Formel (III)

R^1-Y (III)

in welcher
R^1 die in Anspruch 1 angegebene Bedeutung hat,
und
Y in Abhängigkeit von R^1 für Wasserstoff, Halogen oder für C_1-C_4 geradkettiges oder verzweigtes Alkoxy oder Oxyalkoxycarbonyl steht,
oder
[B] Verbindungen der allgemeinen Formel (IV)



(IV)

in welcher
A die oben angegebene Bedeutung hat,
R^{37} für C_1-C_4-Alkyl steht,
mit Verbindungen der allgemeinen Formel (V)

$NH_2-R^{1'}$ (V)

in welcher
$R^{1'}$ für einen der oben unter R^1 aufgeführten Heterocyclen steht,
oder mit Ethyldithioacetat in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base umsetzt,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
und gegebenenfalls weitere Substituenten oder bereits vorhandene funktionelle Gruppen nach üblichen Methoden einführt bzw. derivatisiert,
und gegebenenfalls die Stereoisomere nach üblichen Methoden trennt.

5. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1 zur Verwendung bei der Bekämpfung von Krankheiten.

6. Verwendung von Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1 zur Herstellung von Arzneimitteln.

7. Arzneimittel enthaltend Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1.

– Leerseite –

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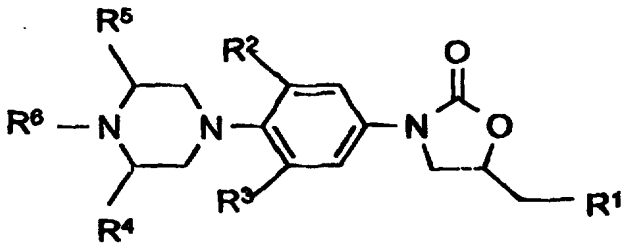
(57) Abstract



(I)

The invention concerns a compound of formula (I) wherein, for example: R^1 is of the formula -NHC(=O)R^a wherein R^a is for example (1-4C)alkyl; R^2 and R^3 are independently hydrogen or fluoro; R^4 and R^5 are independently hydrogen or methyl; R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, and optionally substituted by substituents selected from (1-4C)alkyl (optionally substituted), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro; pharmaceutically-acceptable salts, suitable N-oxides and in-vivo-hydrolysable esters thereof; processes for their preparation; pharmaceutical compositions containing them and their use as antibacterial agents.

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SUBSTITUTED PIPERAZINYL-PHENYL-OXAZOLIDINONE DERIVATIVES AND THEIR USE AS ANTI-BACTERIAL AGENTS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing an oxazolidinone ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly good activity against such pathogens.

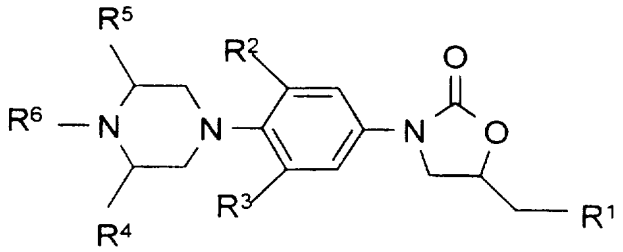
Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant streptococcus pneumoniae and multiply resistant Enterococcus faecium.

The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with nephrotoxicity and ototoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens.

The present inventors have discovered a class of antibiotic compounds containing an oxazolidinone ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams.

We have now discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics. In comparison with compounds described in the art (for example Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165) the compounds also possess a favourable toxicological profile.

Accordingly the present invention provides a compound of the formula (I)



(I)

wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, or of the formula -NHC(=O)R^a wherein R^a is hydrogen, (1-4C)alkoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or R^1 is of the formula -N(Me)C(=O)R^b wherein R^b is hydrogen, methyl or methoxy or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2;

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl (optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2),

(1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; and suitable N-oxides thereof.

In this specification the term "alkyl" includes straight chained and branched structures. For example, (1-6C)alkyl includes propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only.

In this specification a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, includes pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine.

Examples of (1-4C)alkyl include methyl, ethyl, propyl, isopropyl and tert-butyl; examples of halo include fluoro, chloro, bromo and iodo; examples of N-(1-4C)alkylcarbamoyl include methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl; examples of di-(N-(1-4C)alkyl)carbamoyl include di-(methyl)carbamoyl and di-(ethyl)carbamoyl; examples of the (1-4C)alkyl group or groups in N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl being optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl include 2-hydroxyethylaminocarbonyl, bis-(2-hydroxyethyl)aminocarbonyl, 2-methoxyethylaminocarbonyl and methoxycarbonylmethylaminocarbonyl; examples of (1-4C)alkylS(O)$_n$ include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of (1-4C)alkylS(O)$_2$amino include methylsulfonylamino and ethylsulfonylamino; examples of (2-4C)alkenyl include allyl and vinyl; examples of (1-4C)alkoxy include methoxy, ethoxy and propoxy; examples of (1-4C)alkanoylamino include formamido, acetamido and propionylamino; examples of (2-4C)alkanoylamino include acetamido and propionylamino; examples of N-(1-4C)alkylamino include methylamino and ethylamino; examples of di-(N-(1-

4C)alkyl)amino include di-N-methylamino, di-(N-ethyl)amino and N-ethyl-N-methylamino; examples of (1-4C)alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, n- and tert-butoxycarbonyl ; examples of (1-4C)alkanesulfonyloxy include methanesulfonyloxy and ethanesulfonyloxy; and examples of (1-4C)alkylaminocarbonyloxy include methylaminocarbonyloxy and ethylaminocarbonyloxy.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

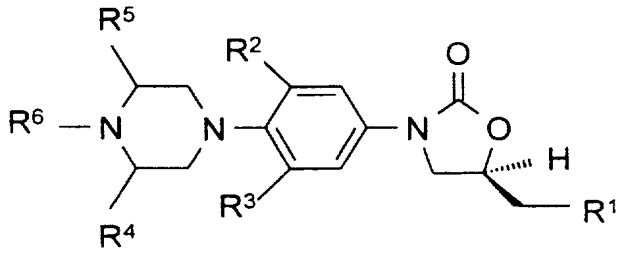
In this specification a suitable N-oxide refers to the N-oxides which may be formed on an available nitrogen atom in either the piperazine ring or in the heteroaryl ring R^b. A suitable N-oxide may be optionally in the form of a pharmaceutically-acceptable salt.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the formula (I).

An in-vivo hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An in-vivo hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino or piperazino linked from a ring nitrogen atom via methylamino to the 3- or 4-position of the benzoyl ring.

The compounds of the present invention have a chiral centre at the C-5 position of the oxazolidinone ring. The pharmaceutically active enantiomer is of the formula (IA):



(IA)

The present invention includes the pure enantiomer depicted above or mixtures of the 5R and 5S enantiomers, for example a racemic mixture. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted above could be either 5R or 5S depending upon the value of R^1. For example, when R^1 is acetamido, the enantiomer depicted above is the 5S enantiomer and when R^1 is hydroxy, the enantiomer depicted above is the 5R enantiomer.

Furthermore, some compounds of the formula (I) may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereo-isomers that possess antibacterial activity.

The invention relates to all tautomeric forms of the compounds of the formula (I) that possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

In a further aspect of the invention there is provided a compound of the formula (I) wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, or R^1 is of the formula -NHC(=O)R^a wherein R^a is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or R^1 is of the formula -$NHSO_2$(1-4C)alkyl

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl [optionally substituted by carboxy or (1-4C)alkoxycarbonyl], (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; and suitable N-oxides thereof.

In another further aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, as defined in the above aspects of the invention, except that suitable N-oxides are excluded.

In a yet further aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, as defined anywhere above, except that the following optional substituents on R^6, namely (1-4C)alkoxy, (1-4C)alkylSO_2amino, (1-4C)alkanoylamino and those N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl substituents with the (1-4C)alkyl group or groups substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl, are excluded; and the number of optional substituents on R^6 is restricted to one or two. For the avoidance of doubt, in the preceding yet further aspect of the invention suitable N-oxides are optionally excluded.

In a preferred aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, wherein the substituents R^1 to R^6 and other optional substituents mentioned above have the values disclosed hereinbefore, or any of the following values :

(a) Preferably R^1 is hydroxy, chloro, fluoro, methanesulfonyloxy, amino, azido, methoxy, methylthio, methylaminocarbonyloxy, or of the formula -NHC(=O)R^a wherein R^a is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or R^1 is of the formula -N(Me)C(=O)R^b wherein R^b is hydrogen, methyl or methoxy or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(b) More preferably R^1 is hydroxy, chloro, fluoro, methanesulfonyloxy, or of the formula -NHC(=O)R^a wherein R^a is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(c) Yet more preferably R^1 is hydroxy, or of the formula -NHC(=O)R^a wherein R^a is (1-4C)alkyl or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(d) When R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2, n is preferably 2.

(e) Yet more preferably R^1 is of the formula -NHC(=O)(1-4C)alkyl.

(f) Most preferably R^1 is acetamido.

(g) In another aspect R^1 is hydroxy.

(h) Preferably one of R^2 and R^3 is hydrogen and the other is fluoro.

(i) Preferably at least one of R^4 and R^5 is hydrogen.

(j) Preferably R^4 and R^5 are both hydrogen.

(k) Preferably the heteroaryl ring in R^6 is pyrimidine, pyridazine or pyrazine.

(l) Yet more preferably the heteroaryl ring in R^6 is pyrimidine or pyrazine.

(m) Still more preferably the heteroaryl ring in R^6 is pyrimidin-2-yl or pyrazin-2-yl.

(n) Most preferably the heteroaryl ring in R^6 is pyrimidin-2-yl.

(o) Preferably optional substituents on the heteroaryl ring are not positioned in the 2-position relative to the ring carbon atom which is attached to the piperazine ring.

(p) Preferably the optional substituents on the heteroaryl ring are independently selected from (1-4C)alkyl (optionally substituted by (1-4C)alkoxy or (2-4C)alkanoylamino), (1-4C)alkylthio, halo, carboxy, (1-4C)alkoxycarbonyl, and carbamoyl.

(q) More preferably the optional substituents on the heteroaryl ring are independently selected from methyl or ethyl (each optionally substituted by methoxy, ethoxy or acetamido), methylthio, ethylthio, chloro, bromo, carboxy, methoxycarbonyl, ethoxycarbonyl and carbamoyl.

(r) Yet more preferably the optional substituents on the heteroaryl ring are independently selected from methyl, ethyl, methoxymethyl, 2-(acetamido)ethyl, methylthio, chloro, bromo, carboxy, methoxycarbonyl and carbamoyl.

(s) Most preferably the optional substituents on the heteroaryl ring are independently selected from (1-4C)alkyl (preferably methyl), halo (preferably chloro), nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

(t) Preferably the heteroaryl ring is unsubstituted or substituted by one substituent.

(u) Most preferably the heteroaryl ring is unsubstituted.

Therefore, especially preferred compounds of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, are those defined above wherein

R^1 is acetamido, one of R^2 and R^3 is hydrogen and the other is fluoro, R^4 and R^5 are both hydrogen, R^6 is pyrimidine or pyrazine and the optional substituents on the heteroaryl ring are independently selected from methyl, chloro, nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

Particular compounds of the present invention include :

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

Further particular compounds of the present invention include :

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(3-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

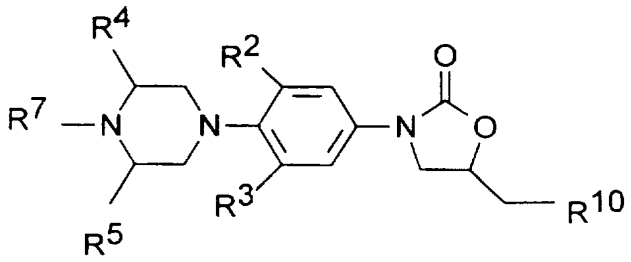
Especially preferred compounds of the invention include

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

In a further aspect the present invention provides a process for preparing a compound of the formula (I), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof. The compounds of the formula (I), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof may be prepared by deprotecting a compound, containing at least one protecting group, of the formula (II), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof :



(II)

wherein R^2, R^3, R^4 and R^5 are as hereinabove defined, R^7 is R^6 or protected R^6 and R^{10} is R^1 or protected R^1 and thereafter if necessary forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, tert-butyl); lower alkoxy lower alkyl groups (eg methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (eg allyl); lower alkanoyl groups (eg acetyl); lower alkoxycarbonyl groups (eg tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (eg trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl); aryl lower alkyl groups (eg benzyl) groups; and triaryl lower alkyl groups (eg triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, eg p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (eg tert-butoxycarbonyl); lower alkenyloxycarbonyl (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (eg trimethylsilyl and tert-butyldimethylsilyl); alkylidene (eg methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, metal- or enzymically-catalysed hydrolysis, for groups such as o-nitrobenzyloxycarbonyl, photolytically and for groups such as silyl groups, fluoride.

Examples of protecting groups for amide groups include aralkoxymethyl (eg. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (eg. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (eg. trimethylsilyl, tert-butyldimethylsilyl,

by reacting the amide with the appropriate chloride and removing with acid, or in the case of the silyl containing groups fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

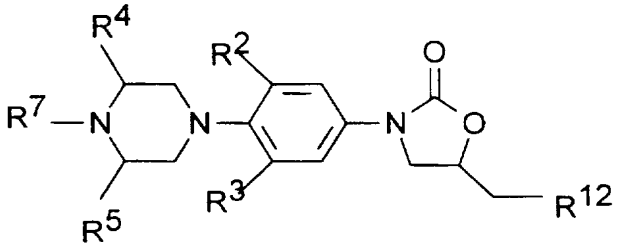
For further examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons).

In another aspect of the present invention the compounds of the formulae (I) and (II), pharmaceutically-acceptable salts, suitable N-oxides and in-vivo hydrolysable esters thereof can be prepared:

(a) by modifying a substituent in or introducing a substituent into another compound of formula (I) or (II);

(b) when R^1 or R^{10} is of the formula - $NHS(O)_n$(1-4C)alkyl, wherein n is 1 or 2, by oxidising a compound of the formula (I) wherein n is 0 or, when n is 2 by oxidising a compound of the formula (I) or (II) wherein n is 1;

(c) when R^1 or R^{10} is azido, by reacting a compound of the formula (III) with a source of azide:



(III)

(d) when R^1 or R^{10} is amino, by reducing a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido;

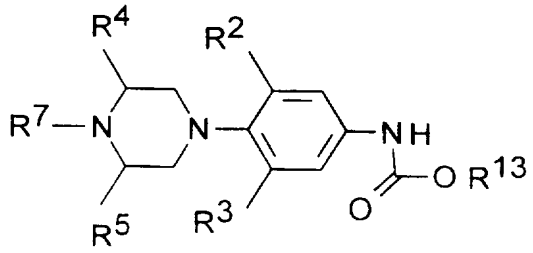
(e) when R^1 or R^{10} is of the formula -$NHC(=O)R^a$, by introducing -$C(=O)R^a$ into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

(f) when R^1 or R^{10} is of the formula -$NHS(O)_n$ (1-4C)alkyl by introducing -$S(O)_n$ (1-4C)alkyl into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

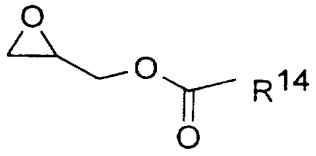
(g) when R^1 or R^{10} is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(h) when R^1 or R^{10} is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (III);

(i) when R^1 or R^{10} is hydroxy, by reacting a compound of the formula (IV) with a compound of the formula (V):

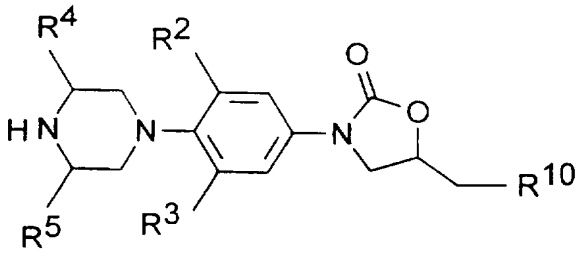


(IV)



(V)

(j) by reacting a compound of the formula (VI) with a compound of the formula (VII):



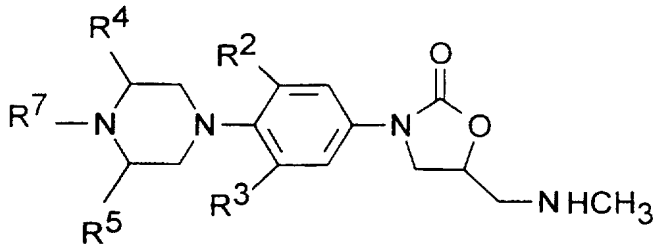
(VI)

R^7-L^1

(VII)

(k) when R^{10} is of the formula -N(CO_2R^{15})CO(1-4C)alkyl; from a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy;

(l) when R^1 or R^{10} is of the formula -N(Me)C(=O)R^b, by introducing the group -C(=O)R^b into a compound of the formula (VIII):



(VIII)

and

(m) when a suitable N-oxide is required, by preparation directly from a corresponding parent compound of the formula (I) or (II), or by assembly from suitable N-oxide starting materials;

wherein R^2 - R^5 and R^7 and R^{10} are as hereinabove defined. R^{12} is mesyloxy or tosyloxy, R^{13} is (1-6C)alkyl or benzyl, R^{14} is (1-6C)alkyl, R^{15} is (1-4C)alkyl or benzyl and L^1 is a leaving goup and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester.

Methods for converting substituents into other substituents are known in the art. For example, an alkylthio group may be oxidised to an alkylsulfinyl or alkysulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, an amino group converted to an acetamido or sulfonamido group, a hydroxy group alkylated to a methoxy group, a carboxy group converted to a carbamoyl group, an N-(1-4C)alkylcarbamoyl or di-(N-(1-4C)alkyl)carbamoyl group, or a bromo group converted to an alkylthio group. Also for example, a chloro group may be introduced at an unsubstituted position in R^7, or a chloro group may be removed from R^7 (by, for example, hydrogenation as in Examples 9 and 31).

Compounds of the formula (I) or (II) wherein R^1 or R^{10} is $-NHS(O)_n$ (1-4C)alkyl can be prepared by oxidising a compound of the formula (I) or (II) with standard reagents known in the art for the oxidation of a thio group to a sulfinyl or sulfonyl group. For example, a thio group may be oxidised to a sulfinyl group with a peracid such as m-chloroperoxybenzoic acid and oxidising agents such as potassium permanganate will

convert a thio group to a sulfonyl group. Compounds of the formula (I) or (II) wherein R^1 or R^{10} is -NHS(1-4C)alkyl can be prepared by reacting compounds of the formula (I) or (II) wherein R^1 or R^{10} is amino with a reagent such as (1-4C)alkylSCl.

A compound of the formula (I) or (II) wherein R^1 or R^{10} is azido may be prepared, for example, by reacting a compound of the formula (III) with sodium azide in an inert solvent such as DMF in a temperature range of ambient to 100°C, normally in the region of 75°C - 85°C. A compound of the formula (III) may be prepared by converting the hydroxy group in a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy into a tosyloxy or mesyloxy group by standard methods known in the art. For example, by reacting the compound of the formula (I) or (II) with tosyl chloride or mesyl chloride in the presence of a mild base such as triethylamine, or pyridine.

Suitable reducing agents for reducing azido to amino in a compound of the formula (I) or (II) include triethylamine/hydrogen sulfide, triphenylphosphine or phosphite ester, or hydrogen in the presence of a catalyst. More specifically the reduction of the azido group may be carried out by heating it in an aprotic solvent, such as 1,2-dimethoxyethane, in the presence of $P(OMe)_3$ and subsequently heating in 6N aqueous hydrochloric acid, or reacting it with hydrogen in the presence of palladium on carbon in a solvent such as DMF or ethyl acetate. For further details on the reduction of azides to amines see USP 4,705,799. The azido compound may be reduced and converted to a compound of the formula (I) or (II), wherein R^1 or R^{10} is acetamido, in situ using acetic anhydride in DMF.

When R^a is (1-4C)alkyl, the group -C(=O)(1-4C)alkyl may be introduced into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino by standard acetylation procedures. For example, the amino group may be acetylated to give an acetamido group using the Schotten-Baumann procedure i.e. reacting the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino with acetic anhydride in aqueous sodium hydroxide and THF in a temperature range of 0°C to ambient temperature. Preferably the acylation is carried out in situ following the catalytic hydrogenation of a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido, by performing the hydrogenation in the presence of acetic anhydride (for example using similar methods to those used in Example 15).

When R^a is hydrogen, the -CHO group may be introduced into the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino (amino compound) by reacting the latter

compound with formic acetic anhydride, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature, or by reacting it with ethyl formate in an inert organic solvent in the temperature range of 50-100°C.

When R^a is (1-4C)alkoxy, the -COO(1-4C)alkyl group may be introduced into the amino compound by reacting the latter compound with (1-4C)alkyl chloroformate, in the presence of an organic base such as triethylamine, in an organic solvent such as dichloromethane and in a temperature range of 0°C to ambient temperature.

When R^a is amino, the $-CONH_2$ group may be introduced into the amino compound by reacting the latter compound either with potassium cyanate in aqueous acid (eg hydrochloric acid) in a temperature range of ambient temperature to 40°C or with phenyl carbamate in glyme at reflux.

When R^a is chloromethyl, dichloromethyl, cyanomethyl or methoxymethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with the appropriate acid chloride under standard conditions. The acid chloride may be prepared from the appropriate acid. When R^a is acetylmethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with diketene, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature.

Alternatively, the amino compound may be reacted with the appropriate acid anhydride, in dichloromethane or THF, in the presence of an organic base such as triethylamine and in a temperature range of 0°C to ambient temperature, or the amino compound may be reacted with the appropriate acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and an organic base such as triethylamine, in an organic solvent such as dichloromethane, in a temperature range of 0°C to ambient temperature.

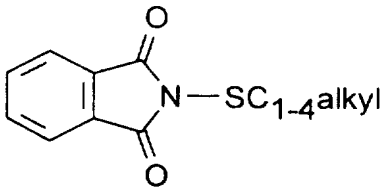
When R^a is methylamino, the -CONHMe group may be introduced into the amino compound by reacting the latter compound with methyl isocyanate in an organic solvent such as THF or acetonitrile, in a temperature range of 0°C to ambient temperature.

When R^a is dimethylamino, the $-CONMe_2$ group may be introduced into the amino compound my reacting the latter compound with dimethylcarbamoyl chloride and triethylamine in an organic solvent such as THF or acetonitrile, in a temperature range of 0°C to ambient temperature.

Standard reaction conditions for the conversion of a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino to a compound of the formula (I) or (II) wherein R^1 or R^{10} is sulfonamido are known in the art. For example, a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino could for example be converted to a compound of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylSO_2NH- by reacting the former compound with a sulfonyl chloride, for example, mesyl chloride, in a mild base such as pyridine.

Alternatively compounds of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylSO_2NH- or (1-4C)alkylSONH- may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 is amino with a compound of the formula (1-4C)alkylSO_2L^2 or (1-4C)SOL^2 wherein L^2 is a phthalimido group.

The phthalimido compound may be prepared by oxidising a compound of the formula (IX):



(IX)

with standard oxidising agents known for the conversion of a thio group to a sulfinyl or sulfonyl group.

Compounds of the formula (IX) can be prepared by reacting phthalimide with an alkylthiochloride ((1-4C)alkylSCl).

A compound of the formula (I) or (II) wherein R^1 or R^{10} is fluoro may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy (hydroxy compound) with a fluorinating agent such as diethylaminosulfur trifluoride in an organic solvent such as dichloromethane in the temperature range of 0°C to ambient temperature.

When R^1 or R^{10} is chloro, the compound of the formula (I) or (II) may be formed by reacting the hydroxy compound with a chlorinating agent. For example, by reacting the hydroxy compound with thionyl chloride in a temperature range of ambient temperature to reflux, optionally in a chlorinated solvent such as dichloromethane or by reacting the hydroxy compound with carbon tetrachloride/triphenyl phosphine in dichloromethane, in a temperature range of 0°C to ambient temperature.

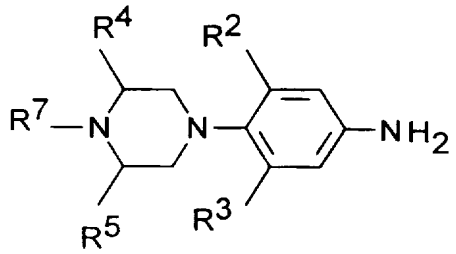
The (1-4C)alkanesulfonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkanesulfonyl chloride in the presence of a mild base such as triethylamine or pyridine.

The (1-4C)alkylaminocarbonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkyl cyanate in an organic solvent such as THF or acetonitrile, in the presence of triethylamine, in a temperature range of 0°C to 50°C.

A compound of the formula (I) or (II) wherein R^1 or R^{10} is chloro may also be prepared from a compound of the formula (III), by reacting the latter compound with lithium chloride and crown ether, in a suitable organic solvent such as THF, in a temperature range of ambient temperature to reflux. A compound of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylthio or (1-4C)alkoxy may be prepared by reacting the compound of the formula (III) with sodium thio(1-4C)alkoxide or sodium (1-4C)alkoxide respectively, in an alcohol or THF, in a temperature range of 0°C to reflux.

Compounds of the formulae (IV) and (V) are conveniently reacted together in the presence of a strong base such as butyl lithium, lithium bistrimethylsilylamide, sodium hydride, lithium tert-butoxide or lithium diisopropylamide. The reaction is conveniently carried out in an inert solvent such as tetrahydrofuran (THF), dimethylformamide (DMF), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidone in a temperature range of -78°C to -50°C for the deprotonation and cyclisation. Suitable values for R^{13} include ethyl and benzyl and suitable values for R^{14} include ethyl and n-propyl, preferably n-propyl.

A compound of the formula (IV) is conveniently prepared by reacting a chloroformate of the formula ($ClCOOR^{13}$) with a compound of the formula (IVA):

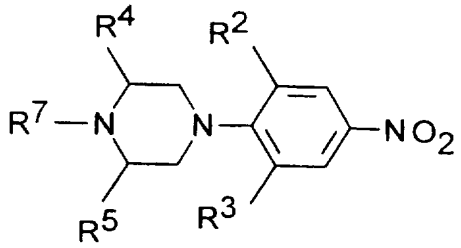


(IVA)

wherein R^2 - R^5 and R^7 are as hereinabove defined. The reaction is conveniently carried out in the presence of an inorganic or organic base such as sodium bicarbonate or an amine base

such as dimethylaniline, the former in a solvent such as acetone/water and the latter in an organic solvent such as THF, toluene, DMF or acetonitrile.

A compound of the formula (IVA) may be prepared by reducing a compound of the formula (IVB):

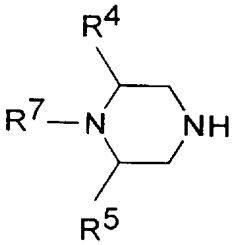


(IVB)

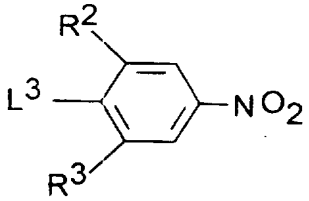
wherein R^2 - R^5 and R^7 are as hereinabove defined.

Many reduction methods suitable for the reduction of a nitro to an amino group are known in the art, for example catalytic hydrogenation, metal reductions or with reducing agents such as sodium hydrosulfite. Suitable catalysts in catalytic hydrogenation include Raney nickel, platinum metal and its oxide, rhodium, palladium-on-charcoal and Wilkinson's catalyst $RhCl(Ph_3P)_3$. Catalyst hydrogenation is conveniently carried out in the temperature range 0°C - 150°C, but preferably at ambient temperature at slightly above atmospheric pressure.

A compound of the formula (IVB) is conveniently prepared by reacting together compounds of the formulae (X) and (IVC):



(X)



(IVC)

wherein R^2 - R^5 and R^7 are as hereinabove defined and L^3 is a leaving group, preferably halo and in particular fluoro.

The reaction between compounds of the formulae (X) and (IVC) is carried out in the presence of an organic or inorganic base such as sodium bicarbonate, potassium carbonate or an amine base such as diisopropylethylamine, in an inert solvent such as acetonitrile, DMF, DMPU or N-methylpyrrolidone, in a temperature range of 50°C - 150°C.

Compounds of the formula (X) are conveniently prepared by reacting the appropriate piperazine ring with a compound of the formula (VII) using similar conditions to those described (see later) for the reaction between compounds of the formulae (VI) and (VII). It may be advantageous to protect one of the ring nitrogen atoms in the piperazine ring prior to the reaction with a compound of the formula (VII) and remove the protecting group thereafter. For compounds of the formula VII in which L^1 is not activated for displacement, more vigorous reaction conditions may be necessary, for example the Buchwald reaction using a strong base (such as potassium tert-butoxide or lithium bistrimethylsilylamide) and a catalyst (such as Pd(0)), as illustrated in Example 15. It is within the ordinary skill of an organic chemist to recognise when such reaction conditions are necessary.

Alternatively, a compound of the formula (IVB) may be formed by reacting the appropriate piperazine ring in which one of the ring nitrogen atoms is protected (with for example a (1-4C)alkoxycarbonyl group) with a compound of the formula (IVC). The ring nitrogen-protecting group may then be removed and R^7 introduced onto the ring nitrogen by reacting the product of the deprotection with a compound of the formula (VII).

Compounds of the formula (VII) may be prepared by introducing substituents into or modifying substituents in a known optionally substituted heteroaryl ring. Such conversions are well known to the skilled chemist, for example a cyano group may be hydrolysed to a carboxy group which in turn may be converted to a carbamoyl or alkoxycarbonyl group or reduced to a hydroxymethyl group; an amino group may be acylated to an alkanoylamino group; a thio group may be alkylated to an alkylthio group which in turn may be oxidised to an alkylsulfinyl or alkylsulfonyl group and a hydroxyalkyl group may be alkylated to an alkoxyalkyl group.

The reaction between compounds of the formulae (VI) and (VII) is conveniently carried out in the presence of a base, in an aprotic polar solvent; preferably one with a high boiling point, such as acetonitrile or dimethylformamide. Suitable bases include amine bases

such as triethylamine. The reaction is preferably carried out in the temperature range 50°C - 150°C. Suitable leaving groups for this reaction include halo, (1-4C)alkylthio, (1-4C)alkanesulfinyl, (1-4C)alkanesulfonyl or phenoxy. Preferably the leaving group is fluoro, chloro or (1-4C)alkanesulfonyl such as methanesulfonyl.

A compound of the formula (II) wherein R^{10} is of the formula $-N(CO_2R^{15})CO(1\text{-}4C)alkyl$ is conveniently prepared by reacting a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy with an amide of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ under Mitsunobu conditions. For example, in the presence of tri-n-butylphosphine and 1,1'-(azodicarbonyl)dipiperidine in an organic solvent such as THF, and in the temperature range 0°C - 60°C, but preferably at ambient temperature. Details of analogous Mitsunobu reactions are contained in Tsunoda et al. Tet. Letts., 34, 1639, (1993). Amides of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ may be prepared by standard procedures of organic chemistry which are within the ordinary skill of an organic chemist.

The group $-C(=O)R^b$ may be introduced into a compound of the formula (VIII) to give the appropriate compound of the formula (I) or (II) wherein R^1 or R^{10} is of the formula $-N(Me)C(=O)R^b$ using similar methods to those described for the introduction of the appropriate $-C(=O)R^a$ group into the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino.

The compound of the formula (VIII) may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino with formaldehyde and sodium borohydride or sodium cyanoborohydride, in an alcholic solvent such as ethanol or isopropanol, in a temperature range of 0°C to ambient temperature.

Suitable N-oxides of compounds of the formula (I) or (II) may be prepared directly from a corresponding parent compound of the formula (I) or (II) using techniques well known to the ordinary skilled organic chemist, such as, for example, using a peracid (such as m-chloroperbenzoic acid) or perphthalic acid in a suitable solvent (such as dioxan or a mixture of water and THF) at a suitable temperature (such as ambient temperature). Example 36 also illustrates possible suitable reagents and conditions for preparing suitable N-oxides. The preparation of suitable N-oxides by assembly from suitable N-oxide starting materials and the

use of the processes described in this specification is within the skill of the ordinary skilled organic chemist, and is illustrated by, for example, Example 18.

It is also possible to convert one R^7 group into another R^7 group as a final step in the preparation of a compound of the formula (I) or (II) (see the specific examples).

When an optically active form of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using an optically active starting material, or by resolution of a racemic form of the compound or intermediate using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof for the therapeutic treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered with one or more known drugs selected from other clinically useful antibacterial agents (for example ß-lactams or aminoglycosides). These may include penicillins, for example oxacillin or flucloxacillin and carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness against methicillin-resistant staphylococci. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein product (BPI) or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100mg and 1g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of the compound of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

Antibacterial Activity

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive

organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity against enterococci, pneumococci and methicillin resistant strains of S. aureus and coagulase negative staphylococci. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The antibacterial properties of the compounds of the invention may also be demonstrated in-vivo in conventional tests. No overt toxicity or other untoward effects are observed when compounds of the formula I are so tested at conventional daily dose levels.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms.

Organism		MIC (µg/ml) Example 1
Staphylococcus aureus:		
	Oxford	0.5
	Novb. Res	1.0
	MRQR	1.0
Coagulase Negative Staphylococci		
	MS	0.25
	MR	0.5
Streptococcus pyogenes		
	C203	1.0

Enterococcus faecalis	1.0
Bacillus subtilis	0.25

Novb. Res = Novobiocin resistant

MRQR = methicillin resistant quinolone resistant

MR = methicillin resistant

MS = methicillin sensitive

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-26°C and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of end-products of the formula I were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected];

(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis; and

(vii) in which :-

®	is a Trademark
DMF	is N,N-dimethylformamide
DMA	is N,N-dimethylacetamide
TLC	is thin layer chromatography
DMSO	is dimethylsulfoxide
$CDCl_3$	is deuterated chloroform
MS	is mass spectroscopy
ESP	is electrospray
THF	is tetrahydrofuran
TFA	is trifluoroacetic acid
NMP	is N-methylpyrrolidone
dba	is dibenzylideneacetone
DMPU	is N,N-dimethylpropyleneurea.

Example 1 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 1.5 trifluoroacetate salt (500 mg, 1 mM) was dissolved in ethanol (20 ml). 2-Chloropyrimidine (125 mg, 1.1 mM) was added, followed by triethylamine (0.36 ml, 2.6 mM) and water (2 ml, to aid solubility), and the solution stirred at ambient temperature for 24 hours. Further 2-chloropyrimidine (62 mg, 0.5 mM) was added, and the mixture refluxed for 16 hours. The solution was evporated to dryness, water (20 ml) added to the residue, and the pH adjusted to 12 with 1N sodium hydroxide solution. The solution was extracted with ethyl acetate (2 x 20 ml), and the combined organic layers dried over magnesium sulfate, and evaporated. The white residue was chromatographed on silica, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (270 mg).

MS (ESP): 415 (MH^+)

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.03 (t, 4H); 3.40 (t, 2H); 3.70 (dd, 1H); 3.87 (t, 4H); 4.08 (t, 1H); 4.69 (m, 1H); 6.65 (t, 1H); 7.09 (t, 1H); 7.17 (dd, 1H); 7.49 (dd, 1H); 8.19 (t, 1H); 8.38 (d, 2H).

The N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 1.5 trifluoroacetate salt starting material was prepared as follows :-

N-[(5S)-3-(3-Fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (PCT patent application WO 93/23384 Example 1 (j), 1 g, 2.3 mM) was dissolved in dichloromethane (50 ml) under argon, and cooled in an ice-bath. TFA (12.7 ml) was added, and the mixture stirred at 0°C for 30 minutes. Solvent was evaporated, and the residue treated four times by evaporation with 30 ml portions of ethyl acetate to remove TFA. The required starting material as a remaining solid analysed for 1.5 moles of residual TFA.

MS (ESP): 337 (MH^+).

NMR (DMSO-D6 + CD_3COOD) δ: ~1.8 (obscured by solvent); 3.21 (t, 4H); 3.28 (t, 4H); 3.45 (t, 2H); 3.74 (dd, 1H); 4.19 (t, 1H); 4.73 (m, 1H); 7.12 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H).

Example 2 : N-[(5S)-3-(3-Fluoro-4-(4-(5-chloropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (6.73 g, 15 mM) was dissolved in DMA (100 ml). Triethylamine (4.37 ml, 31.4 mM) was added, and the whole mixture stirred at ambient temperature under argon for 10 minutes. 2,5-Dichloropyrimidine (2.23 g, 15 mM) was added, and the solution heated to 100°C for 8 hours. After cooling, solvent was evaporated, and the residue slurried with water for 1 hour. Solid was filtered, washed with water (2 x 100 ml) and dried. The residue was chromatographed twice on silica by dry flash chromatography, eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (3.04 g).

Microanalysis: Found: C, 53.4; H, 4.8; N, 18.6%.

Required for $C_{20}H_{22}ClFN_6O_3$: C, 53.6; H, 4.9; N, 18.7%.

MS (ESP): 449 (MH^+) for $C_{20}H_{22}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.02 (t, 4H); 3.39 (t, 2H); 3.69 (dd, 1H); 3.86 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.19 (t, 1H); 8.43 (s, 2H).

The N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt starting material was prepared as follows :-

N-[(5S)-3-(3-Fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (PCT patent application WO 93/23384, 34 g, 78 mM) was dissolved in dichloromethane (500 ml), and cooled in an ice-bath. TFA (50 ml) was added, and the mixture stirred at 0°C for 1.5 hours. Solvent was evaporated, and the residual oil dissolved in ethyl acetate (40 ml). Diethyl ether was added to turbidity (~75 ml), and the solution left to crystallise. Filtration gave product as the mono trifluroacetate salt (32.5 g).

Microanalysis: Found : C, 47.5; H, 5.0; N, 11.8

$C_{18}H_{22}F_4N_4O_5$ requires : C, 48.0; H, 4.9; N, 12.4

Example 3 : N-[(5S)-3-(3-Fluoro-4-(4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (90 mg, 0.2 mM) was dissolved in DMA (3 ml). Triethylamine (58 µL, 0.42 mM) was stirred in, then 2-chloro-4,6-dimethylpyrimidine (28.5 mg, 0.2 mM) was added, and the solution heated under argon at 160°C for 5 hours. After cooling, solvent was evaporated, and the residue chromatographed on a 5 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 3% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (50 mg).

MS (ESP): 443 (MH^+) for $C_{22}H_{27}FN_6O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 2.31 (s, 6H); 3.09 (t, 4H); 3.60-3.71 (m, 2H); 3.75 (dd, 1H); 3.99 (t, 4H); 4.02 (t, 1H); 4.76 (m, 1H); 6.09 (brt, 1H); 6.29 (s, 1H); 6.95 (t, 1H); 7.08 (dd, 1H); 7.44 (dd, 1H).

Example 4 : N-[(5S)-3-(3-Fluoro-4-(4-(3,5-dichloropyridazin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) was dissolved in DMA (15 ml). Triethylamine (306 µL, 2.2 mM) was stirred in, then 3,4,5-trichloropyridazine (184mg, 1 mM) was added, and the solution heated to 100°C for 16 hours. After cooling, the mixture was diluted with water (50 ml) and extracted weith ethyl acetate (2 x 25 ml). The combined extracts were dried over magnesium sulfate, evaporated, and the residue chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (280 mg).

MS (ESP): 483 (MH^+) for $C_{20}H_{21}Cl_2FN_6O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.13 (t, 4H); 3.39 (t, 2H); 3.57 (t, 4H); 3.69 (dd, 1H); 4.06 (t, 1H); 4.70 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 8.21 (brt, 1H); 9.01 (s, 1H).

Example 5 : N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (0.9 g, 2 mM) was dissolved in NMP (25 ml), triethylamine (0.28 ml, 2 mM) and 3,6-dichloropyridazine (298 mg, 2 mM) were added, and the solution heated to 110°C for 24 hours. After cooling, solvent was evaporated, and the residue chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (165 mg).

MS (ESP): 449 (MH^+) for $C_{20}H_{22}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.06 (t, 4H); 3.39 (t, part obscured, 2H); 3.73 (t + m, 5H); 4.07 (t, 1H); 4.68 (m, 1H); 7.09 (t, 1H); 7.17 (dd, 1H); 7.42 (d, 1H); 7.48 (dd, 1H); 7.54 (d, 1H); 8.21 (t, 1H).

Example 6 : N-[(5S)-3-(3-Fluoro-4-(4-(pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (247 mg, 0.55 mM) was dissolved in ethanol (25 ml), and treated with triethylamine (77 µL, 0.55 mM). Palladium catalyst (10% on charcoal, 100 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 2.5% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (79 mg).

MS (ESP): 415 (MH^+) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.06 (t, 4H); 3.38 (t, 2H); 3.70 (br, 5H); 4.06 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.16 (dd, 1H); 7.29 (d, 1H); 7.38 (dd, 1H); 7.49 (dd, 1H); 8.18 (brt, 1H); 8.55 (d, 1H).

Example 7 : N-[(5S)-3-(3-Fluoro-4-(4-(6-carbamoylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (225mg, 0.5 mM) was dissolved in DMA (15 ml), triethylamine (101 mg, 1 mM) was added, and the whole mixture stirred at ambient temperature under argon for 15 minutes. 3-Chloropyridazine-6-carboxamide (Heterocycles, 1992, 34, 225; 79 mg, 0.5 mM) was added, and the solution heated to 120°C for 6 hours. After cooling, solvent was evaporated, the residue dissolved in dichloromethane, and washed with saturated sodium bicarbonate solution. The organic layer was dried (magnesium sulfate) and evaporated, and the residue chromatographed on silica, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (150 mg).

MS (ESP): 458 (MH^+) for $C_{21}H_{24}FN_7O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.08 (t, 4H); 3.37 (t, 2H); 3.69 (dd, 1H); 3.86 (t, 4H); 4.07 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.39 (d, 1H); 7.50 (dd, 1H); 7.53 (brs, 1H); 7.86 (d, 1H); 8.14 (brs, 1H); 8.21 (brt, 1H).

Example 8 : N-[(5S)-3-(3-Fluoro-4-(4-(6-*n*-butyloxycarbonylyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the method and scale of Example 7, but replacing the 3-chloropyridazine-6-carboxamide

with n-butyl 3-chloropyridazine-6-carboxylate (PCT patent application WO 96/03380; 108 mg, 0.5 mM), the title product (162 mg) was obtained after chromatography as in Example 7.

MS (ESP): 515 (MH^+) for $C_{25}H_{31}FN_6O_5$

NMR (DMSO-D6) δ: 0.92 (t, 3H); 1.40 (hextet, 2H); 1.68 (quintet, 2H); 1.81 (s, 3H); 3.09 (t, 4H); 3.38 (t, 2H); 3.69 (dd, 1H); 3.89 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.20 (dd, 1H); 7.33 (d, 1H); 7.50 (dd, 1H); 7.82 (d, 1H); 8.20 (brt, 1H).

Example 9 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(3-chloropyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 25, 0.67 g, 1.5 mM) was dissolved in a mixture of ethanol (100 ml) and DMF (50 ml), and treated with triethylamine (208 µL, 1.5 mM). Palladium catalyst (10% on charcoal, 100 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue azeotroped dry with toluene (100 ml). The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (235 mg).

MS (ESP): 415 (MH^+) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.06 (t, 4H); 3.39 (t, 2H); 3.71 (t + m, 5H); 4.07 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 7.85 (d, 1H); 8.10 (t, 1H); 8.20 (brt, 1H); 8.39 (d, 1H).

Examples 10-14

Examples 10-14 were all prepared using the following procedure :-

Triethylamine (2 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in DMA (20 ml) under argon. The resultant mixture was stirred at room temperature for 15 minutes, and the appropriate halo-heterocycle (1 mM) added. The mixture was heated with stirring at 110°C for 6 hours. After cooling the solvent was removed by centrifugal evaporation. The residue was mixed with water and the solid filtered. The crude solids were dissolved or slurried in dichloromethane and purified by silica Mega Bond Elut® chromatography, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. The relevant fractions were combined and the solvent evaporated to give the following compounds :-

Example 10 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylaminocarbonylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 472 (MH^+) for $C_{22}H_{26}FN_7O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.79 (d, 3H); 3.08 (t, 4H); 3.38 (t, 2H); 3.69 (dd, 1H); 3.84 (t, 4H); 4.06 (t, 1H); 4.69 (m, 1H); 7.09 (t, 1H); 7.18 (dd, 1H); 7.38 (d, 1H); 7.50 (dd, 1H); 7.85 (d, 1H); 8.19 (brt, 1H); 8.77 (brq, 1H).

The appropriate halo-heterocycle, 3-chloro-6-methylaminocarbonylpyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (429 mg, 2 mM) was dissolved in ethanol (10 ml), and a solution of methylamine in ethanol (2M, 4 ml) added. The mixture was stirred at ambient temperature for 1 hour, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 3% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (304 mg).

NMR (DMSO-D6) δ: 2.81 (d, 3H); 8.06 (d, 1H); 8.20 (d, 1H); 9.17 (brs, 1H).

Example 11 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(2-methoxyethylaminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 516 (MH^+) for $C_{24}H_{30}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.09 (t, 4H); 3.26 (s, 3H); 3.39 (t, 2H); 3.47 (m, 4H); 3.69 (dd, 1H); 3.88 (t, 4H); 4.08 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.50 (dd, 1H); 7.86 (d, 1H); 8.20 (brt, 1H); 8.70 (brs, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(2-methoxyethylaminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (429 mg, 2 mM) was dissolved in ethanol (10 ml), and 2-methoxyethylamine (150 mg, 2 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent then removed. The residue was chromatographed on a

10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (76 mg).

MS (ESP): 216 (MH^+) for $C_8H_{10}ClN_3O_2$

NMR (DMSO-D6) δ: 3.26 (s, 3H); 3.49 (m, 4H); 8.08 (d, 1H); 8.21 (d, 1H); 9.14 (brs, 1H).

Example 12 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(2-hydroxyethylaminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 502 (MH^+) for $C_{23}H_{28}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.08 (t, 4H); 3.37 (m, 4H); 3.51 (q, 2H); 3.69 (dd, 1H); 3.85 (t, 4H); 4.07 (t, 1H); 4.67 (m, 1H); 4.74 (t, 1H); 7.09 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.49 (dd, 1H); 7.86 (d, 1H); 8.20 (t, 1H); 8.67 (t, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(2-hydroxyethylaminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and 2-hydroxyethylamine (488 mg, 8 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (637 mg).

MS (ESP): 202 (MH^+) for $C_7H_8ClN_3O_2$

NMR (DMSO-D6) δ: 3.39 (q, 2H); 3.55 (q, 2H); 4.75 (t, 1H); 8.08 (d, 1H); 8.21 (d, 1H); 9.08 (brt, 1H).

Example 13 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(*bis*-(2-hydroxyethyl)aminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 546 (MH^+) for $C_{25}H_{32}FN_7O_6$

^{1}H NMR (DMSO - D6) : 1.83 (s, 3H); 3.08 (t, 4H); 3.40 (t, 2H); 3.49 (t, 2H); 3.55 (overlapping, 8H); 3.69 (dd, 1H); 3.81 (t, 3H); 4.08 (t, 1H); 4.69 (m, 1H); 4.78 (t, 1H); 7.12 (t, 1H); 7.19 (t, 1H); 7.38 (d, 1H); 7.51 (dd, 1H); 7.55 (t, 1H); 8.19 (t, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(*bis*-(2-hydroxyethyl)aminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and bis-(2-hydroxyethyl)amine (488 mg, 8 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (637 mg).

MS (ESP): 202 (MH^+) for $C_7H_8ClN_3O_2$

NMR (DMSO-D6) δ: 3.39 (q, 2H); 3.55 (q, 2H); 4.75 (t, 1H); 8.08 (d, 1H); 8.21 (d, 1H); 9.08 (brt, 1H).

Example 14 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methoxycarbonylmethylaminocarbonyl)-pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 530 (MH^+) for $C_{24}H_{28}FN_7O_6$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.10 (t, 4H); 3.37 (t, 2H); 3.63 (s, 3H); 3.69 (dd, 1H); 3.87 (t, 4H); 4.03 (d, 2H); 4.07 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.50 (dd, 1H); 7.86 (d, 1H); 8.20 (t, 1H); 9.13 (t, 1H).

The appropriate haloheterocycle, 3-chloro-6-methoxycarbonylmethylaminocarbonyl-pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and glycine methyl ester hydrochloride (1 g, 8 mM), and triethylamine (808 mg, 8 mM) added. The mixture was stirred at ambient temperature for 18 hours, and solvent removed. The residue was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a

gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (85 mg). NMR (DMSO-D6) δ: 3.65 (s, 3H); 4.08 (d, 2H); 8.13 (d, 1H); 8.23 (d, 1H); 9.58 (brt, 1H).

Example 15 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

(5R)-5-Azidomethyl-3-(3-fluoro-4-(4-pyrimid-5-ylpiperazin-1-yl)phenyl)oxazolidin-2-one (430 mg, 1.08 mM) was dissolved in DMF (25 ml) and the solution purged with argon. Palladium (10% on carbon, 50 mg) was added, followed by acetic anhydride (240 μL, 2.16 mM) and the mixture hydrogenated at ambient temperature under hydrogen confined in a balloon for 6 hours. The mixture was filtered through celite, evaporated to dryness, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (340 mg).

MS (ESP): 415 (MH^+) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.08 (t, 4H); 3.39 (m, 6H); 3.68 (dd, 1H); 4.07 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 8.20 (t, 1H); 8.53 (s, 2H); 8.61 (s, 1H).

The (5R)-5-azidomethyl-3-(3-fluoro-4-(4-pyrid-2-ylpiperazin-1-yl)phenyl)oxazolidin-2-one used as starting material was prepared as follows :-

Tris(dba)dipalladium (1.0 g, 1.09 mM) was added to a degassed, stirred solution of 5-bromopyrimidine (12.19 g, 77 mM), *N*-benzylpiperazine (40.5 g, 0.23 M), and tri-*o*-tolylphosphine (1.29 g, 4.24 mM) in toluene (500 ml) under argon. A solution of lithium bis(trimethylsilylamide) (1M in THF, 230 ml) was added dropwise with stirring at ambient temperature. The mixture was then heated with stirring at 100°C for 5 hours. After cooling, the mixture was partitioned between dilute hydrochloric acid (2N, 500ml) and diethyl ether (500 ml). The aqueous phase was separated, made basic with aqueous sodium hydroxide, and extracted with diethyl ether (3 x 500 ml). The combined organic extracts were washed with brine (250 ml), dried over magnesium sulfate, filtered and evaporated to dryness. The residue

was chromatographed on silica by dry flash chromatography, eluting with a gradient increasing in polarity from 0 to 2.5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 1-benzyl-4-(pyrimid-5-yl)piperazine as an oil (5.15 g), which the NMR spectrum showed to be contaminated with 1-benzyl-4-(pyrimid-2-yl)piperazine. The mixture was used without further purification.

MS (ESP): 254 (MH^+) for $C_{15}H_{18}N_4$

NMR (DMSO-D6) δ: 2.62 (t, 4H); 3.35 (t, 4H); 7.32 (m, 5H); 8.34 (s, 2H); 8.68 (s, 1H).

Crude 1-benzyl-4-(pyrimid-5-yl)piperazine (5.3 g, 20 mM) and ammonium formate (5.26 g, 0.08 M) were dissolved in a mixture of methanol (100 ml) and water (0.5 ml), and treated with palladium (10% on carbon, 1.3 g) under argon. The mixture was heated to reflux for 3 hours, cooled, filtered through celite, and evaporated to dryness. The residue was treated with aqueous sodium carbonate (2M, 50 ml), and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (magnesium sulfate) and evaporated, to give an oil containing 1-(pyrimid-5-yl)piperazine, mixed with 1-(pyrimid-2-yl)piperazine (3.35 g). The mixture was used as such in the next stage.

MS (ESP): 165 (MH^+) for $C_8H_{12}N_4$

3,4-Difluoronitrobenzene (1.53 ml, 1.38 mM) was dissolved in acetonitrile (60 ml). N,N-diisopropylethylamine (6.93 ml, 40 mM), and the above mixture of piperazines (2.72 g, 16.6 mM) added, and the mixture heated to reflux for 18 hours. Solvent was evaporated, and the residue rougly purified by chromatography on silica by dry flash chromatography, eluting with dichloromethane. Relevant fractions were combined and evaporated. This residue was split into three equal portions (500 mg) which were further purified by chromatography on a 90 g Biotage Kiloprep® silica column, eluting with 2.5% methanol in dichloromethane. Relevant fractions were combined to give 3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)nitrobenzene (1.2 g).

MS (ESP): 304 (MH^+) for $C_{14}H_{14}FN_5O_2$

NMR (DMSO-D6) δ: 3.43 (s, 8H); 7.23 (t, 1H); 8.02 (m, 2H); 8.53 (s, 2H); 8.61 (s, 1H).

3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)nitrobenzene (2.08 g, 6.8 mM) was dissolved in a mixture of ethyl acetate (300 ml) and DMF (20 ml), and the solution flushed with argon. Palladium (10% on carbon, 125 mg) was added, and the mixture hydrogenated at ambient temperature and pressure to greater than the theoretical uptake of gas. The mixture was filtered through celite, washed with water (2 x 150 ml), then brine (100 ml), dried (magnesium sulfate) and evaporated to dryness, to give 5-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluoro-benzene as a solid (1.7 g), which was used as such in the next stage.

MS (ESP): 274 (MH^+) for $C_{14}H_{16}FN_5$

NMR (DMSO-D6) δ: 2.96 (t, 4H); 3.36 (t, 4H); 4.98 (s, 2H); 6.31 (dd, 1H); 6.36 (dd, 1H); 6.80 (t, 1H); 8.50 (s, 2H); 8.58 (s, 1H).

5-Amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.7 g, 6.2 mM) was dissolved in dry dichloromethane (40 ml) under argon, and cooled to -4°C. Pyridine (0.63 ml, 7.79 mM) was added, followed by benzyl chloroformate (0.98 ml, 6.85 mM). The mixture was stirred for 72 hours at ambient temperature. The resulting suspension was diluted with 5% methanol in dichloromethane (100 ml), washed with water (2 x 50 ml), dried (magnesium sulfate), and evaporated to dryness. The residue was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 2.5% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 5-benzyloxycarbonyl-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.31 g).

MS (ESP): 408 (MH^+) for $C_{22}H_{22}FN_5O_2$

NMR (DMSO-D6) δ: 3.34 (m, 8H); 5.13 (s, 2H); 7.01 (t, 1H); 7.16 (d, 1H); 7.35 (complex, 6H); 8.52 (s, 2H); 8.59 (s, 1H); 9.92 (s, 1H).

tert-Butanol (0.354 g, 3.19 mM) and dry THF (25 ml) were stirred under argon, and cooled to -10°C. n-Butyl lithium (1.6 M in *iso*hexane, 2.39 ml, 3.83 mM) was added dropwise, the mixture was stirred 10 minutes, then cooled to -70°C. A solution of 5-benzyloxycarbonyl-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.3 g, 3.19 mM) dissolved in dry DMPU (20 ml) was added dropwise. After stirring for 10 minutes, a solution of (R)-glycidyl-butyrate (0.55 g, 3.83 mM) in dry THF (10 ml) was added, and stirring continued at -78°C for 30 minutes. The temperature was allowed to rise to ambient over 16 hours, the mixture

treated with methanol (10 ml), and stirred for 10 minutes. The reaction was diluted with saturated aqueous sodium bicarbonate (20 ml) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated. The residue, still containing DMPU, was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give (5R)-3-(4-(4-(pyrimid-5-yl)piperazin-1-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (0.70 g).

MS (ESP): 374 (MH^+) for $C_{18}H_{20}FN_5O_3$

NMR (DMSO-D6) δ: 3.10 (m, 4H); 3.40 (m, 4H); 3.53 (m, 1H); 3.65 (m, 1H); 3.77 (t, 1H); 4.03 (t, 1H); 4.66 (m, 1H); 5.19 (t, 1H); 7.10 (t, 1H); 7.21 (d, 1H); 7.54 (d, 1H); 8.21 (s, 2H); 8.60 (s, 1H).

(5R)-3-(4-(4-(pyrimid-5-yl)piperazin-1-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (0.654 g, 1.75 mM) was dissolved in pyridine (15 ml), and cooled under argon to 0°C. Triethylamine (0.292 ml, 2.1 mM) and methanesulfonyl chloride (0.163 ml, 2.1 mM) were added, and stirring continued at 0°C for 10 minutes, before allowing the temperature to reach ambient over 2 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (50 ml). The solution was washed with water (3 x 40 ml), brine (25 ml), dried (magnesium sulfate) and evaporated. The solid residue was triturated with diethyl ether (20 ml), and (5R)-3-(3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one filtered off (0.65 g).

MS (ESP): 452 (MH^+) for $C_{19}H_{22}FN_5O_5S$

NMR (DMSO-D6) δ: 3.13 (m, 4H); 3.23 (s, 3H); 3.42 (m, 4H); 3.80 (dd, 1H); 4.16 (t, 1H); 4.47 (m, 2H); 4.98 (m, 1H); 7.14 (t, 1H); 7.22 (dd, 1H); 7.50 (dd, 1H); 8.54 (s, 2H); 8.61 (s, 1H).

(5R)-3-(3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one (0.6 g, 1.33 mM) was dissolved in dry DMF (15 ml), sodium azide (520 mg, 8 mM) was added, and the mixture was heated at 80°C under argon for 7 hours. Solvent was evaporated, and the residue partitioned between ethyl acetate (50 ml) and water (50 ml). The organic layer was separated, reextracted with ethyl acetate (2 x 25 ml), dried (magnesium

sulfate) and evaporated, to give (5R)-5-azidomethyl-3-(3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)oxazolidin-2-one as a solid (0.46 g).

MS (ESP): 399 (MH^+) for $C_{18}H_{19}FN_8O_2$

NMR (DMSO-D6) δ: 3.12 (t, 4H); 3.41 (t, 4H); 3.66 (dd, 1H); 3.73 (complex, 2H); 4.11 (t, 1H); 4.86 (m, 1H); 7.11 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H); 8.53 (s, 2H); 8.61 (s, 1H).

Examples 16-26

Examples 16-26 (all of which are (5S) chiral compounds are summarised in Table 1 below) were prepared using the following procedure which employed a Zymark robotic system for multiple parallel synthesis :-

Triethylamine (2 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in DMA (15 ml) under argon. The resultant mixture was stirred at room temperature for 10 minutes. This solution was then added to the appropriate halo-heterocycle (1 mM) and the mixture heated with stirring at 110°C for 6 hours. After cooling the solvent was removed by centrifugal evaporation (SAVANT AES2000) with radiant heating for 5 hours. The residue was mixed with water and the solid filtered. The purity at this stage was assessed by TLC. Impure materials were dissolved in a mixture of dichloromethane and methanol and purified by silica Mega Bond Elut® chromatography, using a suitable mixture of the two solvents, as determined from the TLC. The relevant fractions were combined and the solvent removed by centrifugal evaporation (SAVANT AES2000) on medium heat for 3 hours. Compounds so prepared were generally characterised by the presence of the correct molecular ion for MH^+ in their electrospray mass spectra, and by their HPLC retention time (in minutes), using the following system and elution parameters.

Column HYPERSIL ODS 5m

Flow rate 1.0 ml/min

Detector Wavelength 254l

Solvent A 1 mMol TFA/H_2O

Solvent B 1 mMol TFA/CH_3CN

Time	*% Solvent A*	*% Solvent B*
0	95	5
3	95	5
17	5	95
18	95	5
20	95	5

Table 1

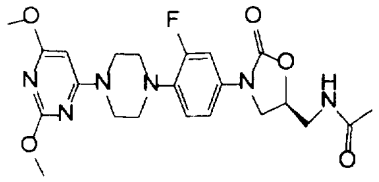
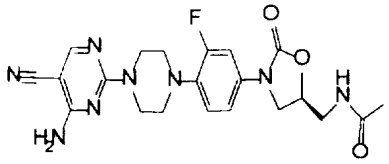
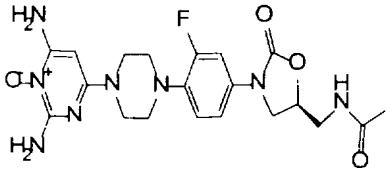
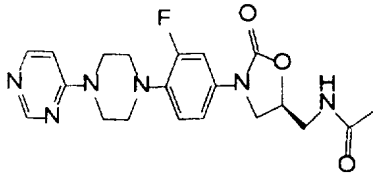
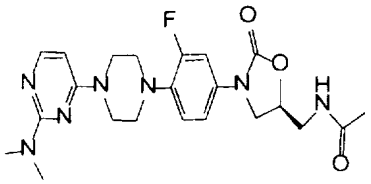
Example	Structure	Starting Material	HPLC RT	Mass ion	Notes
16	CHIRAL 	6-Chloro-2.4-dimethoxypyrimidine	17.6	475.2	2.3
17	CHIRAL 	4-Amino-2-chloro-5-cyanopyrimidine	16.9		2.4
18	CHIRAL 	2,6-Diamino-4-chloro-pyrimidine-1-oxide	15.3	461.4	1
19	CHIRAL 	4-Chloro-pyrimidine	14.7	415.3	1.7
20	CHIRAL 	4-Chloro-2-dimethylamino-pyrimidine	16.6	458.3	1

Table 1 continued

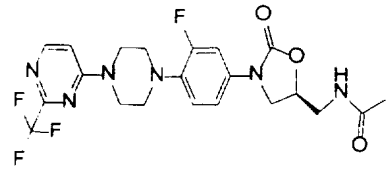
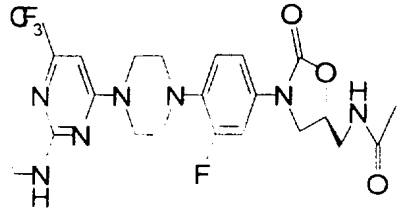
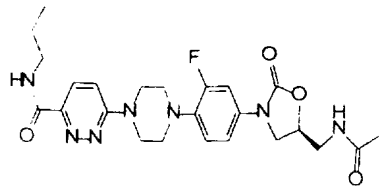
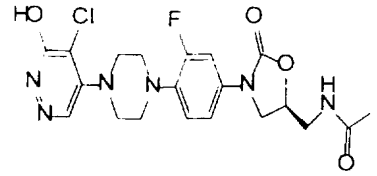
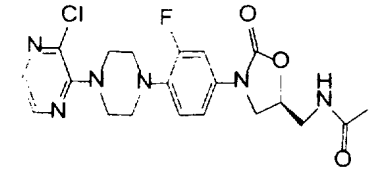
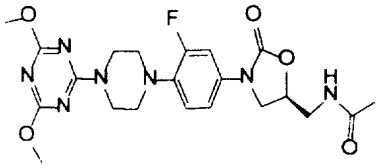
Example	Structure	Starting Material	HPLC RT	Mass ion	Notes
21	CHIRAL 	4-Chloro-2-trifluoromethyl-pyrimidine	20.8	483.2	1.8
22		2-Ethylamino-4-chloro-6-trifluoromethyl-pyrimidine	19.9	526.3	1.11
23	CHIRAL 	N-(n-Propyl)-3-chloro-pyridazine-6-carboxamide	17.7	500.3	1.9
24	CHIRAL 	4.5-Dichloro-3-hydroxy-pyridazine	16.5	465.2	1.10
25	CHIRAL 	2.3-Dichloropyrazine	20.3	449.2	1.5

Table 1 continued

Example	Structure	Starting Material	HPLC RT	Mass ion	Notes
26	CHIRAL 	2-Chloro-4,6-dimethoxy-1,3,5-triazine			2,6

Notes

1. Further purified by chromatography on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity in the range from 0% to 10% methanol in dichloromethane.

2. Obtained pure directly from reaction.

3. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(2,4-dimethoxypyrimid-6-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.51 (dd, 1H); 3.67 (t, 4H); 3.79 (2 x s, 6H); 4.06 (t, 1H); 4.68 (m, 1H); 5.77 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.21 (t, 1H).

4. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimid-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.00 (t, 4H); 3.39 (t, 2H); 3.69 (dd, 1H); 3.89 (t, 4H); 4.08 (t, 1H); 4.70 (m, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.29 (br, 2H); 7.49 (dd, 1H); 8.08 (d, 1H); 8.21 (t, 1H); 8.28 (s, 1H).

5. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(3-chloropyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.13 (t, 4H); 3.39 (t, 2H); 3.52 (t, 4H); 3.70 (dd, 1H); 3.89 (t, 4H); 4.08 (t, 1H); 4.70 (m, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.29 (br, 2H); 7.49 (dd, 1H); 8.08 (d, 1H); 8.21 (t, 1H); 8.28 (s, 1H).

6. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(4,6-dimethoxy-1,3,5-triazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 3.13 (t, 4H); 3.55-3.70 (m, 2H); 3.76 (dd, 1H); 3.97 (s, 6H); 4.02 (t + m, 5H); 4.77 (m, 1H); 6.10 (brt, 1H); 6.95 (t, 1H); 7.09 (dd, 1H); 7.46 (dd, 1H).

7. Preparation of starting material: J. Chem. Soc., 1951, 1218.

8. The appropriate haloheterocycle, 2-trifluoromethyl-4-chloropyrimidine, was prepared as follows :-

2-Trifluoromethyl-4-hydroxypyrimidine (1.06 g, 6.5 mM) was dissolved in thionyl chloride (10 ml) and DMF (10 drops) added. The mixture was heated to reflux for 1 hour, cooled, and solvent evaporated. The residue was partitioned between aqueous 2N potassium carbonate solution (50 ml) and dichloromethane (50 ml). The organic layer was separated, . dried over sodium sulfate and evaporated to give the desired product, slightly contaminated with DMF (0.9 g).

NMR ($CDCl_3$) δ: 7.57 (d, 1H); 8.80 (d, 1H).

9. The appropriate haloheterocycle, N-(n-propyl)-3-chloropyridazine-6-carboxamide, was prepared as follows :-

Ethyl 3-chloropyridazine-6-carboxylate (Ref: Bull.Soc.Chim.France 1959, p 1793; 4.2 g, 22.6 mM) was dissolved in dry 1,2-dimethoxyethane (25 ml), n-propylamine (5 ml, 61 mM) added, and the mixture stirred at ambient temperature for 3 days. Solvent was removed, and the residue purified by dry column chromatography, using diethyl ether as eluant. Relevant

fractions were combined and evaporated, and the residue recrystallised from a mixture of diethyl ether and petrol, to give the desired product, mp 128.5°C-129.5°C (1.71 g).

Microanalysis: Found: C, 48.1; H, 5.4; N, 21.3; Cl, 18.1%

$C_8H_8ClNO_2$ requires: C, 48.1; H, 5.0; N, 21.1; Cl, 17.8%

10. Preparation of starting material: J. Amer. Chem. Soc., 1953, 75, 1909.

11. Characterised by NMR and MS

N-[(5S)-3-(3-Fluoro-4-(4-(2-ethylamino-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 526 (MH+) for $C_{23}H_{27}F_4N_7O_3$

NMR (DMSO-D6) δ: 1.07 (t, 3H); 1.81 (s, 3H); 3.00 (t, 4H); 3.23 (q, 2H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.77 (t, 4H); 4.06 (t, 1H); 4.65 (m, 1H); 6.42 (s, 1H); 7.07 (t, 1H); 7.10 (br, 1H); 7.17 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Example 27 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(*bis*(2-hydroxyethylamino)carbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the method and scale of Examples 10-14, the title product (248 mg) was obtained after chromatography.

MS (ESP): 546 (MH^+) for $C_{25}H_{32}FN_7O_6$

NMR (DMSO-D6) δ: 1.85 (s, 3H); 3.09 (t, 4H); 3.39 (t, 2H); 3.55 (m, 8H); 3.70 (dd, 1H); 3.83 (t, 4H); 4.08 (t, 1H); 4.68 (m, 1H); 4.77 (t, 2H); 7.12 (t, 1H); 7.18 (dd, 1H); 7.37 (d, 1H); 7.51 (dd, 1H); 7.55 (d, 1H); 8.19 (t, 1H).

The appropriate haloheterocycle, 3-chloro-6-(bis(2-hydroxyethyl)aminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and bis(2-hydroxyethyl)amine (841 mg, 8 mM) added. The mixture was stirred at ambient temperature for 24 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient from 0% to 10% methanol in

dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (896 mg).

NMR (DMSO-D6) δ: 3.43 (s, 4H); 3.58 (q, 2H); 3.64 (q, 2H); 4.63 (t, 1H); 4.82 (t, 1H); 7.84 (d, 1H); 8.01 (d, 1H).

Example 28 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (0.9 g, 2 mM) was dissolved in DMA (10 ml), and triethylamine (0.556 ml, 4 mM) added. 3-Chloro-6-methylpyridazine (257 mg, 2 mM) was added and the mixture heated to 100°C for 18 hours. Solvent was evaporated, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 1% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired product (61 mg), slightly contaminated with N-[(5S)-3-(3-fluoro-4-(4-formylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 429 (MH^+) for $C_{21}H_{25}N_6FO_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.42 (s, 3H); 3.06 (t, 4H); 3.37 (t, 2H); 3.66 (t overlapping m, 5H); 4.06 (t, 1H); 4.68 (m, 1H); 7.05 (t, 1H); 7.15 (dd, 1H); 7.23 (d, 1H); 7.29 (d, 1H); 7.48 (dd, 1H); 8.19 (t, 1H).

Example 29 : N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (1.35 g, 3 mM) was dissolved in DMA (30 ml), and triethylamine (606 mg, 6 mM) added under argon. 2,4-Dichloro-6-methylpyrimidine (489 mg, 3 mM) was added and the mixture heated to 110°C for 6 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (100 ml). The solution was washed with water (50 ml), dried over magnesium sulfate and evaporated. The residue was purified by chromatography on a

90 g Biotage Kiloprep® silica column. Elution with 2.5% methanol in dichloromethane gave N-[(5S)-3-(3-fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (312 mg) - Example 29A.

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.27 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.83 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 6.65 (s, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Further elution with 5% methanol in dichloromethane gave N-[(5S)-3-(3-fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (838 mg) - Example 29B.

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.80 (s, 3H); 2.23 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.72 (t, 4H); 4.05 (t, 1H); 4.68 (m, 1H); 6.76 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.18 (t, 1H).

Example 30 : N-[(5S)-3-(3-Fluoro-4-(4-(2-methyl-6-chloropyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (1.35 g, 3 mM) was dissolved in DMA (30 ml), and triethylamine (606 mg, 6 mM) added under argon. 4,6-Dichloro-2-methylpyrimidine (489 mg, 3 mM) was added and the mixture heated to 110° for 6 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (100 ml). The solution was washed with water (50 ml), dried over magnesium sulfate and evaporated to give the desired product plus residual DMA.

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.34 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.76 (t, 4H); 4.05 (t, 1H); 4.67 (m, 1H); 6.79 (s, 1H); 7.06 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Example 31 : N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 29A, 153 mg, 0.33 mM) was dissolved in a mixture of ethanol (40 ml) and DMF (10 ml). Triethylamine (92 µL, 0.66 mM) and palladium catalyst (10% on charcoal, 100 mg) were added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated. The residue was dissolved in dichloromethane (200 ml), washed with water, dried over magnesium sulfate and evaporated to give the title product (90 mg).

MS (ESP): 429 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.26 (s, 3H); 2.98 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.84 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 6.52 (d, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H); 8.21 (d, 1H).

Example 32 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the same technique as Example 31, but starting with N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 29B, 692 mg, 1.5 mM) the title product was obtained (470mg).

MS (ESP): 429 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.25 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.67 (dd, 1H); 3.73 (t, 4H); 4.05 (t, 1H); 4.68 (m, 1H); 6.73 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.18 (t, 1H); 8.37 (s, 1H).

Example 33 : N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the same technique as Example 31, but starting with N-[(5S)-3-(3-Fluoro-4-(4-(2-methyl-6-chloropyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 30, 1.34 g, 2.69 mM) the title product was obtained (690mg).

MS (ESP): 429 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.36 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.72 (t, 4H); 4.07 (t, 1H); 4.68 (m, 1H); 6.66 (d, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.48 (dd, 1H); 8.08 (d, 1H); 8.19 (t, 1H).

Example 34 : N-[(5S)-3-(3-Fluoro-4-(4-(1,2,4-triazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Triethylamine (0.5 ml, 3.6 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (157 mg, 0.34 mM) in acetonitrile (5 ml), and 3-methylsulfinyl-1,2,4-triazine (50 mg, 0.34 mM) added. The resultant mixture was heated with stirring at 75°C for 18 hours. After cooling the solvent was evaporated, the residue dissolved in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (106 mg).

MS (ESP): 416 (MH^+) for $C_{19}H_{22}FN_7O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.06 (t, 4H); 3.38 (t, 2H); 3.69 (t, 1H); 3.94 (t, 4H); 4.07 (t, 1H); 4.69 (m, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.50 (dd, 1H); 8.18 (t, 1H); 8.34 (d, 1H); 8.63 (d, 1H).

The 3-methylsulfinyl-1,2,4-triazine used as starting material was prepared as follows :-

3-Methylthio-1,2,4-triazine (J. Het. Chem., 1970, 7, 767; 254 mg, 2 mM) was dissolved in dichloromethane (5 ml) and stirred at ambient temperature. 3-Chloroperoxybenzoic acid (50% strength, 690 mg, 2 mM) was added in portions over 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate (5 ml), dried (magnesium sulfate), and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 3-methylsulfinyl-1,2,4-triazine as a gum (60 mg).

MS (ESP): 144 (MH^+) for $C_4H_5N_3OS$

NMR (DMSO-D6) δ: 2.97 (s, 3H); 9.05 (d, 1H); 9.58 (d, 1H).

Example 35 : N-[(5S)-3-(3-Fluoro-4-(4-(1,3,5-triazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Triethylamine (0.21 ml, 1.5 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in 1,4-dioxane (20 ml), and 2-phenoxy -1,3,5-triazine (J. Amer. Chem. Soc., 1975, 97, 1851: 173 mg, 1 mM) added. The resultant mixture was heated to reflux for 4 hours. After cooling the solvent was evaporated, the residue dissolved in 5% methanol in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 3% to 11% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the product contaminated with phenol, which was rechromatographed as above eluting with a gradient increasing in polarity from 0% to 7% methanol in dichloromethane to give a pure sample (38 mg).

MS (ESP): 416 (MH^+) for $C_{19}H_{22}FN_7O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.02 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.92 (t, 4H); 4.07 (t, 1H); 4.68 (m, 1H); 7.08 (t, 1H); 7.19 (dd, 1H); 7.50 (dd, 1H); 8.23 (t, 1H); 8.58 (s, 2H).

Example 36 : N-[(5S)-3-(3-Fluoro-4-(1-oxo-4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 1, 207 mg, 0.5 mM) was dissolved in a mixture of methanol (10 ml) and dichloromethane (5 ml), and magnesium monoperoxyphthalate.$6H_2O$ (90%, 279 mg, 0.51 mM) was added. After stirring for 4 hours, precipitated phthalic acid was filtered off, and solvents removed. Solvent was evaporated, the residue preabsorbd on silica, and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 5% to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (38 mg) slightly contaminated with phthalic acid.

MS (ESP): 431 (MH+) for $C_{20}H_{23}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.05 (d, 2H); 3.39 (t, 2H); 3.75 (dd, 1H); 3.92 (quintet, 4H); 4.13 (t, 1H); 4.62 (d, 2H); 4.74 (m, 1H); 6.72 (t, 1H); 7.42 (dd, 1H); 7.64 (dd, 1H); 8.22 (t, 1H); 8.42 (d, 2H); 8.63 (t, 1H).

Example 37 : N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide trifluoroacetate salt (900 mg, 2 mM) was dissolved in DMA (20 ml), and triethylamine (610 mg, 6 mM) added. 2,4-Dichloro-5-methylpyrimidine (326 mg, 2 mM) was added and the mixture heated to 100°C for 18 hours. Solvent was evaporated, and the residue partitioned between dichloromethane (40 ml) and water (20 ml). The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by dry column chromatography on silica eluting with a gradient increasing in polarity from 0% to 7% methanol in dichloromethane. The minor, less polar component (13 mg) was N-[(5S)-3-(3-fluoro-4-(4-(4-chloro-5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37A).

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 2.17 (s, 3H); 3.09 (t, 4H); 3.56-3.71 (m, 2H); 3.75 (dd, 1H); 3.93 (t, 4H); 4.03 (t, 1H); 4.76 (m, 1H); 6.04 (t, 1H); 6.94 (t, 1H); 7.08 (dd, 1H); 7.46 (dd, 1H); 8.10 (s, 1H).

The major, more polar component (400 mg) was N-[(5S)-3-(3-fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37B).

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 2.24 (s, 3H); 3.14 (t, 4H); 3.57-3.69 (m, 2H); 3.74 (t overlapping m, 5H); 4.03 (t, 1H); 4.78 (m, 1H); 6.24 (t, 1H); 6.94 (t, 1H); 7.08 (dd, 1H); 7.45 (dd, 1H); 7.97 (s, 1H).

Example 38 : N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37B; 380 mg, 0.82 mM) was dissolved in methanol (30 ml), and treated with triethylamine (230 µL, 1.7 mM). Palladium catalyst (10% on charcoal, 40 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue partitioned between dichloromethane (20 ml) and water (10 ml). The organic layer was dried over magnesium sulfate and evaporated to give the title product (290 mg).

MS (ESP): 429.4 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 2.26 (s, 3H); 3.17 (t, 4H); 3.63 (t overlapping m, 6H); 3.76 (dd, 1H); 4.03 (t, 1H); 4.77 (m, 1H); 6.29 (t, 1H); 6.96 (t, 1H); 7.09 (dd, 1H); 7.45 (dd, 1H); 8.16 (s, 1H); 8.63 (s, 1H).

Example 39

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	179
	Croscarmellose sodium	12
	Polyvinylpyrrolidone	6
	Magnesium stearate	3

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	229
	Croscarmellose sodium	12
	Polyvinylpyrrolidone	6
	Magnesium stearate	3

(c)	Tablet III	mg/tablet
	Compound X	1
	Lactose Ph.Eur	92
	Croscarmellose sodium	4
	Polyvinylpyrrolidone	2
	Magnesium stearate	1

(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur	389
	Croscarmellose sodium	100
	Magnesium stearate	1

(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	Isotonic aqueous solution	to 100%

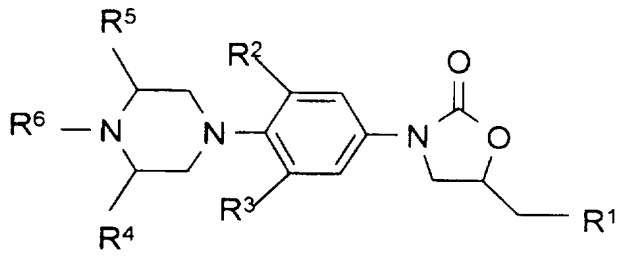
Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A compound of the formula (I)



(I)

wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, or of the formula -NHC(=O)R^a wherein R^a is hydrogen, (1-4C)alkoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or R^1 is of the formula -N(Me)C(=O)R^b wherein R^b is hydrogen, methyl or methoxy or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2;

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl (optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; suitable N-oxides thereof and in-vivo-hydrolysable esters thereof.

2. A compound of the formula (I), as claimed in claim 1, wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, or R^1 is of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or R^1 is of the formula $-NHSO_2$(1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl [optionally substituted by carboxy or (1-4C)alkoxycarbonyl], (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; suitable N-oxides thereof and in-vivo-hydrolysable esters thereof.

3. A compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1 and 2, except that the following optional substituents on R^6, namely (1-4C)alkoxy, (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino and those N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl substituents with the (1-4C)alkyl group or groups substituted by hydroxy, (1-4C)alkoxy or

(1-4C)alkoxycarbonyl, are excluded; and the number of optional substituents on R^6 is restricted to one or two.

4. A compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof as claimed in claims 1-3, wherein :

R^1 is acetamido, one of R^2 and R^3 is hydrogen and the other is fluoro, R^4 and R^5 are both hydrogen, R^6 is pyrimidine or pyrazine and the optional substituents on the heteroaryl ring are independently selected from methyl, chloro, nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

5. A compound of the formula (I), as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

and pharmaceutically-acceptable salts and suitable N-oxides thereof.

6. A compound of the formula (I), as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(3-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

7. A compound of the formula (I), or a pharmaceutically-acceptable salt or suitable

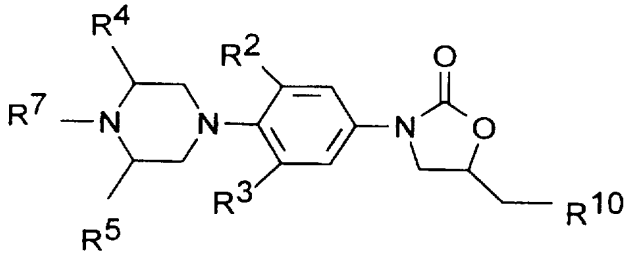
N-oxide thereof, as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide.

8. A process for the preparation of a compound of the formula (I), as claimed in claim 1, which comprises :-

(a) the deprotection of a compound, containing at least one protecting group, of the formula (II), a pharmaceutically-acceptable salt , suitable N-oxide or in-vivo hydrolysable ester thereof :

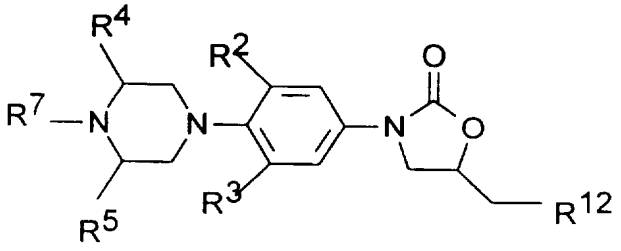


(II)

(b) the modification of a substituent in or the introduction of a substituent into another compound of formula (I) or (II);

(c) when R^1 or R^{10} is of the formula - $NHS(O)_n$(1-4C)alkyl, wherein n is 1 or 2, the oxidation of a compound of the formula (I) wherein n is 0 or, when n is 2 the oxidation of a compound of the formula (I) or (II) wherein n is 1;

(d) when R^1 or R^{10} is azido, the reaction of a compound of the formula (III) with a source of azide:



(III)

(e) when R^1 or R^{10} is amino, the reduction of a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido;

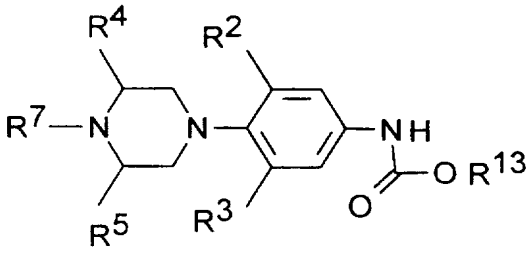
(f) when R^1 or R^{10} is of the formula $-NHC(=O)R^a$, the introduction of $-C(=O)R^a$ into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

(g) when R^1 or R^{10} is of the formula $-NHS(O)_n$ (1-4C)alkyl the introduction of $-S(O)_n$ (1-4C)alkyl into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

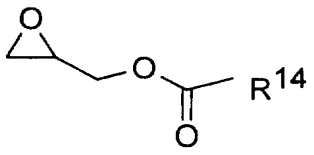
(h) when R^1 or R^{10} is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(i) when R^1 or R^{10} is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (III);

(j) when R^1 or R^{10} is hydroxy, the reaction of a compound of the formula (IV) with a compound of the formula (V):

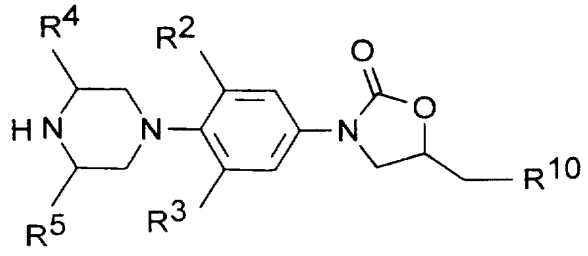


(IV)



(V)

(k) the reaction of a compound of the formula (VI) with a compound of the formula (VII):

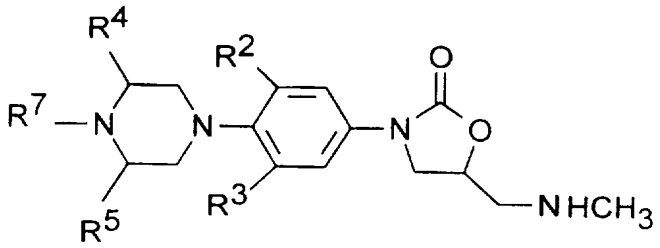


R^7-L^1

(VI) (VII)

(l) when R^{10} is of the formula -N(CO_2R^{15})CO(1-4C)alkyl: from a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy;

(m) when R^1 or R^{10} is of the formula -N(Me)C(=O)R^b, by the introduction of the group -C(=O)R^b into a compound of the formula (VIII):



(VIII)

and

(n) when a suitable N-oxide is required, by preparation directly from a corresponding parent compound of the formula (I) or (II), or by assembly from suitable N-oxide starting materials:

wherein R^2, R^3, R^4 and R^5 are as hereinabove defined, R^7 is R^6 or protected R^6, R^{10} is R^1 or protected R^1, R^{12} is mesyloxy or tosyloxy, R^{13} is (1-6C)alkyl or benzyl, R^{14} is (1-6C)alkyl, R^{15} is (1-4C)alkyl or benzyl and L^1 is a leaving goup and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester;

and when an optically active form of a compound of the formula (I) is required it may be obtained by carrying out one of the above procedures using an optically active starting material, or by resolution of a racemic form of the compound or intermediate using a standard procedure.

9. A pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7 and a pharmaceutically-acceptable diluent or carrier.

10. A method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7.

11. The use of a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 97/01767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/12 A61K31/495 A61K31/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 23384 A (THE UPJOHN COMPANY) 25 November 1993 see claims	1-4,9-11
Y	WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 see claims	1-4,9-11
Y	WO 95 14684 A (THE UPJOHN COMPANY) 1 June 1995 see claims	1-4,9-11
P,X	WO 97 21708 A (PHARMACIA & UPJOHN COMPANY) 19 June 1997 see the whole document	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 1997	26.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/01767

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 10
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 searched 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 97/01767

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(51) International Patent Classification 6 :
C07D 263/20, 417/12, 413/10, 413/04, A61K 31/42, C07D 261/04, 307/32, 471/10 // (C07D 471/10, 235:00, 221:00)

A1

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(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

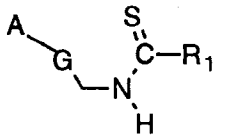
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HESTER, Jackson, B., Jr. [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). NIDY, Eldon, George [US/US]; 3103 Morgan Street, Kalamazoo, MI 49001 (US). PERRICONE, Salvatore, Charles [US/US]; 7011 Division Avenue, Delton, MI 49046 (US). POEL, Toni-Jo [US/US]; 304 Anderson, Wayland, MI 49348 (US).

(74) Agent: YANG, Lucy, X.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, 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: OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY



(I)

(57) Abstract

The present invention provides compounds of Formula (I) or pharmaceutical acceptable salts thereof wherein A, G and R_1 are as defined in the claims which are antibacterial agents.

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OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY

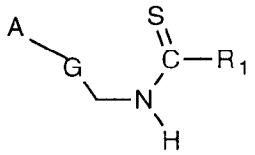
BACKGROUND OF THE INVENTION

The present invention relates to new and useful oxazolidinone compounds and their preparations, and more particularly to oxazolidinone compounds in which the carbonyl functionality of -NH-C(O)-R is converted to a thiocarbonyl functionality, such as a thiourea -NH-C(S)-NH_2, an alkyl thiourea -NH-C(S)-NH-(C_{1-4} alkyl), thioamide -NH-C(S)-(C_{1-4} alkyl) or -NH-C(S)-H.

Replacement of the oxygen atom with a sulfur atom has unexpectedly improved the antimicrobial properties of the compounds. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, Gram-negative organisms such as H. *influenzae* and M. *catarrahlis* 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.

SUMMARY OF THE INVENTION

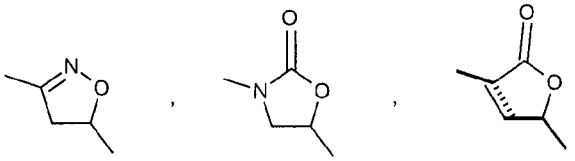
In one aspect the subject invention is a compound of the Formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



R_1 is

a) H,

b) NH_2,

c) NH-C_{1-4} alkyl,

d) C_{1-4} alkyl,

e) -OC_{1-4} alkyl,

f) -S C_{1-4} alkyl,

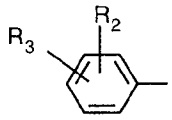
g) C_{1-4} alkyl substituted with 1-3 F, 1-2 Cl, CN or -$COOC_{1-4}$ alkyl,

h) C_{3-6} cycloalkyl,

i) $N(C_{1-4}$ alkyl$)_2$ or

j) $N(CH_2)_{2-5}$;

A is

a) 

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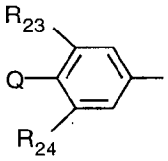
b) 

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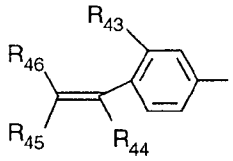
c) 

,

d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O,

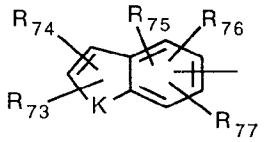
wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

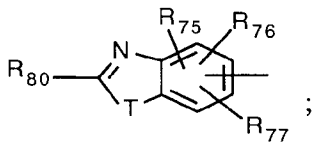
wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{48},

e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,
wherein the heteroaromatic moiety is bonded via a carbon atom,
wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,
wherein the heteroaromatic moiety is optionally substituted with one to three R_{55},

f) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_{55},

g)  , or

h)  ;

wherein R_2 is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl,
f) NO_2, or
g) R_2 and R_3 taken together are -O-$(CH_2)_h$-O-;

R_3 is

a) -S(=O)$_i$ R_4,
b) -S(=O)$_2$-N=S(O)$_j$$R_5$$R_6$,
c) -SC(=O)R_7,
d) -C(=O)R_8,
e) -C(=O)R_9,
f) -C(=O)N$R_{10}$$R_{11}$,

g) $-C(=NR_{12})R_8$,
h) $-C(R_8)(R_{11})-OR_{13}$,
i) $-C(R_9)(R_{11})-OR_{13}$,
j) $-C(R_8)(R_{11})-OC(=O)R_{13}$,
k) $-C(R_9)(R_{11})-OC(=O)R_{13}$,
l) $-NR_{10}R_{11}$,
m) $-N(R_{10})-C(=O)R_7$,
n) $-N(R_{10})-S(=O)_iR_7$,
o) $-C(OR_{14})(OR_{15})R_8$,
p) $-C(R_8)(R_{16})-NR_{10}R_{11}$, or
q) C_{1-8} alkyl substituted with one or more =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{10}R_{11}$, C_{2-5} alkenyl, or C_{2-5} alkynyl;

R_4 is

a) C_{1-4} alkyl optionally substituted with one or more halos, OH, CN, $NR_{10}R_{11}$, or $-CO_2R_{13}$,
b) C_{2-4} alkenyl,
c) $-NR_{16}R_{18}$,
d) $-N_3$,
e) $-NHC(=O)R_7$,
f) $-NR_{20}C(=O)R_7$,
g) $-N(R_{19})_2$,
h) $-NR_{16}R_{19}$, or
i) $-NR_{19}R_{20}$,

R_5 and R_6 at each occurrence are the same or different and are

a) C_{1-2} alkyl, or
b) R_5 and R_6 taken together are $-(CH_2)_k-$;

R_7 is C_{1-4} alkyl optionally substituted with one or more halos;

R_8 is

a) H, or
b) C_{1-8} alkyl optionally substituted with one or more halos, or C_{3-8} cycloalkyl;

R_9 is C_{1-4} alkyl substituted with one or more

a) $-S(=O)R_{17}$,
b) $-OR_{13}$,
c) $-OC(=O)R_{13}$,
d) $-NR_{10}R_{11}$, or

e) C_{1-5} alkenyl optionally substituted with CHO;

R_{10} and R_{11} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{12} is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

R_{13} is

a) H, or

b) C_{1-4} alkyl;

R_{14} and R_{15} at each occurrence are the same or different and are

a) C_{1-4} alkyl, or

b) R_{14} and R_{15} taken together are $-(CH)_l-$;

R_{16} is

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{17} is

a) C_{1-4} alkyl, or

b) C_{3-8} cycloalkyl;

R_{18} is

a) H,

b) C_{1-4} alkyl,

c) C_{2-4} alkenyl,

d) C_{3-4} cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

R_{19} is

a) Cl,

b) Br, or

c) I;

R_{20} is a physiologically acceptable cation;

R_{21} and R_{22} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) C_{1-2} alkyl,

e) CN

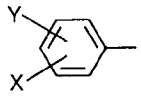
f) OH,

g) C_{1-2} alkoxy,

h) nitro, or

i) amino;

Q is

a) 

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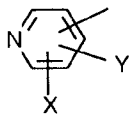
b) 

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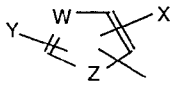
c) 

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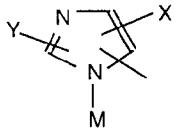
d) 

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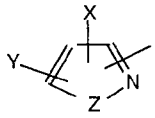
e) 

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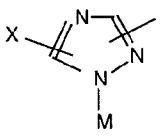
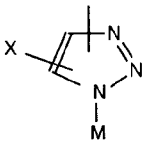
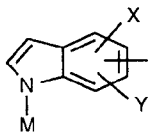
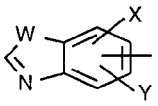
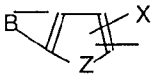
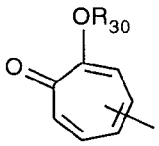
f)  ,

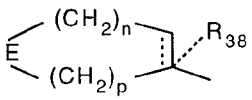
g)  ,

h)  ,

i)  ,

j) 

k)  ,

l)  ,

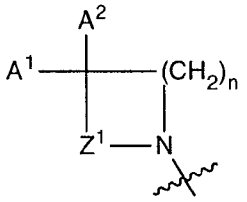
m) a diazinyl group optionally substituted with X and Y,

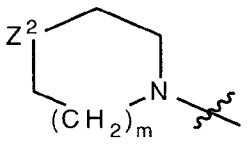
n) a triazinyl group optionally substituted with X and Y,

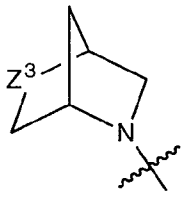
o) a quinolinyl group optionally substituted with X and Y,

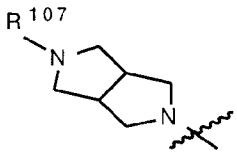
p) a quinoxalinyl group optionally substituted with X and Y,

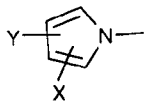
q) a naphthyridinyl group optionally substituted with X and Y,

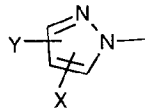
r)  ,

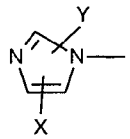
s)  ,

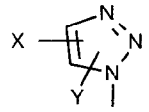
t)  ,

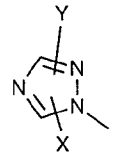
u)  ,

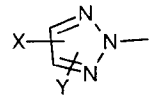
v)  ,

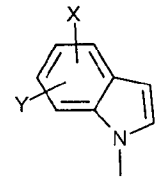
w)  ,

x)  ,

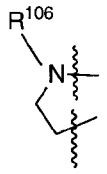
y)  ,

z)  ,

aa)  ,

bb)  or,

Q and R_{24} taken together are



,

wherein Z^1 is

a) $-CH_2-$,
b) $-CH(R^{104})-CH_2-$,
c) -C(O)-, or
d) $-CH_2CH_2CH_2-$;

wherein Z^2 is

a) $-O_2S-$,
b) -O-,
c) $-N(R^{107})-$,
d) -OS-, or
e) -S-;

wherein Z^3 is

a) $-O_2S-$,
b) -O-,
c) -OS-, or
d) -S-;

wherein A^1 is

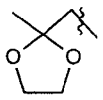
a) H-, or
b) CH_3;

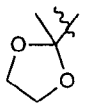
wherein A^2 is

a) H-,
b) HO-,
c) CH_3-,
d) CH_3O-,
e) $R^{102}O-CH_2-C(O)-NH-$
f) $R^{103}O-C(O)-NH-$,
g) (C_1-C_2)alkyl-O-C(O)-,
h) $HO-CH_2-$,
i) CH_3O-NH-,
j) (C_1-C_3)alkyl-O_2C-

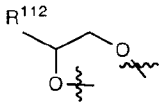
k) CH_3-C(O)-,

l) CH_3-C(O)-CH_2-,

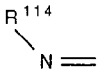
m)  , or

n)  ,

A^1 and A^2 taken together are:

a)  ,

b)  , or

c)  ;

wherein R^{102} is

a) H-,

b) CH_3-,

c) phenyl-CH_2-, or

d) $CH_3C(O)$-;

wherein R^{103} is

a) (C_1-C_3)alkyl-, or

b) phenyl-;

wherein R^{104} is

a) H-, or

b) HO-;

wherein R^{105} is

a) H-,

b) $(C_1\text{-}C_3)$alkyl-,

c) $CH_2 = CH\text{-}CH_2$-, or

d) $CH_3\text{-}O\text{-}(CH_2)_2$-;

wherein R^{106} is

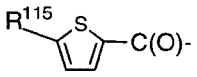
a) $CH_3\text{-}C(O)$-,

b) H-C(O)-,

c) $Cl_2CH\text{-}C(O)$-,

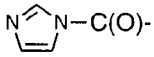
d) $HOCH_2\text{-}C(O)$-,

e) CH_3SO_2-,

f) 

,

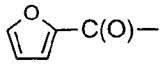
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

j) $H\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

k) 

,

l) $HC\equiv C\text{-}CH_2O\text{-}CH_2\text{-}C(O)$-, or

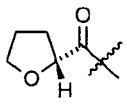
m) phenyl-$CH_2\text{-}O\text{-}CH_2\text{-}C(O)$-;

wherein R^{107} is

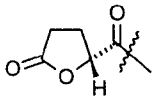
a) $R^{102}O\text{-}C(R^{110})(R^{111})\text{-}C(O)$-,

b) $R^{103}O\text{-}C(O)$-,

c) $R^{108}\text{-}C(O)$-,

d) 

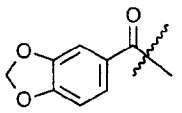
,

e) 

,

f) $H_3C\text{-}C(O)\text{-}(CH_2)_2\text{-}C(O)$-,

g) $R^{109}\text{-}SO_2$-,

h)  ,

i) HO-CH_2-C(O)-,

j) R^{116}-$(CH_2)_2$-,

k) R^{113}-C(O)-O-CH_2-C(O)-,

l) $(CH_3)_2$N-CH_2-C(O)-NH-,

m) NC-CH_2-, or

n) F_2-CH-CH_2-;

wherein R^{108} is

a) H-,

b) $(C_1$-$C_4)$alkyl,

c) aryl -$(CH_2)_p$,

d) ClH_2C-,

e) Cl_2HC-,

f) FH_2C-,

g) F_2HC-, or

h) $(C_3$-$C_6)$cycloalkyl;

wherein R^{109} is

a) -CH_3,

b) -CH_2Cl

c) -$CH_2CH{=}CH_2$,

d) aryl, or

e) -CH_2CN;

wherein R^{110} and R^{111} are independently

a) H-,

b) CH_3-; or

wherein R^{112} is

a) H-,

b) CH_3O-CH_2O-CH_2-, or

c) $HOCH_2$-;

wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2$N-phenyl, or

d) $(CH_3)_2$N-CH_2-;

wherein R^{114} is

a) HO-,

b) CH_3O-,

c) H_2N-,

d) CH_3O-C(O)-O-,

e) CH_3-C(O)-O-CH_2-C(O)-O-,

f) phenyl-CH_2-O-CH_2-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) CH_3O-CH_2-O-$(CH_2)_2$-O-, or

i) CH_3O-CH_2-O-;wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{115} is

a) H-, or

b) Cl-;

wherein R^{116} is

a) HO-

b) CH_3O-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) -$(CH_2)_m$$OR_{13}$, or

e) -$(CH_2)_h$-$NR_{21}R_{22}$;

Z is

a) O,

b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

Y is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl, or
f) NO_2;

X is

a) H,
b) -CN,
c) OR_{27},
d) halo,
e) NO_2,
f) tetrazoyl,
g) -SH,
h) $-S(=O)_iR_4$,
i) $-S(=O)_2-N=S(O)_jR_5R_6$,
j) $-SC(=O)R_7$,
k) $-C(=O)R_{25}$,
l) $-C(=O)NR_{27}R_{28}$,
m) $-C(=NR_{29})R_{25}$,
n) $-C(R_{25})(R_{28})-OR_{13}$,
o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,
p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,
q) $-NR_{27}R_{28}$,
r) $-N(R_{27})C(=O)R_7$,
s) $-N(R_{27})-S(=O)_iR_7$,
t) $-C(OR_{14})(OR_{15})R_{28}$,
u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or
v) C_{1-8} alkyl substituted with one or more halos, OH, =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, C_{2-5} alkenyl, C_{2-5} alkynyl, or C_{3-8} cycloalkyl;

R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{15}, R_{16}, and R_{17} are the same as defined above;

R_{25} is

a) H,
b) C_{1-8} alkyl optionally substituted with one or more halos, C_{3-8}

cycloalkyl, C_{1-4} alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) C_{2-5} alkenyl optionally substituted with CHO, or CO_2R_{13};

R_{26} is

a) R_{28}, or

b) $NR_{27}N_{28}$;

R_{27} and R_{28} at each occurrence are the same or different and are

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) R_{27} and R_{28} taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

R_{29} is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein R_{30} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, or

c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-6} alkoxy;

wherein E is

a) NR_{39},

b) $-S(=O)_i$, or

c) O;

R_{38} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) halo;

R_{39} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl,

d) $-CO_2R_{40}$,

e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

R_{40} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl, or

d) $-(CH_2)_q-OR_{42}$;

R_{41} is

a) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

b) $-(CH_2)_q$-aryl, or

c) $-(CH_2)_q-OR_{42}$;

R_{42} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylthio;

wherein R_{43} is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_{44} is

a) H,

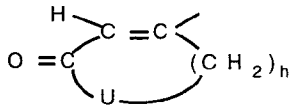
b) CF_3,

c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_{44} and R_{45} taken together are a 5-, 6-, or 7-membered ring of the

formula,

or 

f) R_{44} and R_{45} taken together are $-(CH_2)_k-$, when R_{46} is an electron-withdrawing group;

R_{45} and R_{46} at each occurrence are the same or different and are

a) an electron-withdrawing group,

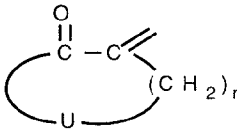
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_{45} or R_{46} is an electron-withdrawing group, or

f) R_{45} and R_{46} taken together are a 5-, 6-, 7-membered ring of the formula

 ;

U is

a) CH_2,

b) O,

c) S, or

d) NR_{47};

R_{47} is

a) H, or

b) C_{1-5} alkyl;

wherein R_{48} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

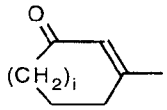
l) $-NR_{49}R_{50}$,

m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,

n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{51},

o) phenyl optionally substituted with one or two R_{51},

p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{51}, or

q)  ;

R_{49} and R_{50} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) C_{5-6} cycloalkyl, or

d) R_{49} and R_{50} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

R_{51} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

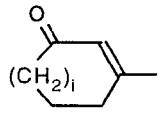
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}\ R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

R_{52} and R_{53} at each occurrence are the same or different and are
a) H,
b) C_{1-6} alkyl, or
c) phenyl;

R_{54} is
a) C_{1-4} alkyl, or
b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_{55} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio
k) C_{1-6} acyl,
l) $-NR_{56}\ R_{57}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{56}R_{57}$,
n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{58},
o) phenyl optionally substituted with one or two R_{58},
p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to

three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{58}, or

q)  ;

R_{56} and R_{57} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl, or

g) R_{56} and R_{57} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{58} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

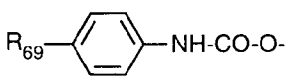
i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) phenyl,

m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or

 ,

n) $-C(=O)NR_{59}R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

R_{54} is the same as defined above;

R_{59} and R_{60} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{61} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

R_{62} and R_{63} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{64} is

a) H, or

b) a sodium ion;

R_{65} and R_{66} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

g) R_{65} and R_{66} taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of

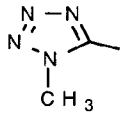
S, N, and O, optionally substituted with, including on the nitrogen

atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

R_{67} is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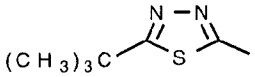
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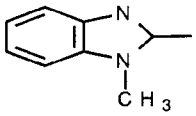
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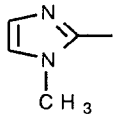

;

R_{68} is C_{1-3} alkyl;

R_{69} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{70} and R_{71} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{72} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

R_{73}, R_{74}, R_{75}, R_{76}, and R_{77} at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) CF_3,

h) $-NO_2$,

i) C_{1-6} alkoxy,

j) C_{1-6} alkoxycarbonyl,

k) C_{1-6} alkythio,

l) C_{1-6} acyl,

m) $-NR_{78}R_{79}$,

n) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{78}R_{79}$, -N(phenyl)(CH_2-CH_2-OH), -O-CH(CH_3)(OCH_2CH_3), or -O-phenyl-[para-NHC(=O)CH_3],

o) C_{2-8} alkenylphenyl optionally substituted with R_{51},

p) phenyl optionally substituted with R_{51}, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with R_{51};

R_{51} is the same as defined above;

R_{78} and R_{79} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) phenyl, or

d) R_{78} and R_{79} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

wherein T is

a) O,

b) S, or

c) SO_2;

R_{75}, R_{76}, and R_{77} are the same as defined above;

R_{80} is

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with

OH, halo, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

R_{81} and R_{82} at each occurrence are the same or different and are

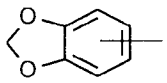
a) H,

b) C_{3-6} cycloalkyl,

c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy, $-NR_{83}R_{84}$, or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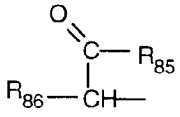
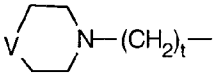
f) 
, or

g) 
;

V is

a) O,

b) CH_2, or

c) NR_{87};

R_{83} and R_{84} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{85} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{88}R_{89}$;

R_{86} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{87} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{88} and R_{89} at each occurrence are the same or different and are

a) H,

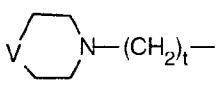
b) C_{1-5} alkyl

c) C_{3-6} cycloalky, or

d) phenyl;

R_{90} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl;

b) 

,

c) phenyl, or

d) pyridyl;

R_{91} is

a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{92} and R_{93} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{94} and R_{95} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) R_{94} and R_{95} taken together are =O;

R_{96} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

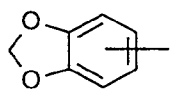
c) morpholinyl,

d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

h)  ;

R_{97} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

The new compounds of the invention can be prepared using known compounds and intermediates of oxzolidinones, isoxazolines and butyolactones as intermediates and synthetic methods known in the art. Thioamides of the invention can typically be prepared by the reaction of the corresponding amide with Lawesson's reagent.

Compounds disclosed in the following publications are suitable intermediates for preparation of the compounds of this invention and are hereby incorporated by reference for their disclosure of suitable compounds that can be converted to the subject thiocarbonyl derivatives.

U.S. Patents 5,225,565; 5,182,403; 5,164,510; 5,247,090; 5,231,188; 5,565,571; 5,547,950; and 5,523,403.

PCT Application and publications PCT/US93/04850, WO94/01110; PCT/US94/08904, WO95/07271; PCT/US95/02972, WO95/25106; PCT/US95/10992, WO96/13502; PCT/US96/05202, WO96/35691; PCT/US96/12766; PCT/US96/13726;

PCT/US96/14135; PCT/US96/17120; PCT/US96/19149; PCT/US97/01970; PCT/US95/12751, WO96/15130; and PCT/US96/00718, WO96/23788.

Chemical conversion techniques for converting various intermediates having a CH_2NH_2 on the oxazolidinone ring to CH_2NH-C(S)-CH_3 is disclosed by Hartke, K., Barrmeyer, S., J. prakt. Chem. 1996, 338, 251-6. Similarly, conversion of $CH_2NHC(=0)CH_3$ to $CH_2NHC(S)NHCH_3$ is reported by Cava, M.P.; Levinson, M.I., Thionation Reactions of Lawesson's Reagents, Tetrahedron 1985, 41, 5061-87.

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, C_{1-4} alkyl refers to alkyl of 1-4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

The terms "C_{1-2} alkyl", "C_{1-3} alkyl", "C_{1-4} alkyl", "C_{1-5} alkyl", "C_{1-6} alkyl", "C_{1-8} alkyl", and "C_{1-16} alkyl" refer to an alkyl group having one to two, one to three, one to four, one to five, one to six, one to eight, or one to sixteen carbon atoms respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof.

The terms "C_{2-4} alkenyl", "C_{2-5} alkenyl", "C_{2-8} alkenyl", "C_{2-14} alkenyl" and "C_{2-16} alkenyl" refer to at least one double bond alkenyl group having two to four, two to five, two to eight, two to fourteen, or two to sixteen carbon atoms, respectively such as, for example, ethenyl, propenyl, butenyl, pentenyl, pentdienyl, hexenyl, hexdienyl, heptenyl, heptdienyl, octenyl, octdienyl, octatrienyl, nonenyl, nonedienyl, nonatrienyl, undecenyl, undecdienyl, dodecenyl, tridecenyl, tetradecenyl and their isomeric forms thereof.

The terms "C_{2-5} alkynyl", "C_{2-8} alkynyl", and "C_{2-10} alkynyl" refer to at least one triple bond alkynyl group having two to five, two to eight, or two to ten carbon atoms respectively such as, for example, ethynyl, propynyl, butynyl, pentynyl, pentdiynyl, hexynyl, hexdiynyl, heptynyl, heptdiynyl, octynyl, octdiynyl, octatriynyl, nonynyl, nonediynyl, nonatriynyl and their isomeric forms thereof.

The terms "C_{3-4} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-6} cycloalkyl", and "C_{3-8} cycloalkyl" refer to a cycloalkyl having three to four, three to six, five to six, or three to eight carbon atoms respectively such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof.

The terms "C_{1-4} alkoxy", "C_{1-6} alkoxy", and "C_{1-8} alkoxy" refer to an alkyl

group having one to four, one to six, or one to eight carbon atoms respectively attached to an oxygen atom such as, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

The terms "C_{1-6} alkylamino", and "C_{1-8} alkylamino" refer to an alkyl group having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, heptylamino, or octoylamino and their isomeric forms thereof.

The terms "C_{1-6} dialkylamino", and "C_{1-8} dialkylamino" refer to two alkyl groups having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, dimethylamino, methylethylamino, diethylamino, dipropylamino, methypropylamino, ethylpropylamino, dibutylamino, dipentylamino, dihexylamino, methylhecylamino, diheptylamino, or dioctoylamino and their isomeric forms thereof.

The terms "C_{1-3} acyl", "C_{1-4} acyl", "C_{1-5} acyl", "C_{1-6} acyl", "C_{1-8} acyl", and "C_{2-8} acyl" refer to a carbonyl group having an alkyl group of one to three, one to four, one to five, one to six, one to eight, or two to eight carbon atoms.

The terms "C_{1-4} alkoxycarbonyl", "C_{1-6} alkoxycarbonyl", and "C_{1-8} alkoxycarbonyl" refer to an ester group having an alkyl group of one to four, one to six, or one to eight carbon atoms.

The term "C_{1-8} alkyl phenyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "C_{2-8} alkenyl phenyl" refers to a at least one double bond alkenyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "C_{1-8} alkyl pyridyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one pyridyl radical.

The term "C_{1-8} hydroxyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a hydroxy group.

The term "C_{1-8} alkylsulfonyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a SO_2 moiety.

The term "C_{1-6} alkylthio" refers to an alkyl group having one to six carbon atoms and isomeric forms thereof attached to a sulfur atom.

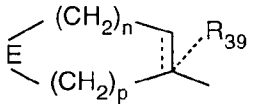
The term "Het" refers to 5 to 10 membered saturated, unsaturated or aromatic heterocyclic rings containing one or more oxygen, nitrogen, and sulfur forming such groups as, for example, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxathiole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 7-oxo-2-isoindolyl,1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone. Each of these moieties may be substituted as appropriate.

The term halo refers to fluoro, chloro, bromo, or iodo.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition 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.

When Q is the structure of



the dotted line in the heterocyclic ring means that this bond can be either single or double. In the case where the dotted line is a double bond, the R_{39} group will not be

present.

The compounds of Formula I of this invention contain a chiral center at C5 of the isoxazoline ring, and as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on substituents, additional chiral centers and other isomeric forms may be present in any of A or R_1 group, and this invention embraces all possible stereoisomers and geometric forms in these groups.

The compounds of this invention are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds 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 according to this invention.

The quantity of active component, that is the compound 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., 2-4 four times per day.

When the compounds 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 or 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 of this invention 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 according to this invention are advantageously administered orally in solid and liquid dosage forms.

MIC Test Method

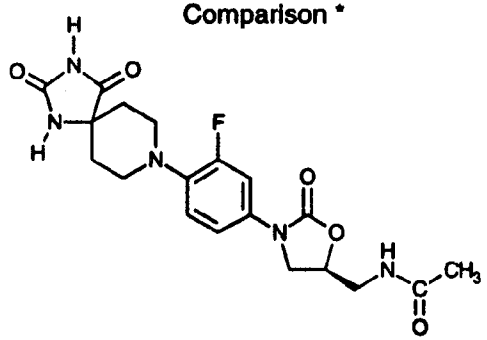
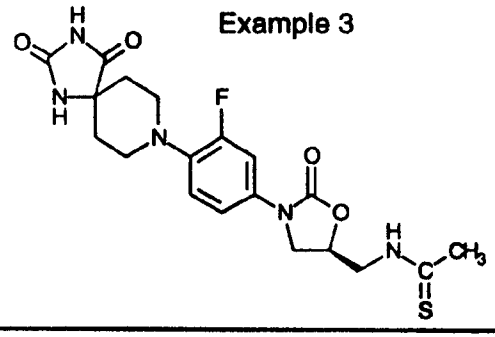
The in vitro MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog is prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug is added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar is mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to

inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension is made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

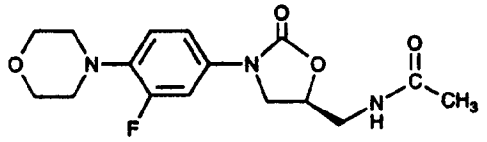
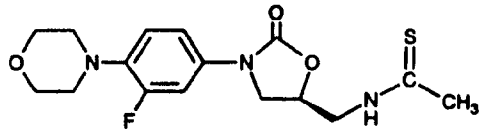
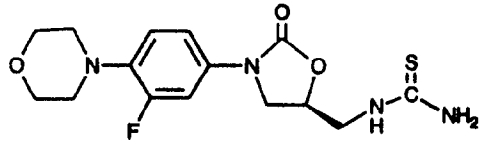
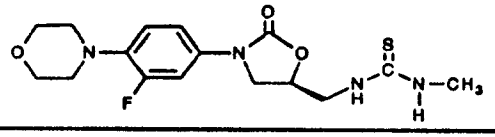
Following incubation the Minimum Inhibitory Concentration (MIC µg/ml), the lowest concentration of drug that inhibits visible growth of the organism, is read and recorded. The data is shown in Tables I and II.

TABLE 1

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	16	4	8	.5	1
Example 3 	4	1	2	.25	.5

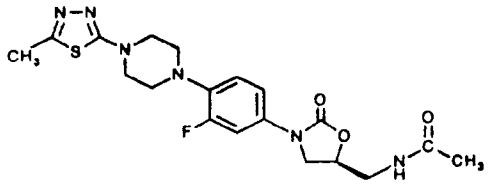
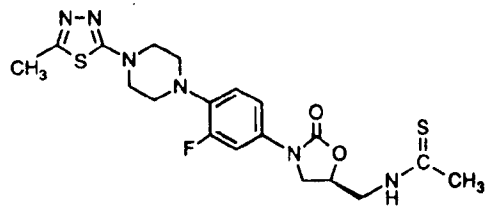
*not a compound of the subject invention

TABLE 1 (cont'd)

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	2	1	2	.5	1
Example 1 	1	.25	.5	.13	.13
Example 5 	1	.25	.5	<.125	.25
Example 6 	2	1	2	.5	1

*not a compound of the subject invention

TABLE 1 (cont'd)

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	.5	.25	1	.13	.25
Example 2 	8	2	4	2	4

SAUR: S. *aureus*
SEPI: S. *epidermidis*
EFAE: E. *faecalis*
SPNE: S. *pneumoniae*
SPYO: S. *pyogenes*

*not a compound of the subject invention

TABLE II

Example No.	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	SPYO 152 MIC	HINF 30063 MIC	MCAT 30610 MIC	EFAE 9217 MIC
1	1	0.25	0.5	<0.125	<0.125	8	1	0.5
2	8	4	8	2	4	>16	>16	4
3	4	1	1	0.25	0.5	16	4	2
5	1	0.5	0.5	<0.125	0.25	4	2	0.5
6	2	2	2	0.5	1	16	8	2
7	0.5	0.25	0.5	<0.125	0.25	4	1	0.5
8	2	1	0.5	<0.125	0.25	4	2	1
9	0.5	0.25	0.25	<0.125	<0.125	2	0.5	0.25
10	2	1	0.5	<0.125	0.25	2	1	1
11	0.25	0.25	0.25	<0.125	0.25	2	1	0.25
12	1	0.5	0.25	<0.125	<0.125	1	0.5	0.5
13	1	1	2	0.5	1	>16	8	2
14	1	0.5	1	0.25	0.5	8	1	1
15	32	16	32	4	8	>64	64	32
16	8	8	16	2	8	>64	32	16
17	2	2	4	1	2	64	16	4
18	2	1	2	<0.5	1	32	4	2
19	32	16	32	16	16	64	32	32
21	4	4	8	2	4	64	16	8
22, 23	0.5	0.5	1	<0.125	0.25	4	2	1
24	1	0.25	0.5	<0.125	0.25	4	2	0.5
25	0.5	0.25	0.5	<0.125	<0.125	2	2	0.5
26	1	0.5	1	0.25	0.5	16	2	1

TABLE II (cont'd)

Example No.	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	SPYO 152 MIC	HINF 30063 MIC	MCAT 30610 MIC	EFAE 9217 MIC
27	0.5	0.5	0.5	<0.125	0.25	4	2	1
28	0.5	0.25	0.5	0.25	0.25	2	1	0.5
29	0.25	0.25	0.25	<0.125	<0.125	2	0.5	0.25
30	4	1	0.5	<0.125	0.25	8	2	1
31	2	1	1	<0.125	0.25	4	1	1
32	16	2	2	0.25	0.25	8	2	4
33	4	2	1	0.25	0.25	4	2	4
34	2	1	2	0.5	1	>16	4	2
35	1	0.5	1	0.25	0.5	16	2	1

Key:

SAUR	9213:	S. *aureus*
SEPI	30593:	S. *epidermidis*
EFAE	12712:	E. *Faecium*
SPNE	9912:	S. *pneumoniae*
SPYO	152:	S. *pyogenes*
HINF	30063:	*Haemophilus influenzae*
MCAT	30610:	*Moraxella catarrhalis*
EFAE	9217:	*Enterococcus faecalis*

As shown in Scheme 1, the intermediates **II** for the compounds of this invention are also intermediates disclosed in the oxazolidinone patents and published applications hereinabove incorporated by reference. The intermediates **IV** for this invention are final products (Examples) from the oxazolidinone patents and published applications hereinabove incorporated by reference.

As shown in Scheme 1, Step 1, and illustrated in Example 5, the isothiocyanates **III** can be conveniently prepared by allowing the amine intermediates (**II**) to react with 1,1'-thiocarbonyldi-2(1H)-pyridone in solvents such as methylene chloride at 0 to 25°C. The thioureas (**Ia**, R' = H, $alkyl_{1-4}$) can then be prepared as shown in Step 2 by the reaction of **III** with ammonia or the appropriate primary amines in solvents such as 1,4-dioxane or tetrahydrofuran at 0-50°C. Alternatively, as illustrated in Example 6 and shown in Step 3, the thioureas can be prepared by allowing **II** to react with an appropriate isothiocyanate (R' - N = C = S) in solvents such as tetrahydrofuran at 0-50°C. Thioamides (**Ib**, R'' = H, $alkyl_{1-4}$) are prepared by allowing **II** to react with an appropriate dithioester (R''' S-C(=S)-R'', Step 4 as illustrated in Example 4. This reaction is carried out in aqueous-alcoholic solvents at 0-50°C in the presence of an equivalent of an alkali metal hydroxide. This reaction, especially when R''' is methyl or ethyl, can be catalyzed by an alkali metal fluoride.

The reaction of II with R'''-S-C(S)-R''' (R'''=CH_3, C_2H_5) to give Ib (Step 4) can also be carried out in the presence of a tertiary amine base such as triethylamine in solvents such as THF, dioxane or methylene chloride at 10-50°C for 3-48 hr.

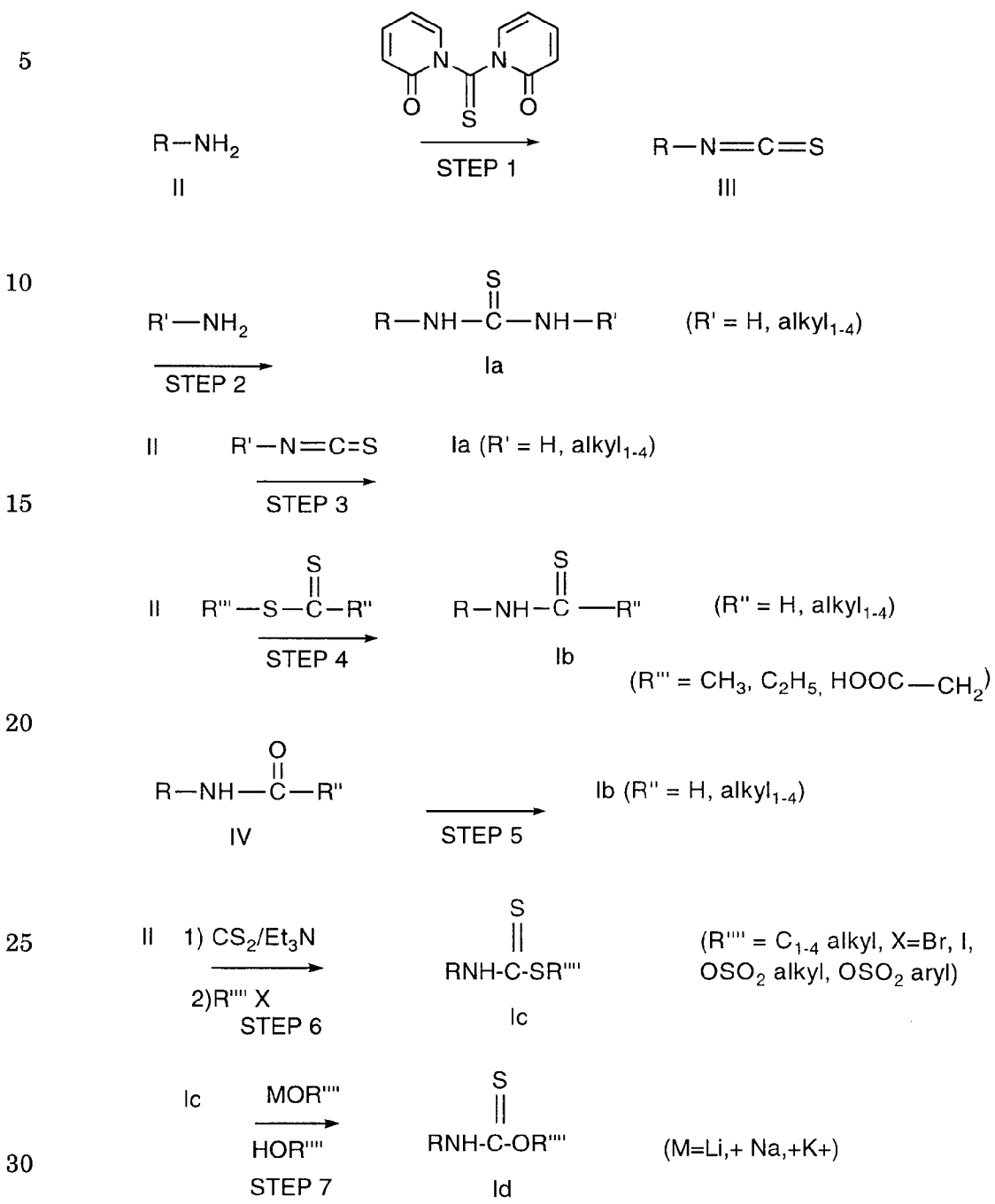
When the reaction conditions are tolerated by the substituents on R (see, for example, Examples 1-3) the thioamides (**Ib**, R'' - H, $alkyl_{1-4}$) can also be conveniently prepared (Step 5) by allowing the appropriate amide intermediates (IV) to react with reagents such as 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (Lawesson's Reagent) in 1,4-dioxane, benzene, toluene or tetrahydrofuran at 60-110°C; phosphorus decasulfide and sodium carbonate in tetrahydrofuran at 20-50°C [Brillon, D., Synthetic Communications, 20, 3085 (1990)] or phosphorus decasulfide and sodium fluoride in 1,2-dimethoxyethane at 20-50°C [Hartke, K., Gerber, H.-D., J. Prakt. Chem., 338, 763 (1996)].

Compounds Ic are prepared (Step 6) by allowing II to react first with carbon disulfide and a tertiary amine base such as triethylamine in solvent mixtures containing water and methanol, ethanol or isopropanol at 10-50°C for 5-24 hours. The resulting intermediate is treated with an alkylating agent (R'''' X where X represents bromo, iodo, alkylsulfonyloxy or arylsulfonyloxy) at 0-30°C to give

compounds Ic. In Step 7, compounds Ic are allowed to react with alkali metal alkoxide such as sodium methoxide or potassium ethoxide in the corresponding alkanol as solvent. This reaction is conveniently carried out at the reflux temperature of the alkanol for 1-24 hr.

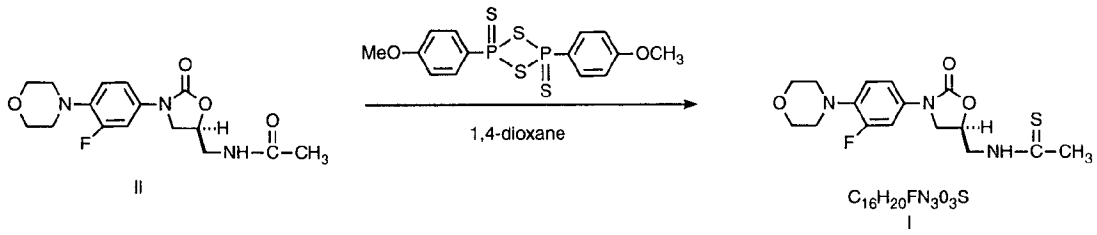
5

SCHEME 1



In order to more fully illustrate the nature of the invention and the manner of practicing the same, the following experimental examples are presented.

EXAMPLE 1: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (I)

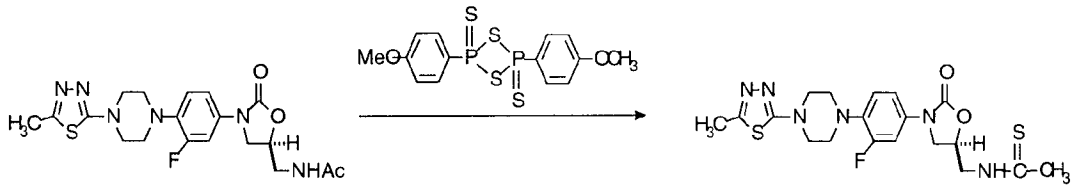


II

$C_{16}H_{20}FN_3O_3S$
I

A stirred mixture of II (PCT/US94/08904, 3.37 g, 10.0 mmol) in dry dioxane (100 mL), under nitrogen was treated with Lawesson's Reagent (4.04g, 10.0 mml), warmed to reflux during 1 h and refluxed for 1.5 h. The reaction was complete by TLC on silica gel with 10% MeOH-$CHCl_3$. It was kept at ambient temperature for 18 h and concentrated in vacuo. Chromatography of the residue on silica gel with mixtures of acetone-methylene chloride containing 10-15% acetone gave the product which was crystallized from acetone-hexane to give 1: mp 157.5-158.5 °C; HRMS theory for $C_{16}H_{20}FN_3O_3S$ (M^+): 353.1209; found: 353.1212. Anal. calcd for $C_{16}H_{20}FN_3O_3S$: C, 54.38; H, 5.38; N, 11.89; S, 9.07. Found: C, 54.21; H, 5.58; N, 11.78; S, 8.93.

EXAMPLE 2: (*S*)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (2)



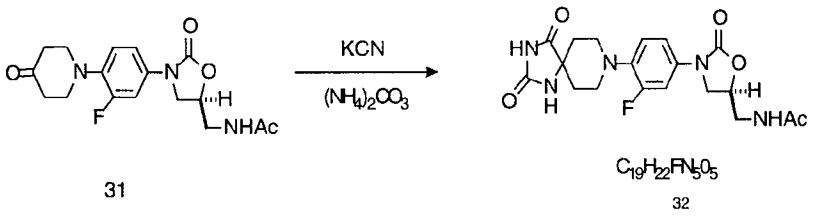
21

$C_{19}H_{23}FN_6O_2S_2$
2

According to Example 1, for the preparation of 1, 21 (PCT/US97/01970) was allowed to react with Lawesson's Reagent in refluxing dioxane to give 2: mp 222-223 °C; HRMS theory for $C_{19}H_{24}FN_6O_2S_2$ ($M+H^+$): 451.1386; found 451.1381.

EXAMPLE 3: (*S*)-N-[[3-[3-Fluoro-4-[2',5'-dioxospiro[piperidine-4,4'-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).

STEP A: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (32).



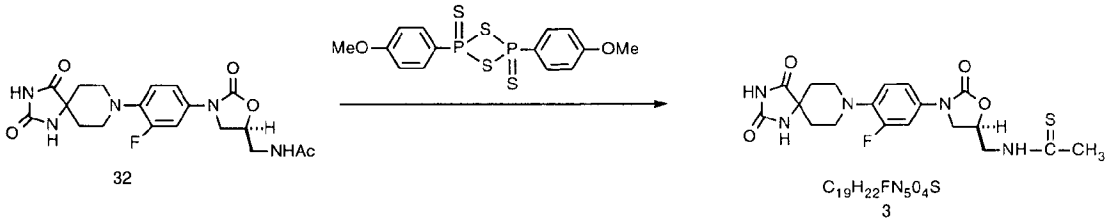
31

$C_{19}H_{22}FN_5O_5$

32

A stirred suspension of 31 (Case 4780.P CP, 0.349 g, 1.00 mmol) in 1:1 EtOH:H_2O (5 mL), under nitrogen, was treated with potassium cyanide (0.130 g, 2.00 mmol) and ammonium carbonate (0.701 g, 7.30 mmol), warmed at 55-60 °C for 5 h 15 min and kept at ambient temperature for 17 h 15 min. It was then chromatographed on silica gel with mixtures of MeOH-NH_4OH-$CHCl_3$ containing 5-20% MeOH and 0.5% NH_4OH to give 0.280 g of 32: HRMS calcd for $C_{19}H_{22}FN_5O_5$: 419.1605 (M^+); found 419.1613; Anal. calcd for $C_{19}H_{22}FN_5O_5 \cdot 1\ H_2O$: C, 52.17; H, 5.53; N, 16.01. Found: C, 52.44; H, 5.30; N, 16.11.

STEP B: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).



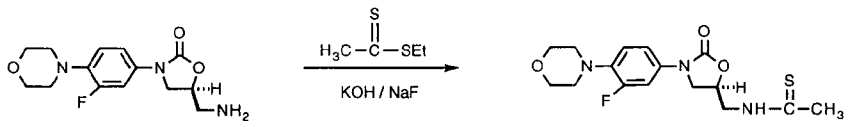
32

$C_{19}H_{22}FN_5O_4S$

3

A stirred suspension of 32 (0.210 g, 0.500 mmol) in dioxane (5.0 mL), under nitrogen was treated with Lawesson's Reagent (0.202 g, 0.500 mmol), refluxed for 4 h and concentrated in vacuo. The residue was chromatographed on silica gel with mixtures of MeOH-NH_4OH-$CHCl_3$ containing 1-10% MeOH and 0.1-0.5% NH_4OH and the resulting product was crystallized from MeOH-$CHCl_3$-EtOAc to give 0.0491 g of 3: mp 218.5 °C; HR FAB MS theory for $C_{19}H_{22}FN_5O_4S$ (M^+): 435.1376; found 435.1370. Anal. calcd for $C_{19}H_{22}FN_5O_4S \cdot 0.5\ H_2O$: C, 51.34; H, 5.21; N, 15.76. Found: C, 51.69; H, 5.00; N, 15.25.

EXAMPLE 4: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (4).

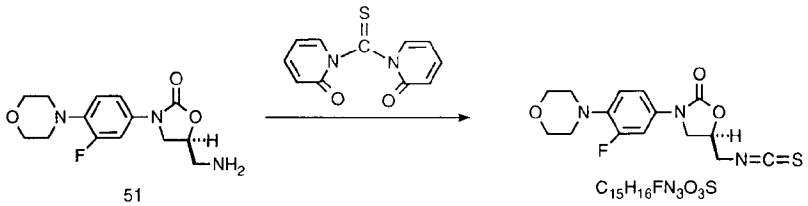


41 $C_{16}H_{20}FN_3O_3S$ 4

A solution of 41 (148 mg, 0.500 mmol) and 0.97 M KOH (0.515 mL) in absolute EtOH (5 mL) was added to a solution of ethyl dithioacetate (57 µL, 0.50 mmol) and sodium fluoride (20 mg, 0.47 mmol) in absolute EtOH (5 mL) and the mixture was kept at ambient temperature for 3 h 40 min. Additional ethyl dithioacetate (5 µL) was added after 1 h 55 min and additional 0.97 M KOH (40 mL) and sodium fluoride (6 mg) were added to the mixture after 3h 5 min. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$ and 30% acetone-CH_2Cl_2. The major product had an R_f on TLC that was the same as that of 4.

EXAMPLE 5: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (5).

STEP A:

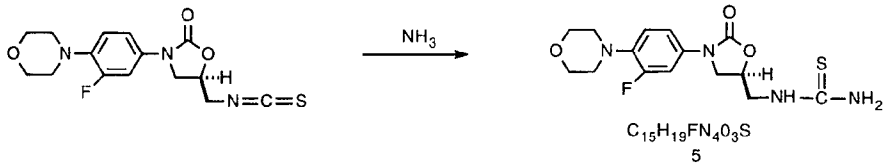


51 $C_{15}H_{16}FN_3O_3S$

A solution of 51 (PCT/US94/08904, 2.07 g, 7.00 mmol) in CH_2Cl_2 was added, dropwise during 30 min, under nitrogen to an ice cold, stirred solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (1.95 g, 8.40 mmol) in CH_2Cl_2 (70 mL). The mixture was warmed slowly to ambient temperature and kept for 18 h. It was then diluted with CH_2Cl_2, washed with water and aqueous NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 10% acetonitrile-CH_2Cl_2 gave 1.60 g of the isothiocyanate: HRMS theory for $C_{15}H_{16}FN_3O_3S$ (M^+): 337.0896; found

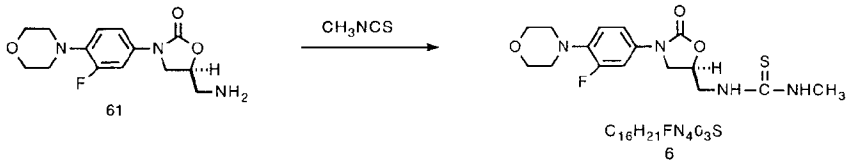
337.0888.

STEP B:



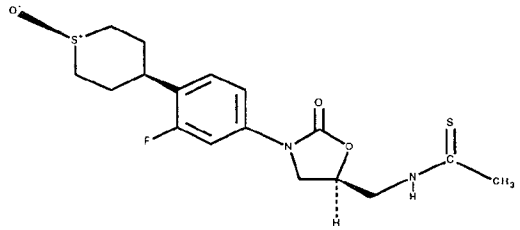
Anhydrous ammonia was bubbled for 7 min through a stirred solution of the product from Step I (1.00 g, 2.96 mmol) in THF (10 mL) and the mixture was kept at ambient temperature for 3 h 25 min and concentrated in vacuo. Crystallization of the residue from acetone-hexane gave 0.861 g of 5: mp 199-199.5 °C; MS *m/z* 354 (M^+). Anal. calcd for $C_{15}H_{19}FN_4O_3S$: C, 50.84; H, 5.40; N, 15.81. Found: C, 50.87; H, 5.39; N, 15.72.

EXAMPLE 6: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea (6).



A stirred solution of methyl isothiocyanate (93 mg, 1.27 mmol) in THF, was treated with 61 (295 mg, 1.00 mmol), kept at ambient temperature for 18 h and concentrated in vacuo. The residue was recrystallized from EtOAc-hexane to give 246 mg of 6: mp 158-160 °C; MS *m/z* 368 (M^+). Anal. calcd for $C_{16}H_{21}FN_4O_3S$: C, 52.16; H, 5.74; N, 15.21. Found: C, 52.20; H, 5.85; N, 15.17.

EXAMPLE 7 (S)-cis-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



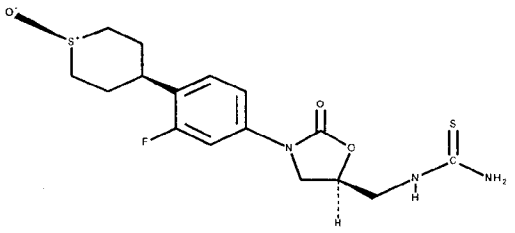
Step 1: A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide (4.50 g, can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) and platinum oxide (697 mg) in methanol (164 mL) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 18 hours. The catalyst is then removed by filtration through Celite, and the filtrate is concentrated under reduced pressure and the residue chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3/97 - 7/93). Pooling and concentration of those fractions with an R_f = 0.44 by TLC (methanol/chloroform, 10/90) gives (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, mp 203 - 204°C.

Step 2: A mixture of the compound prepared in Step 1 (2.50 g) and hydroxylamine hydrochloride (2.36 g) in pyridine (30.6 mL) and ethanol (3.4 mL) is stirred in a screw-cap vial at 100°C for 22 hrs and at ambient temperature for 16 hrs, during which additional hydroxylamine hydrochloride (944 mg) and pyridine (4 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (100 mL) and saline (50 mL), adjusted to pH 11 with solid sodium carbonate and extracted with methanol/methylene chloride (10/90, 5 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (6/94 - 10/90). Pooling and concentration of those fractions with an R_f = 0.14 by TLC (methanol/chloroform, 10/90) gives (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 159 - 161°C.

Step 3: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-

yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 2,(300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 4 hours and was then diluted with methylene chloride (150 mL) and washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and the crude product was triturated with methylene chloride/diethyl ether and filtered to give the title compound, mp 176 - 177°C (dec.).

EXAMPLE 8 (S)-cis-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea

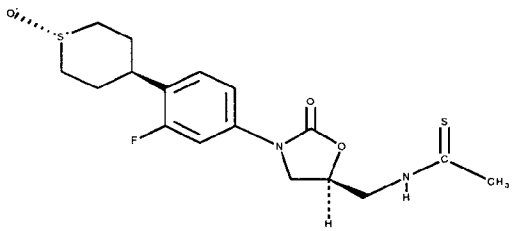


Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (235 mg, 1.01 mmol) in anhydrous methylene chloride (10 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 7, Step 2, (275 mg, 0.843 mmol) in anhydrous methylene chloride (34 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1 hour and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (70 - 230 mesh, 20 g), eluting with acetonitrile/methylene chloride (40/60), and those fractions with an R_f = 0.07 by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-cis-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 187 - 190°C (dec.).

Step 2: A solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 290 mg, 0.787 mmol) in anhydrous tetrahydrofuran (39 mL) at 0°C under a nitrogen atmosphere was treated

(bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 206 - 208°C (dec.).

EXAMPLE 9 (S)-trans-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide

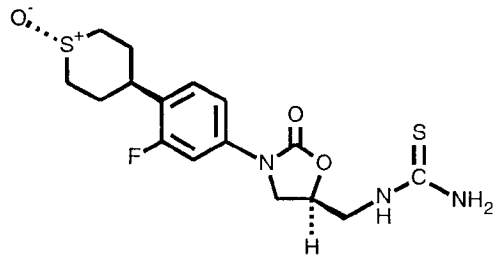


Step 1: (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-ox azolidinyl]methyl]acetamide S-oxide (disclosed in International Publication No. WO 97/09328) may be reduced to the corresponding cis- and trans-sulfoxides by catalytic hydrogenation in the presence of a catalyst and solvent. Alternatively, the sulfide by product of this reduction reaction can be oxidized with an oxidizing agent such $NaIO_4$ or meta-chloroperoxybenzoic acid in solvent to provide the cis- and trans-sulfoxides. The isomeric mixture can then be separated by chromatography to isolate the trans-sulfoxide, mp 211 - 212°C (dec.). A mixture of the trans-sulfoxide, (S)-trans-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (0.90 g) and hydroxylamine hydrochloride (0.85 g) in pyridine (11.0 mL) and ethanol (1.2 mL) is stirred in a screw-cap vial at 100°C for 23 hrs and at ambient temperature for 19 hrs, during which additional hydroxylamine hydrochloride (340 mg) and pyridine (1 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium carbonate (50 mL) and saline (50 mL) and extracted with methanol/methylene chloride (10/90, 6 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of methanol/methylene chloride (7.5/92.5 - 10/90). Pooling and concentration of those fractions with an R_f =

0.14 by TLC (methanol/chloroform, 10/90) gives (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 138 - 140°C.

Step 2: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepare in Step 1, (300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 17 hours and was then diluted with methylene chloride (150 mL), washed with water (2 x 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 35 g), eluting with methanol/methylene chloride (3/97), and those fractions with an R_f = 0.56 by TLC (methanol/chloroform, 10/90) were pooled and concentrated and the residue recrystallized from methylene chloride/diethyl ether to give the title compound, mp 193 - 194°C (dec.).

EXAMPLE 10 (S)-trans-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea

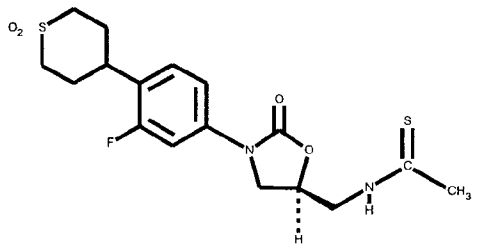


Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (192 mg, 0.827 mmol) in anhydrous methylene chloride (8.3 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 9, Step 1, (225 mg, 0.689 mmol) in anhydrous methylene chloride (28 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 40 minutes and was then diluted with methylene chloride (20 mL), washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (32 - 63 mm, 40 g), eluting with a gradient of acetonitrile/methylene chloride (30/70 -

60/40) under 15 psi N_2, and those fractions with an R_f = 0.12 by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-trans-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4- yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 165 - 167°C.

Step 2: A solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 230 mg, 0.624 mmol) in anhydrous tetrahydrofuran (31.2 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Trituration with methanol/methylene chloride/diethyl ether gave the title compound, mp 209 - 210°C (dec.).

EXAMPLE 11 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide

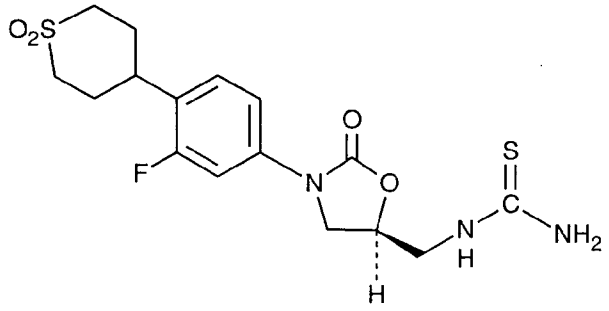


Step 1: Starting with (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as prepared in Example 7, Step 1, and following the general procedure of Step 2, and making non-critical variations by substituting (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (disclosed in International Publication No. WO 97/09328) for (S)-cis-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the product (S)-(-)-3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone is obtained, mp 194°C (dec.).

Step 2: A solution of ethyl dithioacetate (100 mL, 0.876 mmol) and sodium fluoride (37 mg, 0.876 mmol) in ethanol (8.8 mL) under a nitrogen atmosphere was

treated with a mixture of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 1, (300 mg, 0.876 mmol) and aqueous potassium hydroxide (1M, 0.88 mL) in ethanol (43.8 mL). The resulting mixture was stirred at ambient temperature for 26 hours, during which additional ethyl dithioacetate (50 mL, 0.438 mmol), sodium fluoride (19 mg, 0.438 mmol), aqueous potassium hydroxide (1M, 0.44 mL) and ethanol (3.0 mL) was added, and was then diluted with methylene chloride (150 mL), washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was recrystallized from methylene chloride/diethyl ether to give the title compound, mp 186 - 187°C (dec.).

EXAMPLE 12 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea

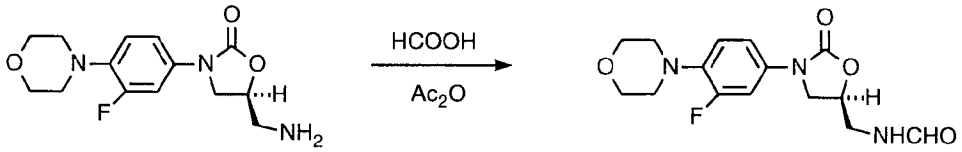


Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (304 mg, 1.31 mmol) in anhydrous methylene chloride (13 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 11, Step 1, (375 mg, 1.09 mmol) in anhydrous methylene chloride (88 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 30 minutes and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with acetonitrile/methylene chloride (7.5/92.5), and those fractions with an R_f = 0.64 by TLC (acetonitrile/methylene chloride, 20/80) were pooled and concentrated to give (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 158 - 162°C (dec.).

Step 2: A solution of (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 380 mg, 0.988 mmol) in anhydrous tetrahydrofuran (49 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 196 - 198°C (dec.).

EXAMPLE 13: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide (7).**

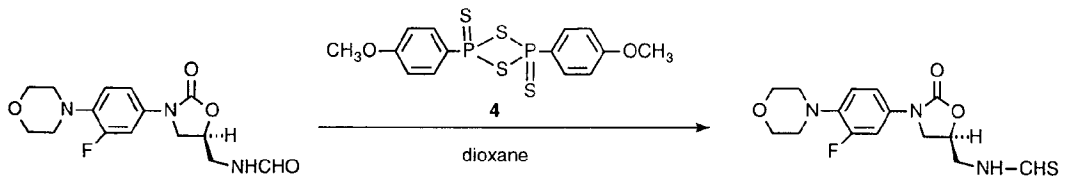
1.



39 6

A stirred mixture of acetic anhydride (0.23 mL, 0.0024 mol) and 95-97% formic acid (0.10 mL, 0.0027 mL) was warmed, under nitrogen at 50-55 °C for 2 h, cooled to ambient temperature and treated, portionwise during 2 min, with **39**[8] (0.45 g, 0.0015 mol). The suspension was kept at ambient temperature for 4 h and the resulting solution was treated with Et_2O (1 mL) and kept at ambient temperature for 18 h. The mixture was diluted with additional Et_2O (10 mL) and the solid was collected by filtration, washed with Et_2O and dried to give 0.38 g of **6**[9]: MS (ES) *m/z* 324 ($M+H^+$), 346 ($M+Na^+$); ^1H NMR (300 mHz, $CDCl_3$) d 3.08 (m, 4H), 3.72 (m, 2H), 3.77 (d,d, 1H), 3.89 (m, 4H), 4.04 (t, 1H), 4.80 (m, 1H), 6.33 (s, 1H), 7.05 (m, 2H), 7.45 (d,d, 1H), 8.27 (s, 1H).

2.

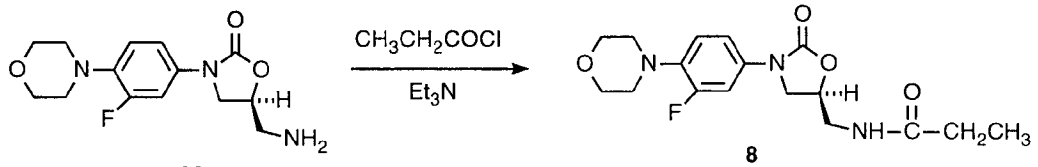


6 7

A stirred mixture of **6** (0.38 g, 0.00118 mol) in dioxane (20 mL), under nitrogen was treated with 4 (0.51 g, 0.00126 mol), warmed to reflux during 30 min and kept at this temperature for 90 min. It was then evaporated under a stream of nitrogen. The residue was chromatographed on silica gel with 1.25% MeOH-CH_2Cl_2 and the slightly impure product was rechromatographed on silica gel with 25% EtOAc-CH_2Cl_2. The resulting product was crystallized from EtOAc-methyl *tert*-butyl ether to give 0.114 g of **7**: mp 150-155 °C (dec); IR (DRIFT) 3322, 1752 cm^{-1}; MS(ES) *m/z* 340 ($M+H^+$), 362 ($M+Na^+$); ^{1}HNMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.72 (m, 4H), 3.77 (d,d, 1H), 3.94 (t, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.33 (d, 1H), 10.59 (s, 1H). Anal. calcd for $C_{15}H_{18}FN_3O_3S$: C, 53.08; H, 5.35; N, 12.38. Found: C, 53.02; H, 5.44; N, 12.36.

EXAMPLE 14: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiopropion-amide (9).**

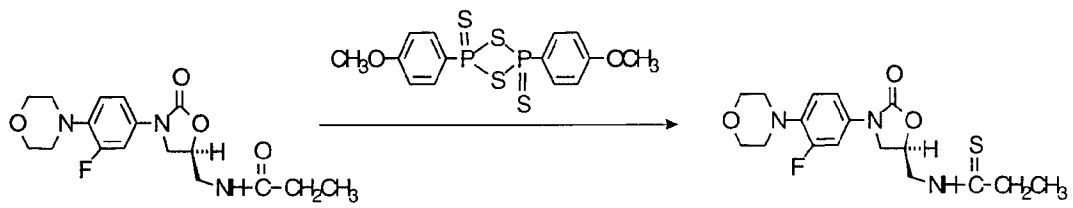
1.



39 8

An ice cold, stirred solution of **39**[8] (0.395 g, 0.00134 mol) and triethyl amine (0.186 mL, 0.0027 mol) in CH_2Cl_2 (20 mL), under nitrogen was treated, dropwise during 2 min, with a solution of propionyl chloride (0.128 mL, 0.00147 mol) in CH_2Cl_2 (3 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 1 h. It was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue (**8**)[9] was used without further purification in the next reaction.

2.



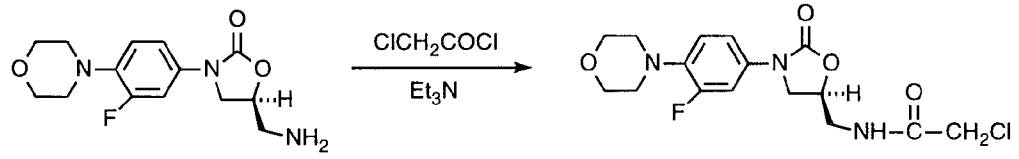
8 9

A stirred mixture of the product (**8**) from the previous reaction and dioxane (20 mL), under nitrogen, was treated, portionwise during 1 min, with Lawesson's reagent

(0.58 g, 0.0014 mol) and refluxed for 2 h; it was then concentrated. The residue was chromatographed on silica gel with 2% MeOH-$CHCl_3$ and the product was crystallized from methyl *tert*-butyl ether to give 0.259 g of **9**: mp 138-139 °C; MS(ES) *m/z* 368 ($M+H^+$), 390 ($M+Na^+$); IR (DRIFT) 3284, 3266, 1748, 1744 cm^{-1}; $[\alpha]^{24}_D$ +20° (MeOH); 1H NMR[300 MHz, $(CD_3)_2SO$] d 1.12 (t, 3H), 2.56 (q, 2H), 2.94 (m, 4H), 3.72 (m, 4H), 3.78 (d,d, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 10.30 (broad s, 1H). Anal. calcd for $C_{17}H_{22}FN_3O_3S$: C, 55.57; H, 6.03; N, 11.44. Found: C, 55.68; H, 6.21; N, 11.37.

EXAMPLE 15: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2-chlorothioacetamide (11).**

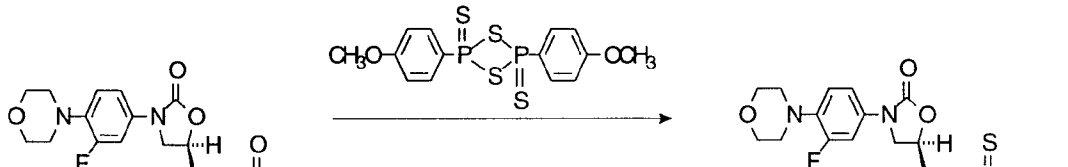
1.



39 10

A stirred solution of **39** (1.54 g, 5.2 mmol) and triethylamine (750 mg, 7.5 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was treated, dropwise, during 15 min with a solution of chloroacetyl chloride (465 mL, 5.8 mmol) in CH_2Cl_2 (30 mL) and kept at ambient temperature for 18 h. It was then washed with saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was flash chromatographed on silica gel with 20-30% acetone-CH_2Cl_2 to give 1.49 g of **10**[9] which was used in the next reaction without further purification.

2.



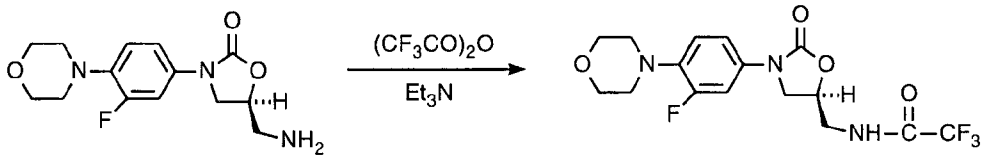
10 11

A stirred mixture of **10** (0.371 g, 1.0 mmol) and Lawesson's reagent (0.420 mg, 1.04 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h and concentrated under reduced pressure. The residue was chromatographed on silica gel with 3-10% acetone-CH_2Cl_2 to give 0.143 g of **11**: MS (CI) *m/z* 388 ($M+H^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.07 (m, 4H), 3.77 (d,d, 1H), 3.88 (m, 4H), 4.04 (m, 1H), 4.12 (t, 1H),

4.35 (m, 1H), 4.61 (s, 2H), 4.98 (m, 1H), 6.96 (t, 1H), 7.08 (d,d, 1H), 7.44 (d,d, 1H), 8.69 (s, 1H). Anal. calcd for $C_{16}H_{19}ClFN_3O_3S$: C, 49.55; H, 4.94; N, 10.83. Found: C, 49.38; H, 5.20; N, 10.27.

EXAMPLE 16: **(*S*)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide (13).**

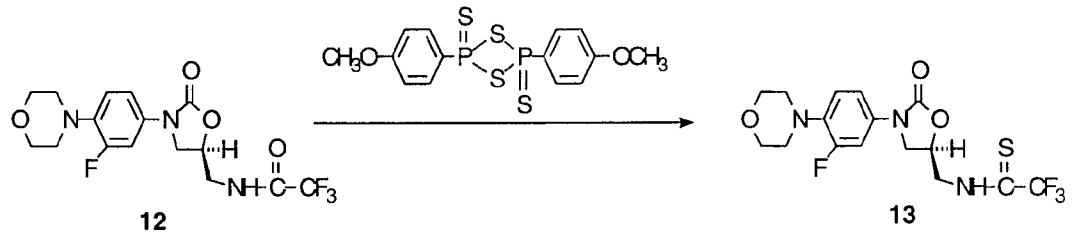
1.



39 12

An ice cold stirred solution of **39** (0.590 g, 2.0 mmol) and triethylamine (640 mL, 4.6 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic anhydride (325 mL, 2.3 mmol) and kept in the ice bath for 10 min and then at ambient temperature. The reaction was followed by TLC on silica gel with 30% acetone-CH_2Cl_2. Additional trifluoroacetic anhydride and triethylamine were added after 3 d (64 mL / 125 mL), 4 d (100 mL / 220 mL) and 6 d (325 mL / 1.0 mL). The reaction was complete 1 h after the last addition; it was mixed with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was recrystallized from acetone-heptane to give 0.566 g of **12**: mp 161-164 °C (dec); MS(EI) *m/z* 391 (M^+). Anal. calcd for $C_{16}H_{17}F_4N_3O_4$: C, 49.11; H, 4.38; N, 10.74. Found: C, 48.99; H, 4.56; N, 10.73.

2.



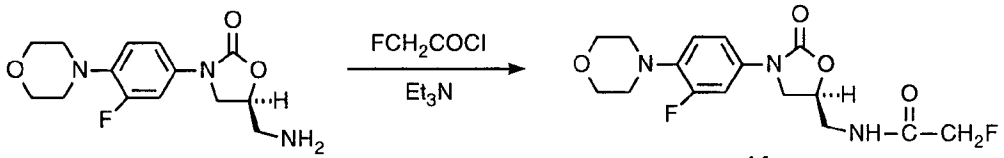
12 13

A stirred mixture of **12** (0.391 g, 1.0 mmol) and Lawesson's reagent (0.422 g, 1.1 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h, cooled slowly to ambient temperature and concentrated in vacuo. The residue was flash chromatographed on silica gel with 5-15% acetone-CH_2Cl_2 and the product was crystallized from acetone-heptane to give 0.249 g of **13**: mp 151-152 °C; MS(EI) *m/z* 407 (M^+), 363, 209, 151, 95; ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (d,d,

1H), 3.87 (m, 4H), 3.95 (m, 1H), 4.14 (t, 1H), 4.32 (m, 1H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.38 (d,d, 1H), 9.03 (s, 1H). Anal. calcd for $C_{16}H_{17}F_4N_3O_3S$: C, 47.17; H, 4.21; N, 10.31. Found: C, 47.09; H, 4.35; N, 10.27.

EXAMPLE 17: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide (15).**

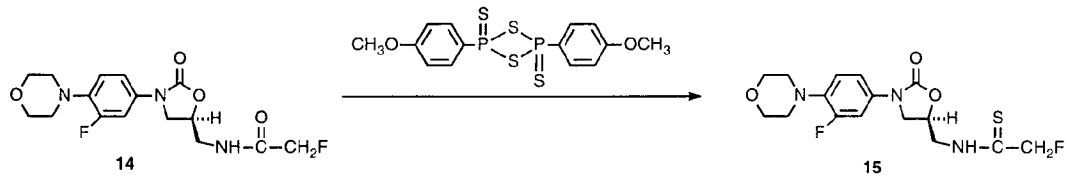
1.



39 14

A stirred, ice cold solution of **39** (0.590 g, 2.0 mmol) and triethylamine (611 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), under nitrogen, was treated, dropwise, with a solution of fluoroacetyl chloride (220 mL, 2.2 mmol) in CH_2Cl_2 (5 mL), kept in the ice bath for 10 min and at ambient temperature for 2 h. It was then diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with 10-30% acetone-CH_2Cl_2 to give 0.180 g of **14**: MS(ES) *m/z* 356 ($M+H^+$), 378 ($M+Na^+$).

2.

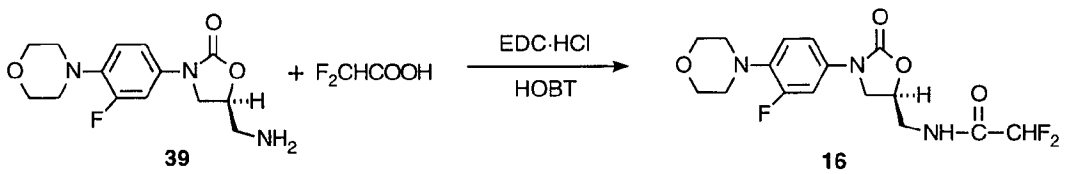


14 15

A solution of **14** (0.180 g, 0.507 mmol) in dioxane, under nitrogen, was treated with Lawesson's reagent (0.206 g, 0.51 mmol), warmed at 90-100 °C for 1 h and concentrated in vacuo. The residue was chromatographed on silica gel with 15% acetone-CH_2Cl_2 to give 0.161 g of **15**: MS(EI) *m/z* 371 (M^+); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.78 (d,d, 1H), 3.87 (m, 4H), 4.03 (m, 1H), 4.11 (t, 1H), 4.38 (m, 1H), 4.98 (m, 1H), 5.07 (s, 1H), 5.23 (s, 1H), 6.93 (t, 1H), 7.08 (dd, 1H), 7.42 (d,d, 1H), 8.42 (s, 1H). Anal. calcd for $C_{16}H_{19}F_2N_3O_3S$: C, 51.74; H, 5.16; N, 11.31. Found: C, 51.79; H, 5.31; N, 11.02.

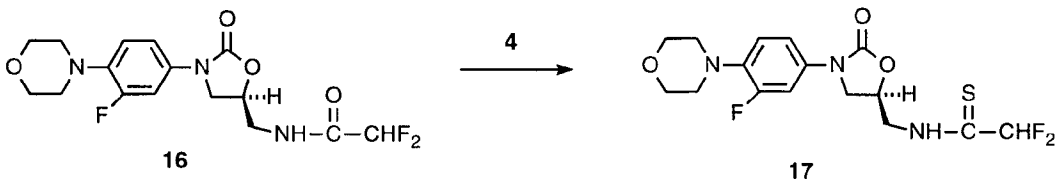
EXAMPLE 18: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide (17).**

1.



A stirred, ice cold mixture of **39** (0.590 g, 2.0 mmol), difluroacetic acid (190 mL, 2.0 mmol), and 1-hydroxybenzotriazole (0.297 g, 2.2 mmol) in DMF (5 mL) under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.843 g, 4.4 mmol) and kept at ambient temperature for 18 h. It was diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was crystallized form EtOAc-heptane to give 0.617 g of **16**: mp 149-150 °C; 1H NMR (300 MHz, CDCl3) d 3.05 (m, 4H), 3.66 (m, 2H), 3.85 (m, 5H), 4.08 (t, 1H), 4.80 (m, 1H), 5.93 (t, J = 53.9 Hz, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.39 (d,d, 1H); MS(EI) m/z 373 (M^+). Anal. calcd for $C_{16}H_{18}F_3N_3O_4$: C, 51.48; H, 4.86; N, 11.26. Found: C, 51.59; H, 4.91; N, 11.29.

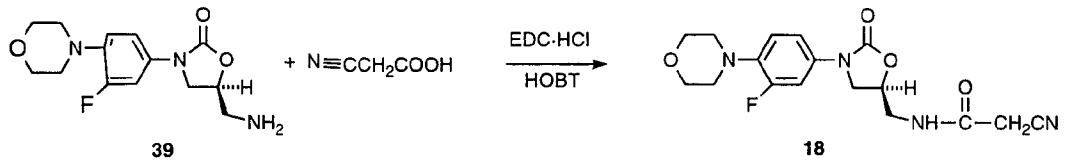
2.



A stirred solution of **16** (0.373 g, 1.00 mmol) in dioxane (10 mL), under nitrogen was treated with Lawesson's reagent (0.404 g, 1.00 mmol), warmed at about 95 °C for 1 h and concentrated in vacuo. Chromatography of the residue on silica gel with 10% acetone-CH_2Cl_2 and cyrstallization of the product from EtOAc-heptane gave 0.276 g of **17**: mp 125-127 °C; MS(EI) m/z 389 (M^+), 345, 305, 247, 209, 195, 151, 138, 123, 109, 95; ^{1}H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.76 (d,d, 1H), 3.86 (m, 4H), 4.01 (m, 1H), 4.12 (t, 1H), 4.30 (m, 1H), 4.99 (m, 1H), 6.20 (t, J = 55.9 Hz, 1H), 6.92 (t, 1H), 7.06 (d,d, 1H), 7.38 (d,d, 1H), 8.78 (broad s, 1H). Anal. calcd for $C_{16}H_{18}F_3N_3O_3S$: C, 49.35; H, 4.66; N, 10.79. Found: C, 49.37; H, 4.71; N, 10.83.

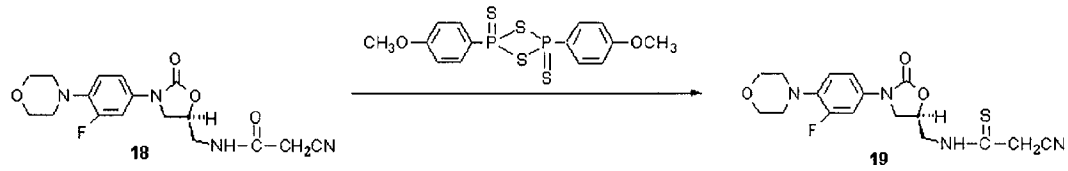
EXAMPLE 19: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide (19).**

1.



An ice cold, stirred mixture of **39** (0.646 g, 2.19 mmol), cyanoacetic acid (0.179 g, 2.1 mmol) and 1-hydroxybenzotriazole (0.351 g, 2.6 mmol) in DMF (5 mL), under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.997 g, 5.2 mmol) and kept at ambient temperature for 24 h. It was diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was crystallized from EtOAc-heptane to give 0.546 g of **18**: mp 172-174 °C: IR (DRIFT) 3316, 2256, 1754, 1684 cm^{-1}; MS(EI) *m/z* 362 (M^+). Anal. calcd for $C_{17}H_{19}FN_4O_4$: C, 56.35; H, 5.28; N, 15.46. Found: C, 56.33; H, 5.30; N, 15.36.

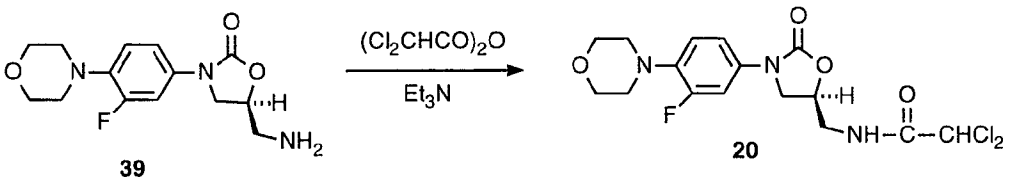
2.



A stirred solution of **18** (0.453 mg, 1.25 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.505 g, 1.25 mmol) and warmed at about 100 °C. When the reaction was over (TLC with 30% acetone-CH_2Cl_2) the mixture was cooled and concentrated in vacuo. Chromatography of the residue on silica gel with 10-20% acetone-CH_2Cl_2 and crystallization of the product from EtOAc-heptane gave 0.110 g of **19**: mp 186-187 °C (dec); MS(ES) *m/z* 379 ($M+H^+$), 401 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.89 (s, 2H), 4.09 (t, 1H), 4.14 (m, 2H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.34 (d,d, 1H), 9.15 (s, 1H); IR (DRIFT) 3244, 2260, 1754 cm^{-1}. Anal. calcd for $C_{17}H_{19}FN_4O_3S$: C, 53.96; H, 5.06; N, 14.81. Found: C, 53.88; H, 5.39; N, 14.61.

EXAMPLE 20: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide (21).**

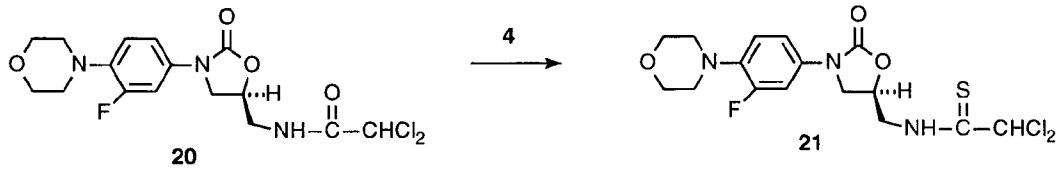
1.



39 20

A stirred, ice cold solution of **39** (0.885 g, 3.00 mmol) and triethylamine (975 mL, 7 mmol) in CH_2Cl_2 (15 mL), under nitrogen was treated, dropwise with a solution of dichloroacetic anhydride (555 mL, 3.5 mmol) in CH_2Cl_2 (5 mL) and kept in the ice bath for 15 min and at ambient temperature for 18 h. It was diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 10% acetone-CH_2Cl_2 and crystallization of the product from acetone-heptane gave 0.463 g of **20**: mp 197-198 °C (dec); MS(ES) *m/z* 406 ($M+H^+$), 428 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (m, 3H), 3.86 (m, 4H), 4.07 (t, 1H), 4.83 (m, 1H), 5.94 (s, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.41 (d,d, 1H).

2.

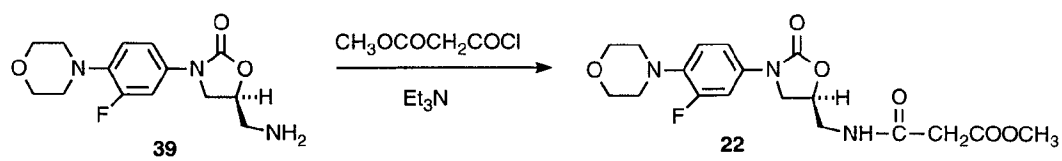


20 21

A stirred solution of **20** (0.305g, 0.75 mmol) in dioxane (5 ml), under nitrogen, was treated with Lawesson's reagent (0.202g, 0.5 mmol), warmed at about 90°C for 1 hour, cooled and concentrated in vacuo. Chromatography of the residue on silica gel first with 30% acetone-heptane and then with 10% acetone-methylene chloride and crystallization of rh product form methylene chloride - heptane gave 0.203g with **21**: mp 143-144°cd.; HR17S (EI) calculated for $C_{16}H_{18}cl_2$ F N_3 O_3 S(M) 421.0431. Anal. calcd for $C_{16}H_{18}cl_2$ F N_3 O_3 S, C, 45.51; H, 4.30; N, 9.95. Found: C, 45.47; H, 4.24; H, 9.88.

EXAMPLE 21: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide (23).**

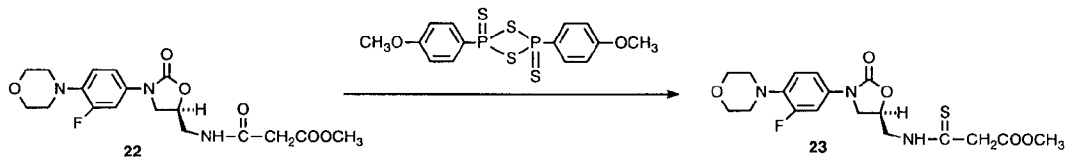
1.



39 22

A stirred solution of **39** (0.955 g, 3.2 mmol) and triethylamine (650 mL, 4.5 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was treated, dropwise during 15-20 min with a solution of methyl malonyl chloride (475 mL, 4.3 mmol) in CH_2Cl_2 (10 mL) and kept at ambient temperature for 3 days. It was then washed with water and dilute NaCl, dried and concentrated. The residue was flash chromatographed on silica gel with 15-30% acetone-CH_2Cl_2 and the product was crystallized form acetone-hexane to give 0.873 g of **22**: mp 150-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) d 3.03 (m, 4H), 3.34 (s, 2H), 3.67 (s, 3H), 3.69 (m, 2H), 3.76 (d,d, 1H), 3.85 (m, 4H), 4.00 (t, 1H), 4.78 (m, 1H), 6.90 (t, 1H), 7.06 (d,d, 1H), 7.41 (d,d, 1H), 7.57 (t, 1H); MS(ES) *m/z* 396 ($M+H^+$), 418 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}FN_3O_6$ ($M+H^+$) 396.1571, found 396.1579. Anal. calcd for $C_{18}H_{22}FN_3O_6$: C, 54.68; H, 5.61; N, 10.63. Found: C, 54.69; H, 5.68; N, 10.58.

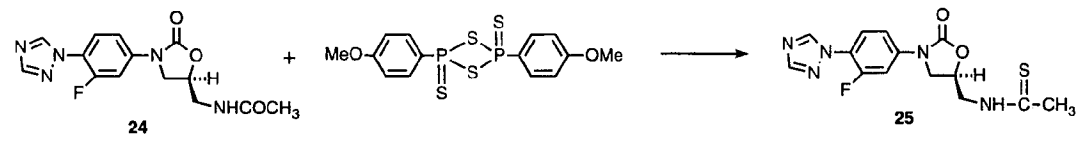
2.



22 23

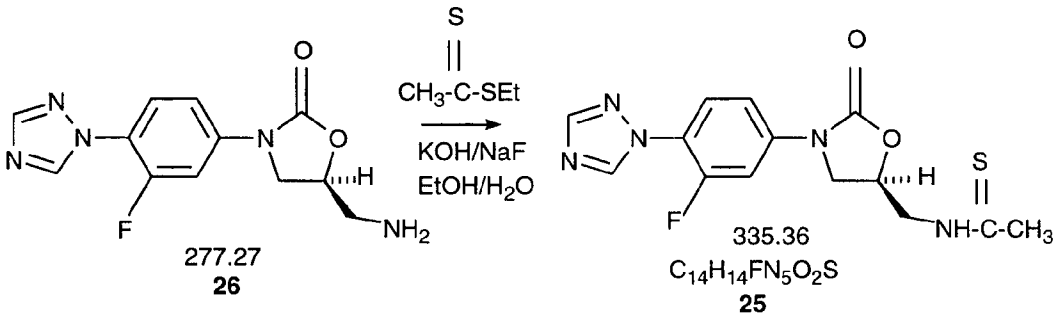
A stirred solution of **22** (0.395 g, 1.0 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.202 g, 0.5 mmol) and kept at ambient temperature for 4 h 10 min and at 80-90 °C for 1.5 h. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$. At this time a new, less polar product had begun to form. It was kept at ambient temperature for 18 h and at 80 °C for 2 h; additional Laewsson's reagent (40 mg, 0.099 mmol) was added and warming at 80 °C was continued for 2 h; some starting material still remained. The mixture was concentrated and the residue was chromatographed on silica gel with 15% acetone-CH_2Cl_2 to give 0.348 g of **23**: ^{1}H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.71 (s, 3H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.88 (s, 2H), 4.07 (t, 1H), 4.19 (m, 2H), 4.99 (m, 1H), 6.91 (t, 1H), 7.07 (d,d, 1H), 7.42 (d,d, 1H), 9.52 (s, 1H); IR (DRIFT) 3269, 1743 cm^{-1}; MS(EI) *m/z* 411 (M^+). Anal. calcd for $C_{18}H_{22}FN_3O_5S$: C, 52.54; H, 5.39; N, 10.21. Found: C, 52.58; H, 5.43; N, 10.14.

EXAMPLE 22: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**



A stirred mixture of **24**[10,11] (0.150 g, 0.470 mmol) and dioxane (12.5 mL), under nitrogen, was treated with Lawesson's reagent (0.20 g, 0.50 mmol), refluxed for 1.5 h, kept at ambient temperature for 18 h and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave the product which was crystallized from MeOH to give 0.100 g (63.4%) of **25**: mp 161-163 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.43 (s, 3H), 3.87 (m, 3H), 4.22 (t, 1H), 4.99 (m, 1H), 7.51 (d, 1H), 7.77 (m, 2H), 8.26 (s, 1H), 8.97 (d, 1H), 10.35 (broad s, 1H); IR (mull) 3259, 3226, 3044, 1752 cm^{-1}; MS(ES) *m/z* 336 ($M+H^+$), 358 ($M+Na^+$). Anal. calcd for $C_{14}H_{14}FN_5O_2S$: C, 50.14; H, 4.21; N, 20.88. Found: C, 50.18; H, 4.26; N, 20.94.

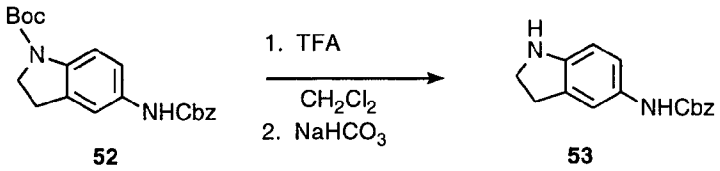
EXAMPLE 23: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**



A stirred mixture of **26**[10,12] (0.26 g, 0.938 mmol), ethyl dithioacetate (0.12 g, 0.998 mmol), sodium fluoride (0.040 g, 0.953 mmol) and absolute EtOH (10 mL), under nitrogen, was treated during 5 min with a solution of 0.97 M KOH (1.03 mL) in EtOH and kept at ambient temperature for 2 h. It was then diluted with CH_2CL_2 (75mL), washed with water, 1M $KHSO_4$, water and brine and evaporated. The residue was flash chromatographed on silica gel with 5% MeOH-$CHCl_3$ and the product was crystallized from MeOH to give 0.118 g, mp 164-165°C (dec) and 0.026 g, mp 162-163°C (dec) of **25**.

EXAMPLE 24: **(*S*)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (28).**

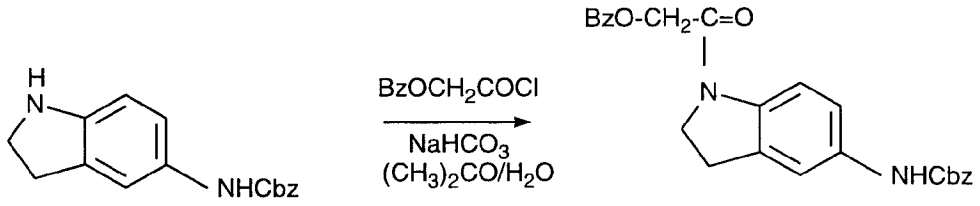
1.



52 53

A stirred, ice cold solution of **52**[13,14] (8.80 g, 0.0240 mol) in CH_2Cl_2 (25 mL) was treated during 20 min with a solution of trifluoroacetic acid (25 mL) in CH_2Cl_2 (10 mL). The mixture was kept in the ice bath for 2 h 15 min and concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 was washed with saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was used in the next reaction without further purification. A sample of this material (**53**) had: ^1H NMR (300 MHz, $CDCl_3$) d 3.00 (t, 2H), 3.54 (t, 2H), 3.85 (broad s, 1H), 5.17 (s, 2H), 6.59 (d, 1H), 6.66 (broad s, 1H), 6.91 (d, 1H), 7.23 (s, 1H), 7.36 (m, 5H); MS *m/z* 269 ($M+H^+$).

2.



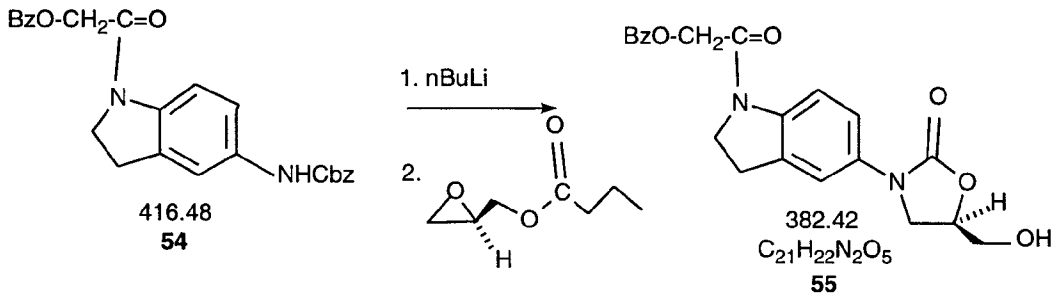
268.22
$C_{16}H_{16}N_2O_2$
53

416.48
$C_{25}H_{24}N_2O_4$
54

An ice cold, stirred mixture of **53** (crude product from the previous reaction), acetone (200 mL), saturated $NaHCO_3$ (200 mL) and water (30 mL) was treated, dropwise during 20 min, with a solution of benzyloxyacetyl chloride (4.70 mL, 0.030 mol) in acetone (55 mL), warmed slowly to ambient temperature and kept for 18 h. Additional benzyloxytacetyl chloride (1.0 mL) in acetone 35 mL) was added dropwise and the mixture was kept at ambient temperature for an additional 3 h and diluted with EtOAc and water. A solid was collected by filtration and dried to give 4.00 g of crude product. The EtOAc solution was dried (Na_2SO_4) and concentrated to give 5.36 g of additional crude product. Crystallization of the product from EtOAc gave a total of 6.35 g of **54**[14], mp 157-159.5°C. The analytical sample had: mp 158-159.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3,16 (t,2H), 4.01(t,2H), 4.21 (s, 2H), 4.69 (s,

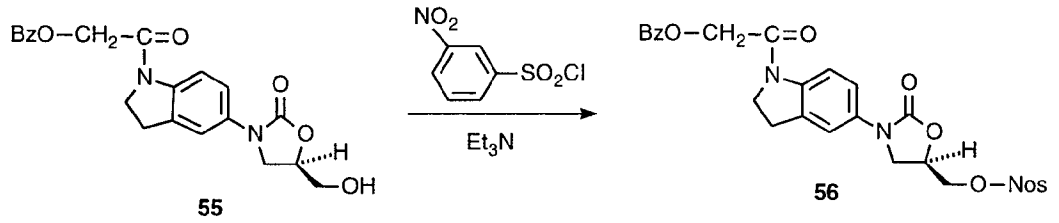
2H), 5.19 (s, 2H), 6.67 (s, 1H), 6.97 (d, 1H), 7.36 (m, 10H), 7.50 (braod s, 1H), 8.15 (d, 1H); MS(EI) *m/z* (relative intensity) 416 (M^+, 9), 310 (8), 202 (10), 133 (8), 92 (8), 91 (99), 79 (7), 77 (9), 65 (12), 51 (6); IR (mull) 2381, 1722, 1659, 1608, 1558 cm^{-1}. Anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.05; H, 5.86; N, 6.68.

3.



A stirred suspension of **54** (1.16 g, 2.78 mmol) in THF (42 mL) was cooled, under nitrogen, to -78°C and treated, dropwise, during 5 min with 1.6 M n-BuLi in hexane (1.83 mL). It was kept at -78°C for 50 min, treated, dropwise, during 5 min with a solution of (R)-(-)-glycidyl butyrate (0.500 g, 3.47 mmol) in THF (2 mL), allowed to warm to ambient temperature during 3 h and kpet for 18 h. It was then diluted with EtOAc, washed with saturated NH_4Cl, water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 3% MeOH-0.2% NH_4OH-$CHCl_3$ gave 0.60 g (56%) of **55**[14]: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 3.14 (t, 2H), 3.59 (m, 2H), 3.79 (d,d, 1H), 4.03 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.65 (m, 1H), 5.20 (t, 1H), 7.31 (m, 6H), 7.55 (s, 1H), 8.03 (d, 1H); MS(ES) *m/z* 383 ($M+H^+$), 405 ($M+Na^+$).

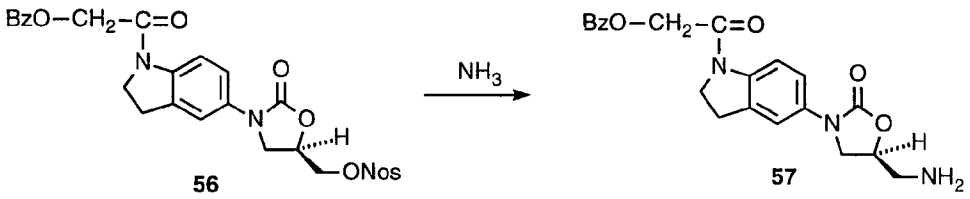
4.



An ice cold, stirred mixture of **55** (0.60 g, 1.57 mmol), triethylamine (2.2 mL), and CH_2Cl_2 (12 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (0.44 g, 1.99 mmol) and kept in the ice bath for 30 min and at ambient temperature for 60 min. It was then diluted with CH_2Cl_2, washed with water and brine, dried

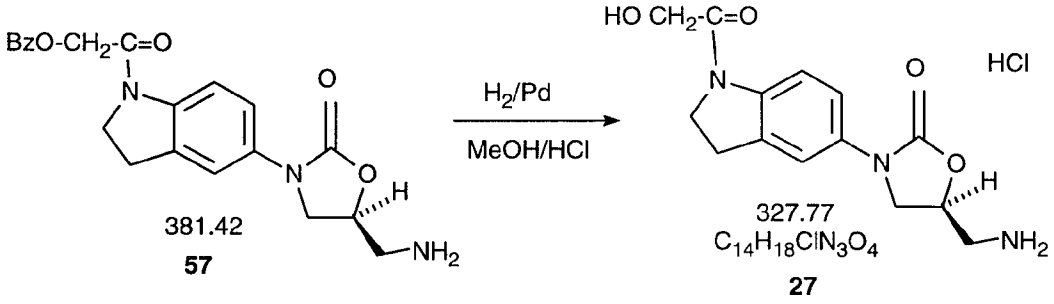
(Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 15% CH_3CN-CH_2Cl_2 gave 0.70 g of **56**: ^1H NMR (300 MHz, $CDCl_3$) d 3.19 (t, J = 8.3 Hz, 2H), 3.88 (d,d, 1H), 4.04 (t, J = 8.4 Hz, 2H), 4.14 (t, 1H), 4.23 (s, 2H), 4.42 (m, 2H), 4.70 (s, 2H), 4.84 (m, 1H), 6.97 (m, 1H), 7.34 (m, 5H), 7.58 (s, 1H), 7.81 (t, 1H), 8.22 (m, 2H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) m/z 568 ($M+H^+$), 590 ($M+Na^+$).

5.



A stirred mixture of **56** (crude product from 0.00314 mol of **55**), acetonitride (70 mL), isopropanol (70 mL) and 29% ammonium hydroxide (70 mL) was warmed at 40-44 °C for 7h and kept at ambient temperature for 18 h. It was concentrated in vacuo to an aqueous residue with was extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 8% MeOH-0.5% NH_4OH-$CHCl_3$ gave 1.05 g of **57**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.78 (m, 2H), 3.13 (t, 2H), 3.82 (d,d, 1H), 4.01 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.58 (m, 1H), 7.31 (m, 6H), 7.54 (broad s, 1H), 8.03 (d, 1H); MS(ES) m/z 382 ($M+H^+$), 404 ($M+Na^+$).

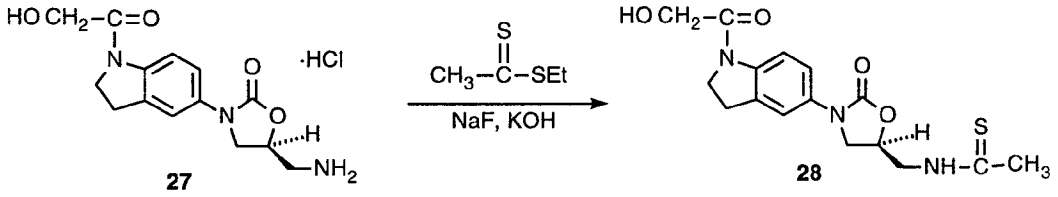
6.



A mixture of **57** (0.46 g, 1.21 mmol), MeOH (150 mL), 1 M HCl (1.2 mL) and 5% palladium-on-carbon catalyst (250 mg) was hydrogenated at an initial pressure of 49 psi for 5 h. Additional 1M HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 18 h. The catalyst was removed by filtration and

the filtrate was concentrated to give 0.34 g of **27**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 3.15 (t, 2H), 3.22 (broad s, 2H), 3.84 (d,d, 1H), 4.00 (t, 2H), 4.15 (s, 2H), 4.15 (m, 1H), 4.92 (m, 1H), 7.24 (q, 1H), 7.50 (d, 1H), 8.03 (d, 1H), 8.37 (broad s, 3H); MS(ES) *m/z* 2.92 ($M+H^+$).

7.

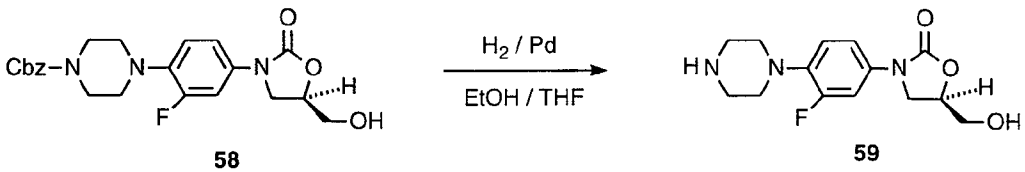


27 28

A suspension of **27** (0.10 g, 0.34 mmol) in a mixture of EtOH (15 mL) and 0.97 M KOH (0.7 mL) was added, under nitrogen to a stirred mixture of ethyl dithioacetate (0.0412 g, 0.343 mmol) and sodium fluoride (0.0137 g, 0.326 mmol) in EtOH (5 mL) and the mixture was kept at ambient temperature for 2h 15 min. Additional 0.97 M KOH (0.2 mL), sodium iodide (6 mg) and ethyl dithioacetate (20 mg) were added and the mixture was stirred for 2 h, mixed with CH_2Cl_2 (150 mL), washed with water, 1M $KHSO_4$ and brine, dried (Na_2SO_4) and concentrated. The residue was crystallized from acetone to give 0.0404 g of **28**: mp 175-176 °C (dec); MS (FAB) *m/z* 350 ($M+H^+$), 349 (M^+), 331, 316, 205, 73; HR MS (FAB) calcd for $C_{16}H_{20}N_3O_4S$ ($M+H^+$) 350.1174, found 350.1183; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.14 (t, 2H), 3.79 (d,d, 1H), 3.89 (t, 2H), 4.00 (t, 2H), 4.12 (m, 3H), 4.83 (t, 1H), 4.90 (m, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 8.03 (d, 1H), 10.35 (s, 1H); IR (DRIFT) 3255, 3223, 3068, 1747, 1639, 1614 cm^{-1}.

EXAMPLE 25: **(*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (30).**

1.



58 59