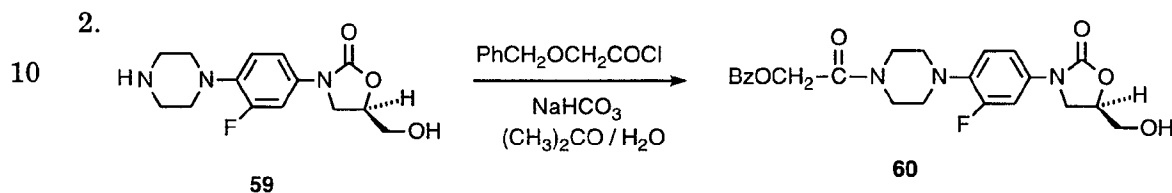


A mixture of **58**<sup>15</sup> (3.00 g, 7.00 mmol), THF (60 mL), absolute EtOH (100 mL) and 10% palladium-on-carbon catalyst (415 mg) was hydrogenated at an initial pressure of 58 psi for 2 h 50 min. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 2.67 g of **59** which was used without further

5 purification in the next reaction: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.16 (broad s), 3.02 (m, 8H), 3.73 (d,d, *J* = 3.9, 12.6 Hz, 1H), 3.96 (m, 3H), 4.72 (m, 1H), 6.92 (t, *J* = 9.2 Hz, 1H), 7.11 (m, 1H), 7.43 (d,d, *J* = 2.6, 14.3 Hz, 1H); MS(ES) *m/z* 296 (M+H<sup>+</sup>).

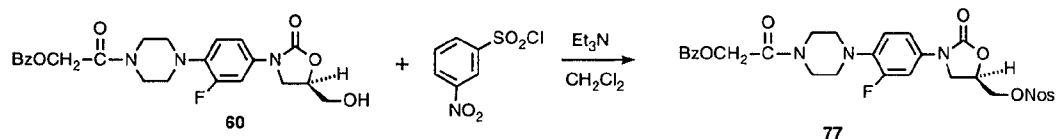


A stirred, ice cold mixture of **59** (2.67 g from the previous reaction), acetone (190 mL) and saturated NaHCO<sub>3</sub> (70 mL) was treated, dropwise during 2-3 min with a solution of benzyloxyacetyl chloride (1.34 mL, 8.61 mmol) in acetone (25 mL), kept in the ice bath for 1 h and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic solution was washed with dilute NaCl, dried and concentrated. Chromatography of the residue on silica gel with 30% acetone-CH<sub>2</sub>Cl<sub>2</sub>

20 gave 2.64 g of **60**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.28 (broad s, 1H), 3.00 (m, 4H), 3.66 (m, 2H), 3.77 (m, 3H), 3.96 (m, 3H), 4.22 (s, 2H), 4.61 (s, 2H), 4.74 (m, 1H), 6.88 (t, *J* = 9.2 Hz, 1H), 7.12 (m, 1H), 7.35 (s, 5H), 7.46 (d,d, *J* = 2.6, 14.2 Hz, 1H); IR (mull) 3406, 1748, 1647 cm<sup>-1</sup>; HRMS(EI) calcd for C<sub>23</sub>H<sub>26</sub>FN<sub>3</sub>O<sub>5</sub> (M<sup>+</sup>) 443.1856, found 443.1842.

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3.



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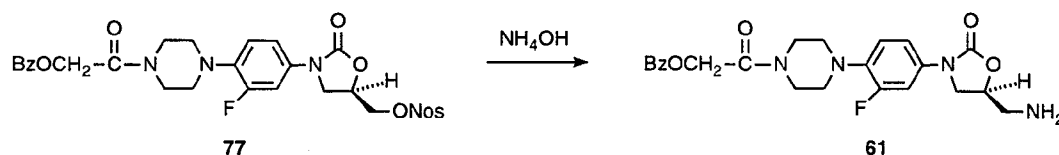
A stirred, ice cold mixture of **60** (2.64 g, 6.00 mmol) and triethylamine (1.14 mL, 8.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (1.78 g, 8.04 mmol), warmed to ambient temperature and kept for 5 h 20 min. Additional 3-nitrobenzenesulfonyl chloride (180 mg) and triethylamine (0.20 mL) were added and the mixture was kept at ambient

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temperature for 18 h, diluted with  $\text{CH}_2\text{Cl}_2$  and washed with water and dilute NaCl, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography of the residue on silica gel with 40-60% acetone-hexane gave 3.36 g of **77**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) d 3.02 (broad s, 4H), 3.66 (broad s, 2H), 3.78 (broad s, 2H), 3.87 (d,d,  $J = 5.9, 9.1$  Hz, 1H), 4.09 (t,  $J = 9.2$  Hz, 1H), 4.22 (s, 2H), 4.41 (m, 2H), 4.61 (s, 2H), 4.84 (m, 1H), 6.88 (t,  $J = 9.1$  Hz, 1H), 7.02 (m, 1H), 7.35 (m, 6H), 7.82 (t,  $J = 8.0$  Hz, 1H), 8.23 (m, 1H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES)  $m/z$  629 ( $\text{M}+\text{H}^+$ ).

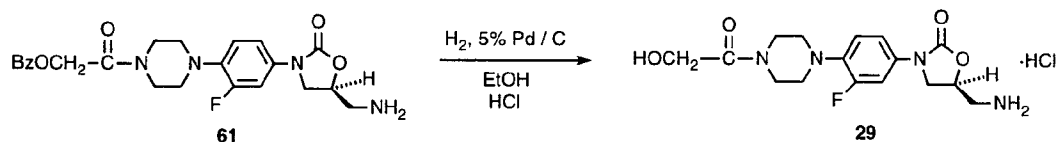
4.

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A solution of **77** (3.36 g, 5.34 mmol) in a mixture of acetonitrile (90 mL), isopropanol (90 mL) and concentrated ammonium hydroxide (90 mL) was warmed at 40-45 °C for 18 h, treated with additional ammonium hydroxide (30 mL), warmed at 40-45 °C for 8 h, treated with additional ammonium hydroxide (25 mL) and warmed at 45 °C for 18 h. It was then mixed with water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with dilute NaCl, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5%  $\text{NH}_4\text{OH-CHCl}_3$  gave 2.44 g of **61**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) d 1.50 (broad s), 3.04 (m, 6H), 3.65 (broad s, 2H), 3.81 (m, 3H), 3.99 (t, 1H), 4.21 (s, 2H), 4.61 (s, 2H), 4.66 (m, 1H), 6.88 (t, 1H), 7.12 (m, 1H), 7.33 (m, 5H), 7.47 (d,d, 1H); MS(ES)  $m/z$  443 ( $\text{M}+\text{H}^+$ ).

25 5.

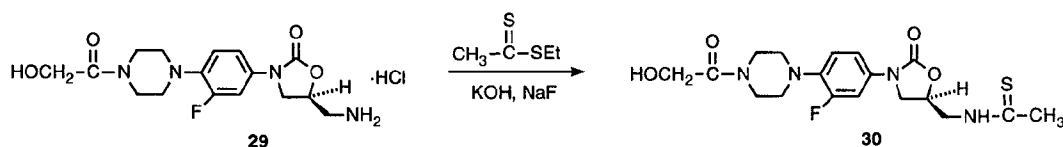


A solution of **61** (1.45 g, 3.3 mmol) and 1.0 N HCl (3.65 mL) in 95% EtOH (150 mL) was treated with 5% palladium-on-carbon catalyst (500 mg) and hydrogenated at an initial pressure of 54 psi for 20 h 15 min. Additional 1.0 N HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 20 h 30 min at an initial pressure of 60 psi. The reaction was complete by TLC; it was neutralized with concentrated  $\text{NH}_4\text{OH}$ , filtered and concentrated in vacuo to give 1.18 g of **29**:  $^1\text{H}$  NMR [300 MHz,  $(\text{CD}_3)_2\text{SO}$ ] d 2.94 (broad s, 4H), 3.19 (m, 2H), 3.48 (broad s, 2H),

3.60 (broad s, 2H), 3.84 (m, 1H), 4.14 (m, 3H), 4.66 (broad s, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.16 (d,d, 1H), 7.48 (d,d, 1H), 8.04 (broad s); IR (mull) 3420, 3099, 3040, 3008, 1755, 1641  $\text{cm}^{-1}$ ; MS(ES)  $m/z$  353 ( $\text{M}+\text{H}^+$ ). Anal. calcd for  $\text{C}_{16}\text{H}_{22}\text{ClFN}_4\text{O}_4$ : C, 49.42; H, 5.70; Cl, 9.12; N, 14.41. Found: C, 48.16; H, 5.82; Cl, 10.00; N, 14.28.

5

6.

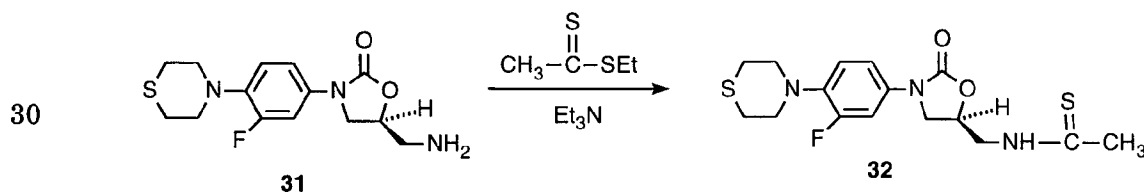


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A stirred mixture of ethyl dithioacetate (180 mL, 1.56 mmol), sodium fluoride (72 mg, 1.7 mmol), **29** (500 mg, 1.29 mmol) and EtOH (70 mL) under nitrogen, was treated with 0.97M KOH (1.46 mL, 1.42 mmol) and the resulting solution was kept at ambient temperature for 3 h 35 min, diluted with  $\text{CHCl}_3$ , washed with water and dilute NaCl, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5%  $\text{NH}_4\text{OH}-\text{CHCl}_3$  and crystallization of the resulting product from absolute EtOH gave 0.238 mg (44.9%) **30**: mp 163-165  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.60 (s, 3H), 3.06 (m, 4H), 3.45 (m, 2H), 3.61 (m, 1H), 3.82 (m, 3H), 4.07 (m, 2H), 4.25 (m, 3H), 4.97 (m, 1H), 6.91 (t, 1H), 7.07 (m, 1H), 7.45 (d,d, 1H), 7.91 (broad s, 1H); MS(FAB)  $m/z$  (relative intensity) 411 ( $\text{M}+\text{H}^+$ , 100), 410 ( $\text{M}^+$ , 66.5), 266 (3.1); IR 3292, 1733, 1653  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{18}\text{H}_{23}\text{FN}_4\text{O}_4\text{S}$ : C, 52.67; H, 5.65; N, 13.65. Found: C, 52.76; H, 5.58; N, 13.64.

20

25 **EXAMPLE 26:** (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (**32**).



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An ice cold, stirred mixture of **31** (0.38 g, 0.0012 mol) and triethylamine (0.38 mL, 0.0027 mol) in THF (12 mL), under nitrogen, was treated with ethyl dithioacetate (0.16 mL, 0.0014 mol) and then kept at ambient temperature for 24.5 h and concentrated in vacuo. A solution of the residue in  $\text{CH}_2\text{Cl}_2$  was washed with

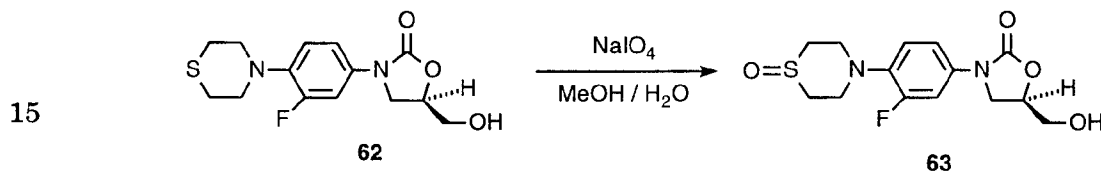
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saturated  $\text{NaHCO}_3$ , water and brine, dried ( $\text{MgSO}_4$ ) and concentrated.

Crystallization of the residue from EtOAc-hexane gave 0.355 g of **32**: mp 155-156 °C; MS(ES)  $m/z$  370 ( $\text{M}+\text{H}^+$ ), 392 ( $\text{M}+\text{Na}^+$ ); IR (DRIFT) 3206, 3042, 1759, 1738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) d 2.60 (s, 3H), 2.95 (s, 4H), 3.43 (m, 4H), 3.82 (d, d, 1H), 4.08 (m, 2H), 4.27 (m, 1H), 4.98 (m, 1H), 7.06 (m, 1H), 7.33 (broad s, 1H), 7.51 (d, 1H), 8.03 (broad s, 1H). Anal. calcd for  $\text{C}_{16}\text{H}_{20}\text{FN}_3\text{O}_2\text{S}_2$ : C, 52.01; H, 5.46; N, 11.37. Found: C, 51.86; H, 5.43; N, 11.20.

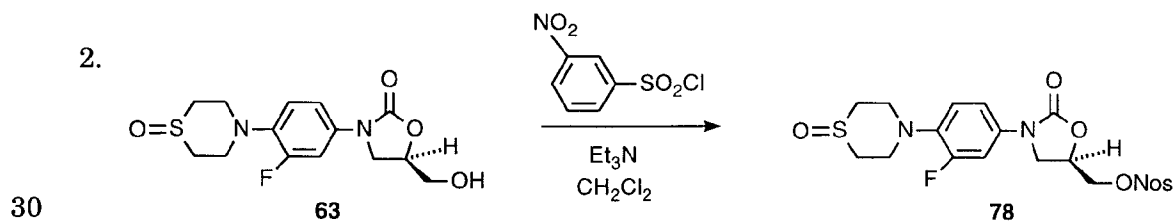
EXAMPLE 27: (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S-oxide (**34**).

1.



An ice cold, stirred mixture of sodium metaperiodate (1.08 g, 5.05 mmol) and water (12 mL), under nitrogen, was treated with **62**<sup>16</sup> (1.5 g, 4.8 mmol) and MeOH (17 mL) and kept at 6 °C for 18 h and at 4 °C for 3 h. It was then treated with additional sodium metaperiodate (0.1 g), kept at 4 °C for 3 h and extracted with  $\text{CHCl}_3$ . The extract was dried ( $\text{MgSO}_4$ ) and concentrated to give 1.4 g of **63**:  $^1\text{H}$  NMR [300 MHz,  $(\text{CD}_3)_2\text{SO}$ ] d 2.84 (m, 2H), 3.01 (m, 2H), 3.16 (m, 2H), 3.50 (m, 3H), 3.65 (m, 1H), 3.77 (d,d, 1H), 4.03 (t, 1H), 4.66 (m, 1H), 5.18 (t, 1H), 7.16 (m, 2H), 7.52 (m, 1H); MS(ES)  $m/z$  329 ( $\text{M}+\text{H}^+$ ), 351 ( $\text{M}+\text{Na}^+$ ).

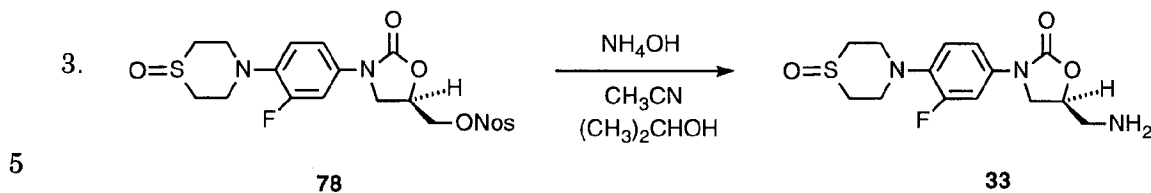
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An ice cold, stirred mixture of **63** (1.27 g, 3.87 mmol) and triethylamine (0.732 mL, 5.25 mmol) in  $\text{CH}_2\text{Cl}_2$  (130 mL), under nitrogen, was treated with *m*-nitrobenzenesulfonyl chloride (1.15 g, 5.19 mmol) and kept at ambient temperature for about 24 h. It was diluted with  $\text{CH}_2\text{Cl}_2$ , washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give **78** which was used in the next reaction without

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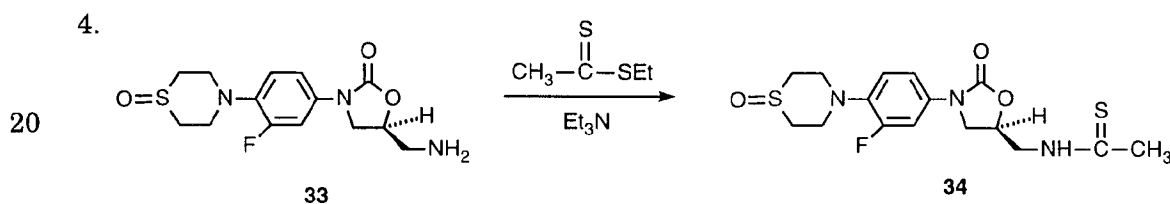
purification.



A stirred mixture of the product (**78**) from the previous reaction, acetonitrile (70 mL) and isopropanol (70 mL) was treated with concentrated ammonium hydroxide (70 mL, 29.9% NH<sub>3</sub>) and kept at 40 °C for 2 h, at ambient temperature for 18 h and at 40-45 °C for 4 h; it was concentrated to about 50 mL, diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-CHCl<sub>3</sub> gave 0.58 g of **33**: MS(ES) *m/z* 328 (M+H<sup>+</sup>), 350 (M+Na<sup>+</sup>); <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] d 2.81 (m, 4H), 3.01 (m, 2H), 3.16 (m, 2H), 3.30 (broad s), 3.49 (m, 2H), 3.80 (d,d, 1H), 4.01 (t, 1H), 4.58 (m, 1H), 7.19 (m, 2H), 7.51 (m, 1H).

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A stirred suspension of **33** (3.7 g, 0.011 mol) and triethylamine (3.5 mL, 0.025 mol) in THF (120 mL) was cooled, in an ice bath, under nitrogen, treated, dropwise during 2 min, with a solution of ethyl dithioacetate (1.47 mL, 0.0128 mol) in THF (2 mL) and kept at ambient temperature for 22 h. The resulting solution was concentrated and the residue crystallized from acetonitrile to give 3.61 g of **34**: mp 176-177 °C ; <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] d 2.42 (s, 3H), 2.85 (m, 2H), 3.01 (m, 2H), 3.18 (m, 3H), 3.50 (m, 2H), 3.78 (d,d, 1H), 3.89 (broad s, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.49 (m, 1H), 10.33 (s, 1H); IR (DRIFT) 3186, 3102, 1741 cm<sup>-1</sup>; MS(ES) *m/z* 386 (M+H<sup>+</sup>), 408 (M+Na<sup>+</sup>). Anal. calcd for C<sub>16</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·0.5 H<sub>2</sub>O: C, 48.71; H, 5.37; N, 10.65; S, 16.26; H<sub>2</sub>O, 2.38. Found: C, 48.75; H, 5.17; N, 10.72; S, 16.07; H<sub>2</sub>O, 1.72.

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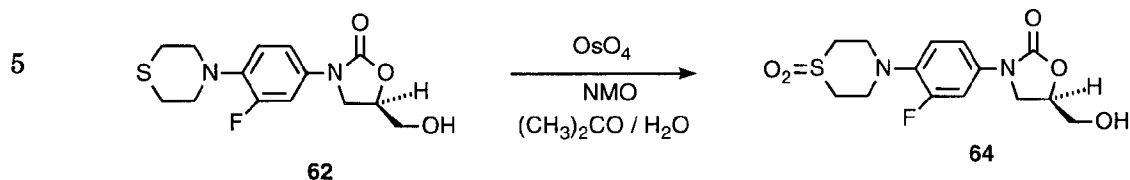
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EXAMPLE 28: (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-

## oxazolidinyl)methyl]thio-acetamide, thiomorpholine S, S-dioxide (36).

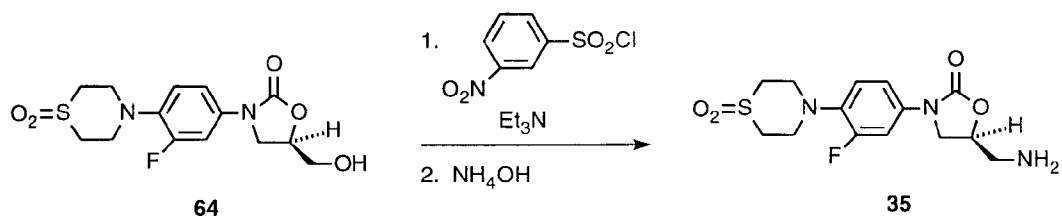
1.



A stirred mixture of **62**<sup>16</sup> (0.399 g, 0.00128 mol) in 25% water/acetone (12 mL),  
 10 under nitrogen was treated with N-methylmorpholine, N-oxide (0.45 g, 0.00384 mol)  
 and 0.1 mL of a 2.5 wt% solution of osmium tetroxide in *tert*-butanol. It was kept at  
 ambient temperature for 18 h, mixed with saturated NaHSO<sub>3</sub> (50 mL) and extracted  
 with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with saturated NaHSO<sub>3</sub> and brine, dried  
 (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was mixed with 3.5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> and  
 15 filtered; the solid was dissolved in 15% MeOH-CH<sub>2</sub>Cl<sub>2</sub> and concentrated to give 0.29  
 g of **64**. The filtrate was chromatographed on silica gel with 3.5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> to  
 give 0.1 of additional **64**: MS(ES) *m/z* 345 (M+H<sup>+</sup>), 367 (M+Na<sup>+</sup>); <sup>1</sup>H NMR [300  
 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 3.26 (m, 4H), 3.44 (m, 4H), 3.60 (m, 2H), 3.80 (d,d, 1H), 4.05 (t,  
 1H), 4.69 (m, 1H), 7.22 (m, 2H), 7.54 (d, 1H).

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2.



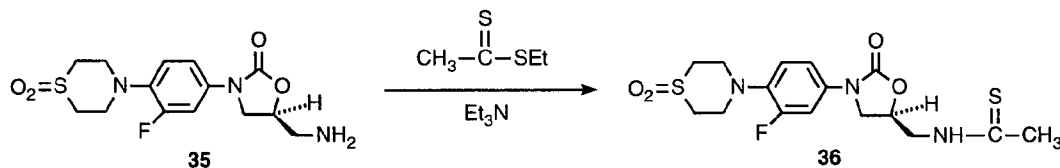
25

A stirred mixture of **64** (0.39 g, 0.00113 mol) and triethylamine (0.214 mL, 0.00154  
 mol) in CH<sub>2</sub>Cl<sub>2</sub> (37 mL) was cooled, under nitrogen, in an ice bath and treated,  
 30 portionwise during 5 min, with 3-nitrobenzenesulfonyl chloride (0.335 g, 0.00151  
 mol). The mixture was kept in the ice bath for 20 min and at ambient temperature  
 for 18 h and concentrated in vacuo. A stirred solution of the residue in 2-propanol  
 (25 mL) and acetonitrile (25 mL), under nitrogen, was treated with 30% NH<sub>4</sub>OH (25  
 mL), warmed at 50-55 °C for 6 h and kept at ambient temperature for 48 h. It was  
 35 concentrated to remove the organic solvents, diluted with water and extracted with  
 CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water and brine, dried (MgSO<sub>4</sub>) and

concentrated. Flash chromatography of the residue on silica gel with 6% MeOH-0.4% NH<sub>4</sub>OH-CHCl<sub>3</sub> gave 0.29 g of **35**: <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 1.59 (broad s, 2H), 2.78 (m, 2H), 3.24 (m, 4H), 3.43 (m, 4H), 3.81 (d,d, 1H), 4.01 (t, 1H), 4.57 (m, 1H), 7.18 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 344 (M+H<sup>+</sup>), 366 (M+Na<sup>+</sup>).

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3.

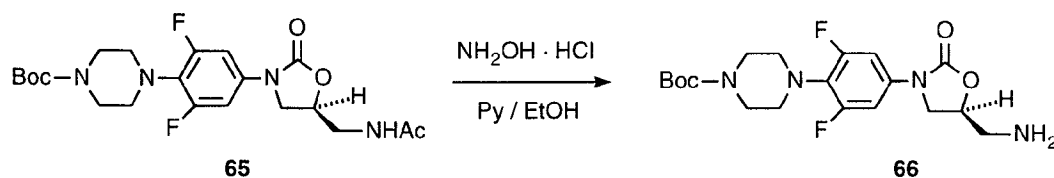


10 A stirred, ice cold suspension of **35** (0.28 g, 0.85 mmol) in a mixture of Et<sub>3</sub>N (0.26 mL, 1.9 mmol) and THF (10 mL) was treated with ethyl dithioacetate (0.11 mL, about 6 drops) and kept in the ice bath for 20 min and then at ambient temperature; the reaction was followed by TLC. After 20 h there was still a suspension and only partial reaction; additional THF (10 mL) and ethyl dithioacetate (3 drops) were  
15 added. After an additional 48 h the reaction was still incomplete; the suspension was treated with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and kept for 72 h. At this time almost complete solution and an almost complete conversion to product had been obtained. An additional drop of ethyl dithioacetate was added and the mixture was kept at ambient temperature for 5 d and concentrated in vacuo. The residue was mixed  
20 with EtOAc, washed with saturated NaHCO<sub>3</sub>, water and brine, dried (MgSO<sub>4</sub>) and concentrated. Crystallization of the residue from MeOH-EtOAc gave 0.209 g of **36**: mp 197-198 °C; <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 2.42 (s, 3H), 3.24 (m, 4H), 3.43 (m, 4H), 3.78 (d,d, 1H), 3.88 (m, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.50 (m, 1H), 10.37 (broad s, 1H); IR (mull) 3300, 3267, 1743 cm<sup>-1</sup>; MS(ES) *m/z* 424  
25 (M+Na<sup>+</sup>). Anal. calcd for C<sub>16</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>: C, 47.87; H, 5.02; N, 10.47. Found: C, 47.84; H, 5.23; N, 10.28.

**EXAMPLE 29: (S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (38).**

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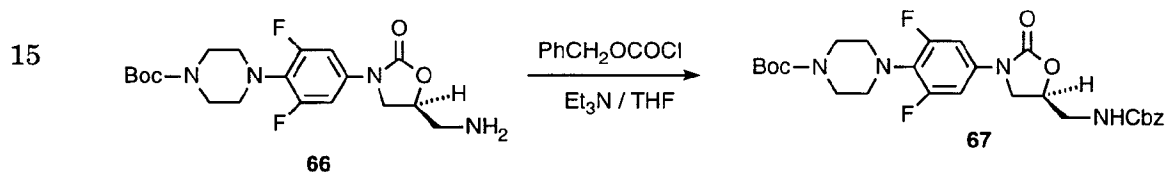
1.



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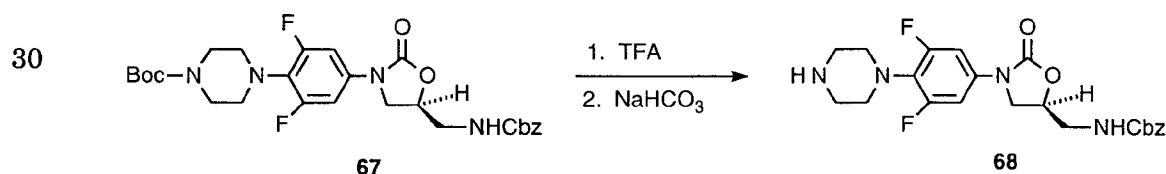
A stirred mixture of **65**<sup>17,18</sup> (1.8 g, 0.00396 mol), pyridine (30 mL) and absolute EtOH (3 mL), under nitrogen, was treated with hydroxylamine hydrochloride (1.44 g, 0.0207 mol), warmed to the reflux temperature during 2 h, refluxed for 3.5 h, kept at ambient temperature for 18 h and at reflux for 4 h. It was concentrated in vacuo and the residue was mixed with water, adjusted to pH 11 with saturated NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.35% NH<sub>4</sub>OH-CHCl<sub>3</sub> gave 0.75 g of recovered **65** and 0.72 g of **66**: <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] d 1.40 (s, 9H), 1.72 (broad s, 2H), 2.78 (m, 2H), 2.97 (m, 4H), 3.40 (m, 4H), 3.80 (d,d, 1H), 4.00 (t, 1H), 4.59 (m, 1H), 7.27 (d, 2H); MS(ES) *m/z* 413 (M+H<sup>+</sup>), 435 (M+Na<sup>+</sup>).

2.



An ice cold, stirred mixture of **66** (0.75 g, 0.0018 mol) and triethylamine (0.315 mL, 0.00225 mol) in THF (12 mL), under nitrogen, was treated, dropwise with benzyl chloroformate (0.29 mL, 0.0020 mol), kept in the ice bath for 15 min and at ambient temperature for 2 h and concentrated in vacuo. The residue was mixed with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaHCO<sub>3</sub>, water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. This residue was mixed with Et<sub>2</sub>O and filtered to give 0.939 g of **67**: mp 116-118 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) d 1.48 (s, 9H), 3.08 (m, 4H), 3.53 (m, 4H), 3.60 (m, 2H), 3.73 (m, 1H), 3.96 (t, 1H), 4.76 (m, 1H), 5.10 (s, 2H), 5.21 (m, 1H), 7.07 (d, 2H), 7.31 (s, 5H); MS(ES) *m/z* 547 (M+H<sup>+</sup>), 569 (M+Na<sup>+</sup>).

3.

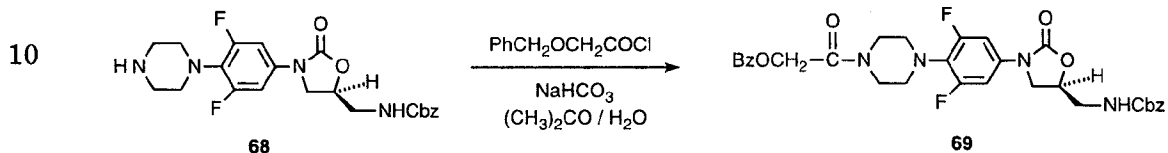


Compound **67** (0.805 g, 0.00147 mol) was added with stirring, portionwise during 5 min, under nitrogen, to ice cold trifluoroacetic acid (9 mL). The resulting solution was kept in the ice bath for 1 h and then concentrated under a stream of nitrogen.



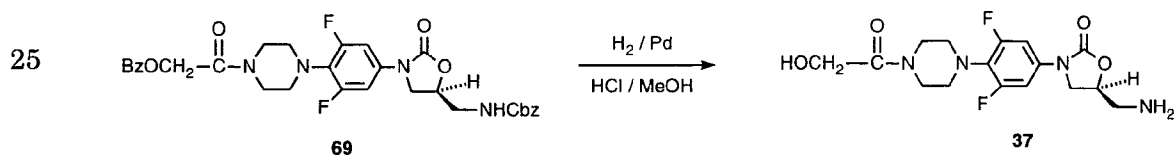
The residue was mixed with ice and saturated  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ ; the extract was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give 0.63 g of product. The combined aqueous layer was reextracted with EtOAc; the extracts were washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to  
5 give additional product. The combined product amounted to 0.68 g of **68** which was used in the next reaction without further purification.

4.



An ice cold, stirred mixture of **68** (0.68 g, 0.00152 mol), saturated  $\text{NaHCO}_3$  (15.2  
15 mL) and acetone (40 mL), under nitrogen was treated, dropwise during 15 min, with a solution of benzyloxycarbonyl chloride (0.29 mL, 0.0019 mol) in acetone (5 mL), kept at ambient temperature for 6 h, diluted with EtOAc and washed with water and brine. The extract was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give 0.72 g of  
20 **69**: MS(ES)  $m/z$  395 ( $\text{M}+\text{H}^+$ ), 617 ( $\text{M}+\text{Na}^+$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.12 (m, 4H), 3.59 (m, 4H), 3.74 (m, 3H), 3.96 (t, 1H), 4.22 (s, 2H), 4.62 (s, 2H), 4.75 (broad s, 1H), 5.10 (s, 2H), 5.22 (m, 1H), 7.08 (d, 2H), 7.33 (m, 10H).

5.

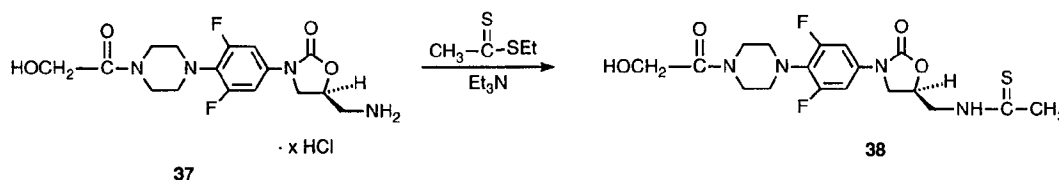


A mixture of **69** (0.72 g, 0.0012 mol), MeOH and 5% palladium-on-carbon catalyst  
30 (0.4 g) was hydrogenated at an initial pressure of 45 psi for 4 h. By TLC (8% MeOH-0.5%  $\text{NH}_4\text{OH}$ - $\text{CHCl}_3$ ) the starting material had been reduced and two products formed. 1M Hydrochloric acid (1.34 mL) was added and hydrogenation was continued at an initial pressure of 40 psi for 21 h. By TLC only the more polar product remained. The catalyst was removed by filtration and the filtrate was  
35 concentrated to give 0.40 g of **37**: MS(ES)  $m/z$  371 ( $\text{M}+\text{H}^+$ ), 393 ( $\text{M}+\text{Na}^+$ );  $^1\text{H}$  NMR [300 MHz,  $(\text{CD}_3)_2\text{SO}$ ]  $\delta$  3.02 (s, 4H), 3.20 (m, 2H), 3.43 (s, 2H), 3.56 (s, 2H), 3.84 (m,

1H), 3.84 (broad s), 4.10 (s, 2H), 4.14 (t, 1H), 4.96 (m, 1H), 7.26 (d, 2H), 8.41 (broad s, 3H).

6.

5

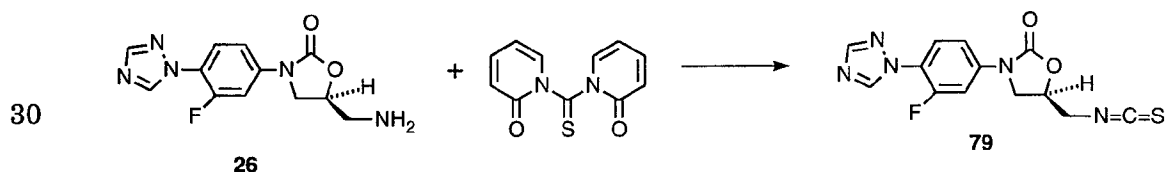


10 A stirred suspension of **37** (0.38 g) in a solution of  $\text{Et}_3\text{N}$  (0.31 mL) and THF (10 mL), under nitrogen, was treated with ethyl dithioacetate (0.13 mL, about 7 drops) and kept at ambient temperature for 7 d; the reaction was followed by TLC (8% MeOH-0.5%  $\text{NH}_4\text{OH}$ - $\text{CHCl}_3$ ). Additional ethyl dithioacetate (2 drops) was added after 24 h; after 30 h  $\text{CH}_2\text{Cl}_2$  (10 mL) and ethyl dithioacetate (3 drops) were added; after 48 h  
15 additional triethylamine (0.3 mL) was added. The mixture was concentrated in vacuo and the residue was mixed with ice and saturated  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was chromatographed on silica gel with 2.5% MeOH- $\text{CH}_2\text{Cl}_2$  and the product was crystallized from MeOH to give 0.182 g of **38**: mp 110-  
20 111 °C (dec); MS(ES)  $m/z$  429 ( $\text{M}+\text{H}^+$ ), 451 ( $\text{M}+\text{Na}^+$ ); HRMS (FAB) calcd for  $\text{C}_{18}\text{H}_{23}\text{F}_2\text{N}_4\text{O}_4\text{S}$  ( $\text{M}+\text{H}^+$ ) 429.1408, found 429.1415; IR (DRIFT) 1760, 1652, 1639  $\text{cm}^{-1}$ ;  $[\alpha]_{\text{D}}^{24}$  8° (MeOH).

EXAMPLE 30: (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-

25 oxazolidinyl]methyl]thiourea (**44**).

1.

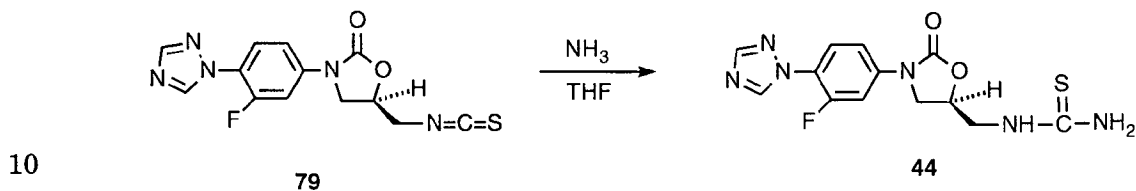


A solution of **26** (0.190 g, 0.685 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added, dropwise during 20 min, under nitrogen, to an ice cold, stirred solution of 1,1'-thiocarbonyldi-  
35 2(1H)-pyridone (0.193 g, 0.831 mmol) in  $\text{CH}_2\text{Cl}_2$  (7 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, diluted with  $\text{CH}_2\text{Cl}_2$ ,

washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated. Chromatography of the residue on silica gel with 10-15%  $\text{CH}_3\text{CN}-\text{CH}_2\text{Cl}_2$  gave 0.11 g of **79** which was used in the next reaction without further purification: MS(ES)  $m/z$  320 ( $\text{M}+\text{H}^+$ ), 342 ( $\text{M}+\text{Na}^+$ ).

5

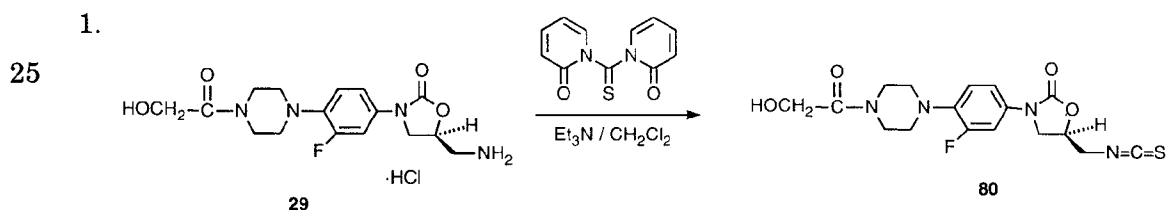
2.



A stirred, ice cold solution of **79** (0.10 g, 0.31 mmol) in THF (15 mL) was treated with excess anhydrous ammonia and kept in the ice bath for 90 min. It was then evaporated under a stream of nitrogen to a volume of about 5 mL to give a solid which was collected by filtration and washed with cold THF to give 0.105 g of **44**: mp 214-215 °C;  $^1\text{H}$  NMR [300 MHz,  $(\text{CD}_3)_2\text{SO}$ ]  $\delta$  3.82 (m, 3H), 4.18 (t, 1H), 4.89 (broad s, 1H), 7.20 (broad s, 2H), 7.50 (d, 1H), 7.79 (m, 2H), 7.93 (t, 1H), 8.26 (s, 1H), 8.97 (s, 1H); MS(ES)  $m/z$  337 ( $\text{M}+\text{H}^+$ ), 359 ( $\text{M}+\text{Na}^+$ ). Anal. calcd for  $\text{C}_{13}\text{H}_{13}\text{FN}_6\text{O}_2\text{S}$ : C, 46.42; H, 3.90; N, 24.99. Found: C, 46.22; H, 3.98; N, 24.55.

20

EXAMPLE 31: (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea (**45**).

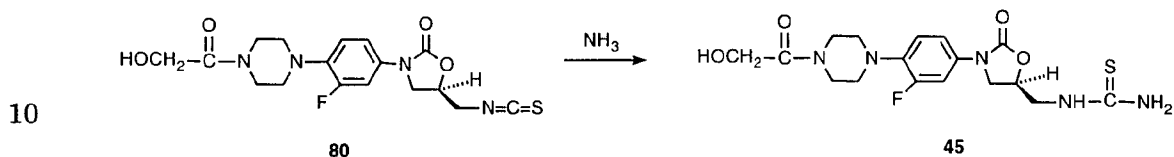


30 An ice cold, stirred solution of 1,1'-thiocarbonyl-2(1H)-dipyridone (0.123 g, 0.530 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL), under nitrogen, was treated with a suspension of **29** (0.17 g, 0.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) and then during 10 min with a solution of triethylamine (0.111 mL, 0.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL). It was kept in the ice bath for 30 min, at ambient temperature for 2 h and at  $< 0$  °C for 18 h. It was then

35 diluted with  $\text{CH}_2\text{Cl}_2$ , washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue (**80**) was used without further purification in the next

reaction. A sample of **80** that was purified by flash chromatography on silica gel with 10-20% acetonitrile-CH<sub>2</sub>Cl<sub>2</sub> had: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.60 (broad s), 3.07 (m, 4H), 3.45 (m, 2H), 3.85 (m, 4H), 3.97 (d,d, 1H), 4.16 (t, 1H), 4.21 (s, 2H), 4.82 (m, 1H), 6.95 (t, 1H), 7.13 (d,d, 1H), 7.47 (d,d, 1H); MS *m/z* 395 (M+H<sup>+</sup>); 417 (M+Na<sup>+</sup>).

2.



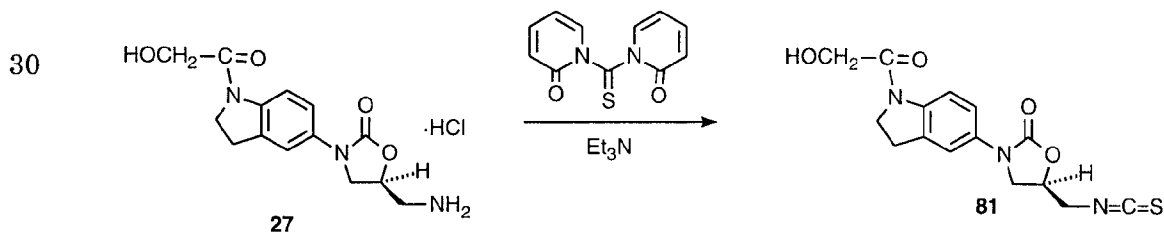
Excess anhydrous ammonia was bubbled into a stirred, ice cold solution of **80** (crude product from the previous reaction) in THF (25 mL) and the mixture was kept in the ice bath for 90 min and concentrated under a stream of nitrogen. The residue was chromatographed on silica gel with 5% MeOH-0.4% NH<sub>4</sub>OH-CHCl<sub>3</sub> and the product was crystallized from acetonitrile to give 0.0544 g of **45**: mp 209-210 °C; <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 2.94 (broad s, 4H), 3.47 (broad s, 2H), 3.60 (broad s, 2H), 3.78 (broad s, 3H), 4.07 (t, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 4.63 (t, *J* = 5.5 Hz, 1H), 4.81 (broad s, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.15 (broad s, 2H), 7.49 (d,d, 1H), 7.91 (t, 1H); IR (mull) 3443, 3403, 3321, 3202, 3081, 1753, 1655, 1648 cm<sup>-1</sup>; HRMS (FAB) calcd for C<sub>17</sub>H<sub>23</sub>FN<sub>5</sub>O<sub>4</sub>S (M+H<sup>+</sup>) 412.1454, found 412.1447. Anal. calcd for C<sub>17</sub>H<sub>22</sub>FN<sub>5</sub>O<sub>4</sub>S: C, 49.63; H, 5.39; N, 17.02. Found: C, 49.63; H, 5.48; N, 16.99.

15

20

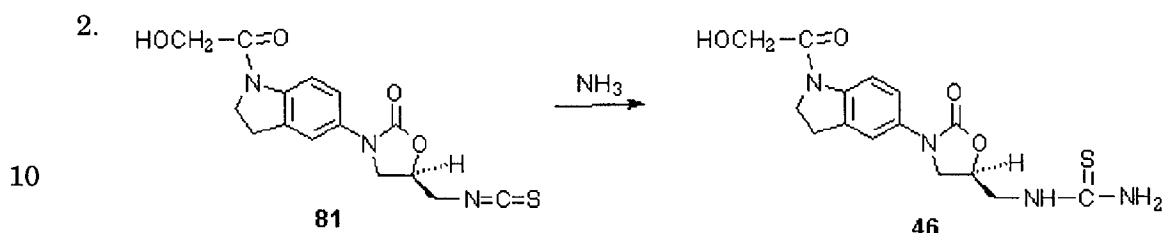
25 **EXAMPLE 32: (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (46).**

1.



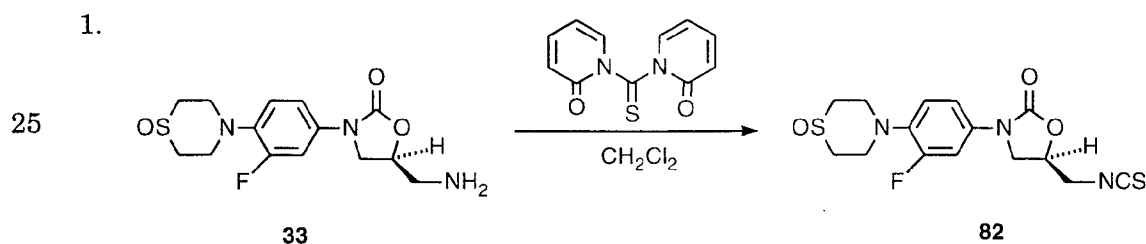
35

An ice cold, stirred solution of 1,1*ϵ*-thiocarbonyldi-2(1H)-pyridone (0.096 g, 0.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was treated with a suspension of **27** (0.10 g, 0.34 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and then with 0.05 mL (0.36 mmol) of triethylamine. It was kept in the ice bath for 30 min and at ambient temperature for 2 h, diluted with CH<sub>2</sub>Cl<sub>2</sub>,  
5 washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with 20-40% CH<sub>3</sub>CN-CH<sub>2</sub>Cl<sub>2</sub> gave 0.04 g of **81**.



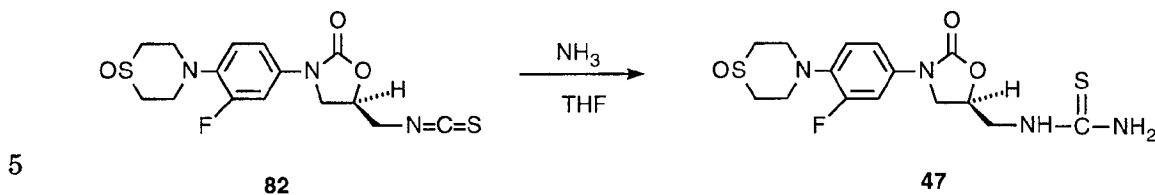
Excess anhydrous ammonia was bubbled into an ice cold solution of **81** (0.04 g) in THF (30 mL) and the mixture was kept in the ice bath for 80 min and concentrated under a stream of nitrogen. The residue was crystallized from CH<sub>3</sub>CN to give  
15 0.0151 g of **46**: mp 214-215 °C (dec); MS (FAB) *m/z* 351 (M+H<sup>+</sup>), 350 (M<sup>+</sup>), 319, 304, 147; HRMS (FAB) calcd for C<sub>15</sub>H<sub>19</sub>N<sub>4</sub>O<sub>4</sub>S (M+H<sup>+</sup>) 351.1127, found 351.1130; IR (DRIFT) 3329, 3296, 3196, 1746, 1655, 1626 cm<sup>-1</sup>.

20 **EXAMPLE 33: (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea, thiomorpholine S-oxide (47).**



A suspension of **33** (0.30 g, 0.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) was added, during 20 min,  
30 to an ice cold, stirred mixture of 1,1*ϵ*-thiocarbonyldi-2(1H)-pyridone (0.258 g, 1.11 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, mixed with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Chromatography of the product on silica gel with 20-50% CH<sub>3</sub>CN-CH<sub>2</sub>Cl<sub>2</sub> gave 0.27 g of **82** which was used in the next reaction:  
35 MS(ES) *m/z* 370 (M+H<sup>+</sup>), 392 (M+Na<sup>+</sup>).

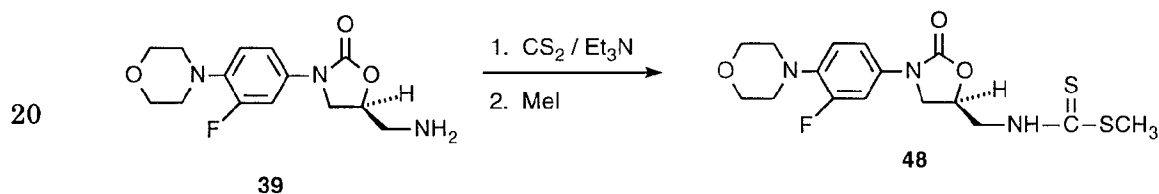
2.



A stirred, ice cold solution of **82** (0.27g , 0.73 mmol) in THF (15 mL), under nitrogen, was treated with excess anhydrous ammonia, kept in the ice bath for 1 h and concentrated; crystallization of the residue from MeOH gave 0.175 g of **47**; mp 212-  
 10 213 °C; <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 2.83 (m, 2H), 3.01 (m, 2H), 3.17 (m, 2H), 3.50 (t, 2H), 3.78 (broad s, 3H), 4.08 (t, 1H), 4.80 (broad s, 1H), 7.17 (m, 2H), 7.17 (broad s, 2H), 7.50 (d, 1H), 7.90 (t, 1H); MS(ES) *m/z* 409 (M+Na<sup>+</sup>); IR (mull) 3335, 3284, 3211, 3175, 3097, 1750, 1630 cm<sup>-1</sup>. Anal. calcd for C<sub>15</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>: C, 46.62; H, 4.95; N, 14.50. Found: C, 46.50; H, 4.95; N, 14.40.

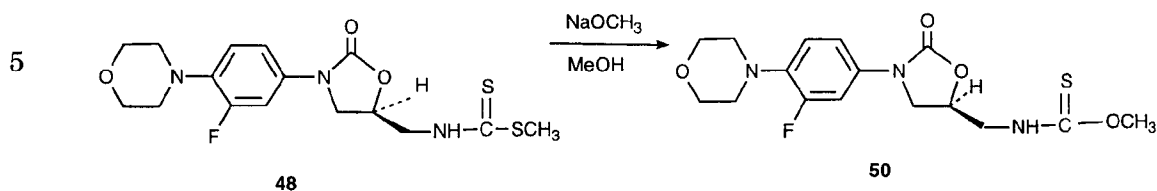
15

EXAMPLE 34: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-S-methyldithiocarbamate (**48**).



An ice cold, stirred mixture of **39**<sup>8</sup> (0.59 g, 0.0020 mol), EtOH (1.5 mL), water (2 drops) and triethylamine (0.613 mL, 0.00440 mol), under nitrogen, was treated with  
 25 carbon disulfide (0.066 mL, 0.0011 mol) and kept in the ice bath for 2 h and at ambient temperature for 18 h. (A solution was obtained after the addition of carbon disulfide; a white precipitate began to form soon after the mixture was warmed to ambient temperature.) The thick suspension was treated, dropwise during 2 min, with a solution of methyl iodide (0.137 mL, 0.00220 mol) in EtOH (2 mL) and the  
 30 mixture was kept at ambient temperature for 1.5 h and concentrated in vacuo. A solution of the residue in EtOAc was washed with saturated NaHCO<sub>3</sub>, water and brine, dried (MgSO<sub>4</sub>) and concentrated. The residue was chromatographed on silica gel with 1.8% MeOH-CH<sub>2</sub>Cl<sub>2</sub> and the product was crystallized from EtOAc to give 0.197 g of **48**: mp 154-155 °C; IR (mull) 3354, 3346, 1726 cm<sup>-1</sup>. Anal. calcd for  
 35 C<sub>16</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>: C, 49.85; H, 5.23; N, 10.90. Found: C, 49.73; H, 5.25; N, 10.82.

EXAMPLE 35: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-O-methylthiocarbamate (50).

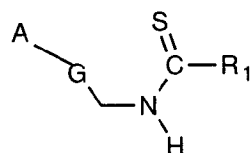


A stirred mixture of **48** (0.200 g, 0.518 mmol), sodium methoxide (0.003 g, 0.06  
 10 mmol) and MeOH (5 mL), under nitrogen, was refluxed for 4 h and kept at ambient  
 temperature for 18 h. It was found that the starting material and product had  
 similar mobilities on TLC. the reaction was therefore followed by MS(ES). Starting  
 material was still present. The mixture was refluxed for 3 h, additional sodium  
 methoxide (0.005 g) was added and reflux was continued for 2 h. It was kept at  
 15 ambient temperature for 18 h, refluxed for 1 h, kept at ambient temperature 1.5 h  
 and concentrated in vacuo. The residue was mixed with ice, the pH was adjusted to  
 9-10 with 1M KHSO<sub>4</sub> and saturated NaHCO<sub>3</sub> and the mixture was extracted with  
 CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water and brine, dried (MgSO<sub>4</sub>) and  
 concentrated. The residue was chromatographed on silica gel with 5% acetone-  
 20 CH<sub>2</sub>Cl<sub>2</sub> and the product was crystallized from EtOAc-hexane to give 0.107 g of **50**:  
 mp 128-129 °C; MS(ES) *m/z* 370 (M+H<sup>+</sup>), 392 (M+Na<sup>+</sup>); IR (DRIFT) 3282, 3251,  
 1753, 1735 cm<sup>-1</sup>; <sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 2.94 (m, 4H), 3.47, 374 (m,m,  
 7H), 3.86, 3.91 (s,s, 3H), 4.10 (m, 1H), 4.73, 4.86 (m,m, 1H), 7.05 (t, 1H), 7.16 (d,d,  
 1H), 7.47 (d,d, 1H), 9.41, 9.50 (s,s, 1H). Anal. calcd for C<sub>16</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub>S: C, 52.02;  
 25 H, 5.46; N, 11.38. Found: C, 51.97; H, 5.49; N, 11.35.

## WHAT IS CLAIMED:

1. A compound of the formula I

5



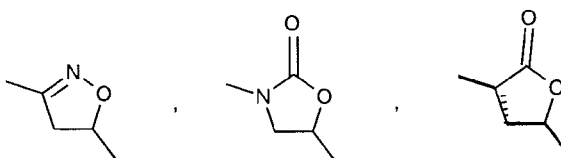
10

I

or pharmaceutical acceptable salts thereof wherein:

G is

15

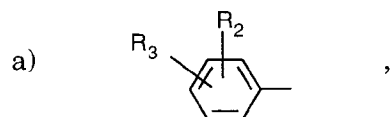


R<sub>1</sub> is

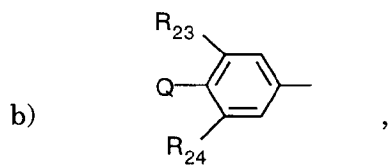
- 20
- a) H,
  - b) NH<sub>2</sub>,
  - c) NH-C<sub>1-4</sub> alkyl,
  - d) C<sub>1-4</sub> alkyl,
  - e) -OC<sub>1-4</sub> alkyl,
  - f) -S C<sub>1-4</sub> alkyl,
  - 25 g) C<sub>1-4</sub> alkyl substituted with 1-3 F, 1-2 Cl, CNor -COOC<sub>1-4</sub> alkyl,
  - h) C<sub>3-6</sub> cycloalkyl,
  - i) N(C<sub>1-4</sub>) alkyl)<sub>2</sub> or
  - j)  $\overline{\text{N}}(\text{CH}_2)_{2-5}$ ;

A is

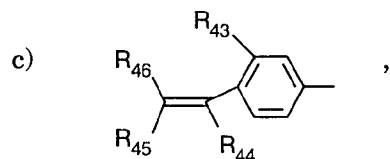
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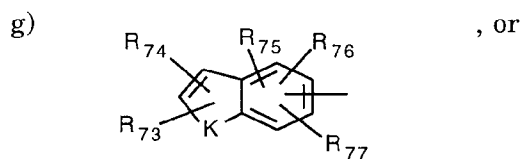
d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O, wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

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,

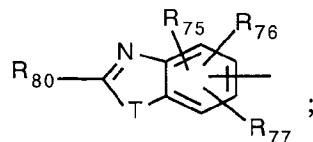
wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring, wherein the heteroaromatic moiety is optionally substituted with one to three  $R_{55}$ ,

f) a  $\beta$ -carbolin-3-yl, or indolizinyll bonded via the 6-membered ring, optionally substituted with one to three  $R_{55}$ ,



35

h)



5

wherein R<sub>2</sub> is

- a) H,
- b) F,
- 10 c) Cl,
- d) Br,
- e) C<sub>1-3</sub> alkyl,
- f) NO<sub>2</sub>, or
- g) R<sub>2</sub> and R<sub>3</sub> taken together are -O-(CH<sub>2</sub>)<sub>h</sub>-O-;

15 R<sub>3</sub> is

- a) -S(=O)<sub>i</sub>R<sub>4</sub>,
- b) -S(=O)<sub>2</sub>-N=S(O)<sub>j</sub>R<sub>5</sub>R<sub>6</sub>,
- c) -SC(=O)R<sub>7</sub>,
- d) -C(=O)R<sub>8</sub>,
- 20 e) -C(=O)R<sub>9</sub>,
- f) -C(=O)NR<sub>10</sub>R<sub>11</sub>,
- g) -C(=NR<sub>12</sub>)R<sub>8</sub>,
- h) -C(R<sub>8</sub>)(R<sub>11</sub>)-OR<sub>13</sub>,
- i) -C(R<sub>9</sub>)(R<sub>11</sub>)-OR<sub>13</sub>,
- 25 j) -C(R<sub>8</sub>)(R<sub>11</sub>)-OC(=O)R<sub>13</sub>,
- k) -C(R<sub>9</sub>)(R<sub>11</sub>)-OC(=O)R<sub>13</sub>,
- l) -NR<sub>10</sub>R<sub>11</sub>,
- m) -N(R<sub>10</sub>)-C(=O)R<sub>7</sub>,
- n) -N(R<sub>10</sub>)-S(=O)<sub>i</sub>R<sub>7</sub>,
- 30 o) -C(OR<sub>14</sub>)(OR<sub>15</sub>)R<sub>8</sub>,
- p) -C(R<sub>8</sub>)(R<sub>16</sub>)-NR<sub>10</sub>R<sub>11</sub>, or
- q) C<sub>1-8</sub> alkyl substituted with one or more =O other than at alpha position, -S(=O)<sub>i</sub>R<sub>17</sub>, -NR<sub>10</sub>R<sub>11</sub>, C<sub>2-5</sub> alkenyl, or C<sub>2-5</sub> alkynyl;

R<sub>4</sub> is

- 35 a) C<sub>1-4</sub> alkyl optionally substituted with one or more halos, OH, CN, NR<sub>10</sub>R<sub>11</sub>, or -CO<sub>2</sub>R<sub>13</sub>,

- b) C<sub>2-4</sub> alkenyl,  
 c) -NR<sub>16</sub>R<sub>18</sub>,  
 d) -N<sub>3</sub>,  
 e) -NHC(=O)R<sub>7</sub>,  
 5 f) -NR<sub>20</sub>C(=O)R<sub>7</sub>,  
 g) -N(R<sub>19</sub>)<sub>2</sub>,  
 h) -NR<sub>16</sub>R<sub>19</sub>, or  
 i) -NR<sub>19</sub>R<sub>20</sub>,

R<sub>5</sub> and R<sub>6</sub> at each occurrence are the same or different and are

- 10 a) C<sub>1-2</sub> alkyl, or  
 b) R<sub>5</sub> and R<sub>6</sub> taken together are -(CH<sub>2</sub>)<sub>k</sub>-;

R<sub>7</sub> is C<sub>1-4</sub> alkyl optionally substituted with one or more halos;

R<sub>8</sub> is

- a) H, or  
 15 b) C<sub>1-8</sub> alkyl optionally substituted with one or more halos, or C<sub>3-8</sub>  
 cycloalkyl;

R<sub>9</sub> is C<sub>1-4</sub> alkyl substituted with one or more

- a) -S(=O)R<sub>17</sub>,  
 b) -OR<sub>13</sub>,  
 20 c) -OC(=O)R<sub>13</sub>,  
 d) -NR<sub>10</sub>R<sub>11</sub>, or  
 e) C<sub>1-5</sub> alkenyl optionally substituted with CHO;

R<sub>10</sub> and R<sub>11</sub> at each occurrence are the same or different and are

- a) H,  
 25 b) C<sub>1-4</sub> alkyl, or  
 c) C<sub>3-8</sub> cycloalkyl;

R<sub>12</sub> is

- a) -NR<sub>10</sub>R<sub>11</sub>,  
 b) -OR<sub>10</sub>; or  
 30 c) -NHC(=O)R<sub>10</sub>;

R<sub>13</sub> is

- a) H, or  
 b) C<sub>1-4</sub> alkyl;

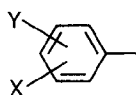
R<sub>14</sub> and R<sub>15</sub> at each occurrence are the same or different and are

- 35 a) C<sub>1-4</sub> alkyl, or  
 b) R<sub>14</sub> and R<sub>15</sub> taken together are -(CH)<sub>1</sub>-;

- R<sub>16</sub> is
- a) H,
  - b) C<sub>1-4</sub> alkyl, or
  - c) C<sub>3-8</sub> cycloalkyl;
- 5 R<sub>17</sub> is
- a) C<sub>1-4</sub> alkyl, or
  - b) C<sub>3-8</sub> cycloalkyl;
- R<sub>18</sub> is
- a) H,
  - 10 b) C<sub>1-4</sub> alkyl,
  - c) C<sub>2-4</sub> alkenyl,
  - d) C<sub>3-4</sub> cycloalkyl,
  - e) -OR<sub>13</sub> or
  - f) -NR<sub>21</sub>R<sub>22</sub>;
- 15 R<sub>19</sub> is
- a) Cl,
  - b) Br, or
  - c) I;
- R<sub>20</sub> is a physiologically acceptable cation;
- 20 R<sub>21</sub> and R<sub>22</sub> at each occurrence are the same or different and are
- a) H,
  - b) C<sub>1-4</sub> alkyl, or
  - c) -NR<sub>21</sub>R<sub>22</sub> taken together are -(CH<sub>2</sub>)<sub>m</sub>-;
- wherein R<sub>23</sub> and R<sub>24</sub> at each occurrence are the same or different and are
- 25 a) H,
  - b) F,
  - c) Cl,
  - d) C<sub>1-2</sub> alkyl,
  - e) CN
  - 30 f) OH,
  - g) C<sub>1-2</sub> alkoxy,
  - h) nitro, or
  - i) amino;
- 35

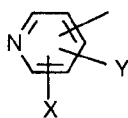
Q is

a) ,



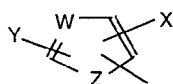
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b) ,



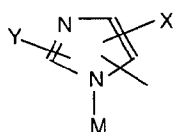
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c) ,



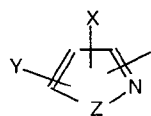
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d) ,



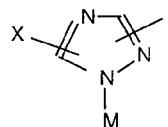
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e) ,



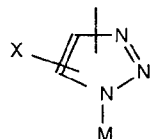
25

f) ,



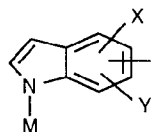
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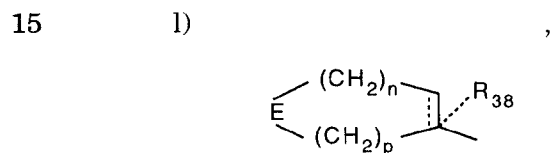
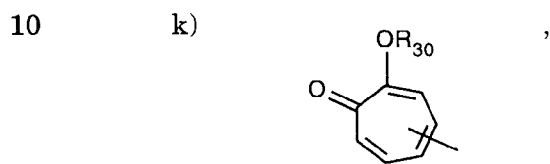
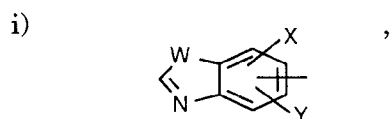
g) ,



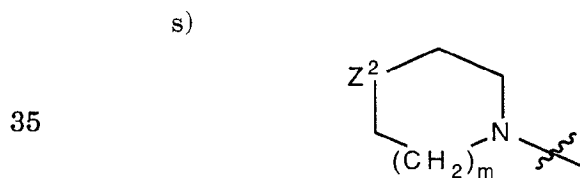
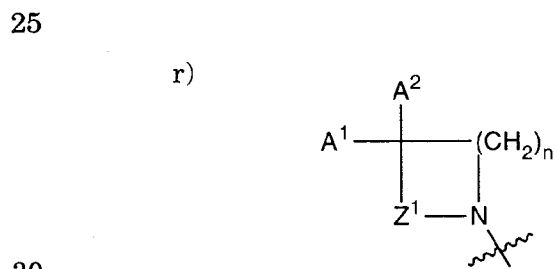
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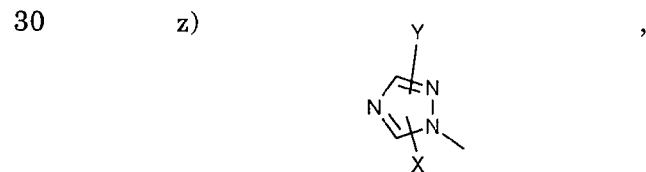
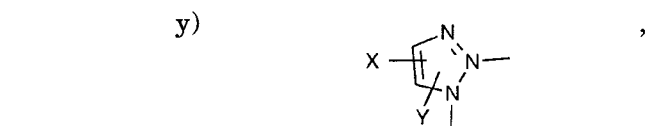
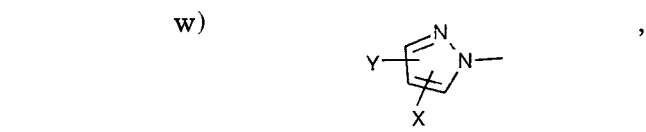
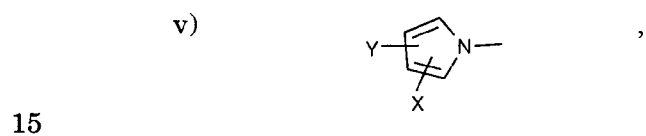
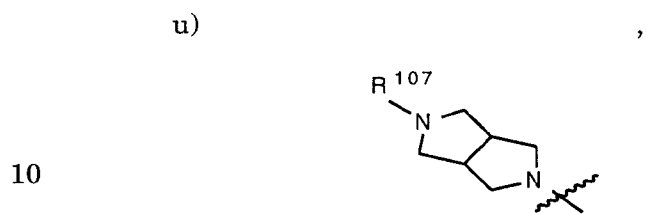
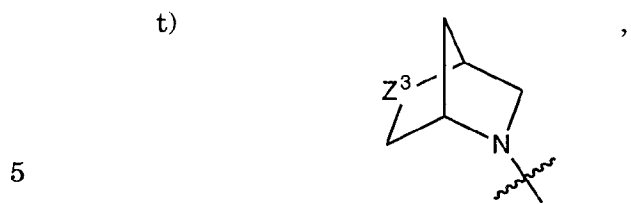
h) ,



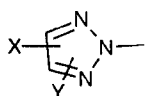


- 20 m) a diazinylyl group optionally substituted with X and Y,  
 n) a triazinyl group optionally substituted with X and Y,  
 o) a quinolinyl group optionally substituted with X and Y,  
 p) a quinoxalinylyl group optionally substituted with X and Y,  
 q) a naphthyridinylyl group optionally substituted with X and Y,





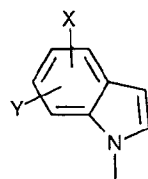
aa)



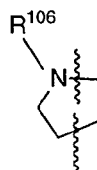
,

5

bb)



or

10 Q and R<sub>24</sub> taken together are

,

15 wherein Z<sup>1</sup> is

- a) -CH<sub>2</sub>-,
- b) -CH(R<sup>104</sup>)-CH<sub>2</sub>-,
- c) -C(O)-, or
- d) -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-;

20 wherein Z<sup>2</sup> is

- a) -O<sub>2</sub>S-,
- b) -O-,
- c) -N(R<sup>107</sup>)-,
- d) -OS-, or

25 e) -S-;

wherein Z<sup>3</sup> is

- a) -O<sub>2</sub>S-,
- b) -O-,
- c) -OS-, or

30 d) -S-;

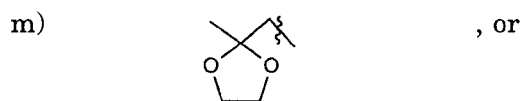
wherein A<sup>1</sup> is

- a) H-, or
- b) CH<sub>3</sub>;

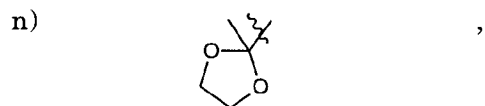
wherein A<sup>2</sup> is35 a) H-,  
b) HO-,



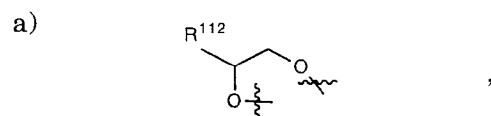
- c)  $\text{CH}_3^-$ ,  
 d)  $\text{CH}_3\text{O}-$ ,  
 e)  $\text{R}^{102}\text{O}-\text{CH}_2-\text{C}(\text{O})-\text{NH}-$   
 f)  $\text{R}^{103}\text{O}-\text{C}(\text{O})-\text{NH}-$ ,  
 5 g)  $(\text{C}_1-\text{C}_2)\text{alkyl}-\text{O}-\text{C}(\text{O})-$ ,  
 h)  $\text{HO}-\text{CH}_2-$ ,  
 i)  $\text{CH}_3\text{O}-\text{NH}-$ ,  
 j)  $(\text{C}_1-\text{C}_3)\text{alkyl}-\text{O}_2\text{C}-$   
 k)  $\text{CH}_3-\text{C}(\text{O})-$ ,  
 10 l)  $\text{CH}_3-\text{C}(\text{O})-\text{CH}_2-$ ,



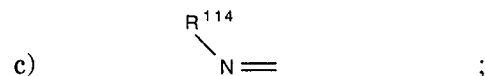
15



20  $\text{A}^1$  and  $\text{A}^2$  taken together are:



25 b)  $\text{O}=\text{C}$  , or

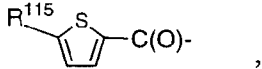
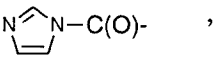
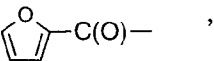
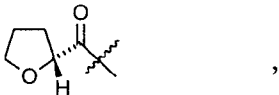


30 wherein  $\text{R}^{102}$  is

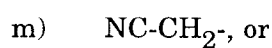
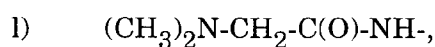
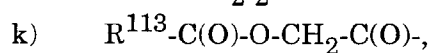
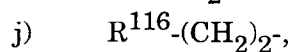
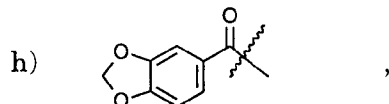
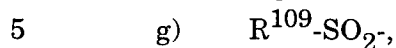
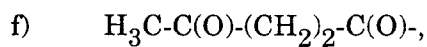
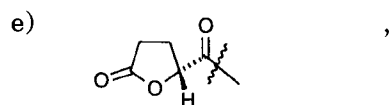
- a)  $\text{H}-$ ,  
 b)  $\text{CH}_3-$ ,  
 c) phenyl- $\text{CH}_2-$ , or  
 d)  $\text{CH}_3\text{C}(\text{O})-$ ;

35 wherein  $\text{R}^{103}$  is

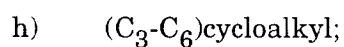
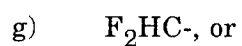
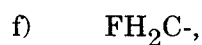
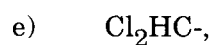
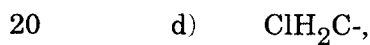
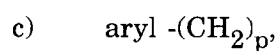
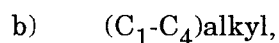
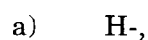
- a)  $(\text{C}_1-\text{C}_3)\text{alkyl}-$ , or

- b) phenyl-;  
 wherein R<sup>104</sup> is
- a) H-, or  
 b) HO-;
- 5 wherein R<sup>105</sup> is
- a) H-,  
 b) (C<sub>1</sub>-C<sub>3</sub>)alkyl-,  
 c) CH<sub>2</sub> = CH-CH<sub>2</sub>-, or  
 d) CH<sub>3</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-;
- 10 wherein R<sup>106</sup> is
- a) CH<sub>3</sub>-C(O)-,  
 b) H-C(O)-,  
 c) Cl<sub>2</sub>CH-C(O)-,  
 d) HOCH<sub>2</sub>-C(O)-,  
 15 e) CH<sub>3</sub>SO<sub>2</sub>-,
- f)  ,
- g) F<sub>2</sub>CHC(O)-,
- 20 h)  ,
- i) H<sub>3</sub>C-C(O)-O-CH<sub>2</sub>-C(O)-,  
 j) H-C(O)-O-CH<sub>2</sub>-C(O)-,  
 k)  ,
- 25 l) HC≡C-CH<sub>2</sub>O-CH<sub>2</sub>-C(O)-, or  
 m) phenyl-CH<sub>2</sub>-O-CH<sub>2</sub>-C(O)-;
- wherein R<sup>107</sup> is
- a) R<sup>102</sup>O-C(R<sup>110</sup>)(R<sup>111</sup>)-C(O)-,  
 30 b) R<sup>103</sup>O-C(O)-,  
 c) R<sup>108</sup>-C(O)-,
- d)  ,

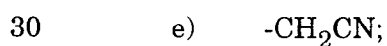
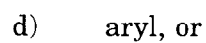
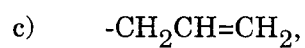
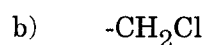
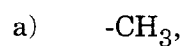
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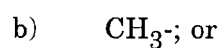
wherein  $\text{R}^{108}$  is



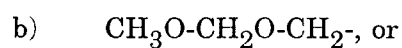
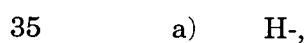
25 wherein  $\text{R}^{109}$  is



wherein  $\text{R}^{110}$  and  $\text{R}^{111}$  are independently



wherein  $\text{R}^{112}$  is



- c) HOCH<sub>2</sub>-;
- wherein R<sup>113</sup> is
- a) CH<sub>3</sub>-,
- b) HOCH<sub>2</sub>-,
- 5 c) (CH<sub>3</sub>)<sub>2</sub>N-phenyl, or
- d) (CH<sub>3</sub>)<sub>2</sub>N-CH<sub>2</sub>-;
- wherein R<sup>114</sup> is
- a) HO-,
- b) CH<sub>3</sub>O-,
- 10 c) H<sub>2</sub>N-,
- d) CH<sub>3</sub>O-C(O)-O-,
- e) CH<sub>3</sub>-C(O)-O-CH<sub>2</sub>-C(O)-O-,
- f) phenyl-CH<sub>2</sub>-O-CH<sub>2</sub>-C(O)-O-,
- g) HO-(CH<sub>2</sub>)<sub>2</sub>-O-,
- 15 h) CH<sub>3</sub>O-CH<sub>2</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-O-, or
- i) CH<sub>3</sub>O-CH<sub>2</sub>-O-; wherein R<sup>113</sup> is
- a) CH<sub>3</sub>-,
- b) HOCH<sub>2</sub>-,
- c) (CH<sub>3</sub>)<sub>2</sub>N-phenyl, or
- 20 d) (CH<sub>3</sub>)<sub>2</sub>N-CH<sub>2</sub>-;
- wherein R<sup>115</sup> is
- a) H-, or
- b) Cl-;
- wherein R<sup>116</sup> is
- 25 a) HO-
- b) CH<sub>3</sub>O-, or
- c) F;
- B is an unsaturated 4-atom linker having one nitrogen and three carbons;
- M is
- 30 a) H,
- b) C<sub>1-8</sub> alkyl,
- c) C<sub>3-8</sub> cycloalkyl,
- d) -(CH<sub>2</sub>)<sub>m</sub>OR<sub>13</sub>, or
- e) -(CH<sub>2</sub>)<sub>h</sub>-NR<sub>21</sub>R<sub>22</sub>;
- 35 Z is
- a) O,

- b) S, or  
c) NM;
- W is
- 5 a) CH,  
b) N, or  
c) S or O when Z is NM;
- Y is
- 10 a) H,  
b) F,  
c) Cl,  
d) Br,  
e) C<sub>1-3</sub> alkyl, or  
f) NO<sub>2</sub>;
- X is
- 15 a) H,  
b) -CN,  
c) OR<sub>27</sub>,  
d) halo,  
e) NO<sub>2</sub>,
- 20 f) tetrazoyl,  
g) -SH,  
h) -S(=O)<sub>i</sub>R<sub>4</sub>,  
i) -S(=O)<sub>2</sub>-N=S(O)<sub>j</sub>R<sub>5</sub>R<sub>6</sub>,  
j) -SC(=O)R<sub>7</sub>,
- 25 k) -C(=O)R<sub>25</sub>,  
l) -C(=O)NR<sub>27</sub>R<sub>28</sub>,  
m) -C(=NR<sub>29</sub>)R<sub>25</sub>,  
n) -C(R<sub>25</sub>)(R<sub>28</sub>)-OR<sub>13</sub>,  
o) -C(R<sub>25</sub>)(R<sub>28</sub>)-OC(=O)R<sub>13</sub>,
- 30 p) -C(R<sub>28</sub>)(OR<sub>13</sub>)-(CH<sub>2</sub>)<sub>h</sub>-NR<sub>27</sub>R<sub>28</sub>,  
q) -NR<sub>27</sub>R<sub>28</sub>,  
r) -N(R<sub>27</sub>)C(=O)R<sub>7</sub>,  
s) -N(R<sub>27</sub>)-S(=O)<sub>i</sub>R<sub>7</sub>,  
t) -C(OR<sub>14</sub>)(OR<sub>15</sub>)R<sub>28</sub>,
- 35 u) -C(R<sub>25</sub>)(R<sub>16</sub>)-NR<sub>27</sub>R<sub>26</sub>, or  
v) C<sub>1-8</sub> 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

- 5 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  $CO_2R_{13}$ ;

10  $R_{26}$  is

- a)  $R_{28}$ , or  
 b)  $NR_{27}R_{28}$ ;

$R_{27}$  and  $R_{28}$  at each occurrence are the same or different and are

- 15 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 -  
 20  $(CH_2)_2N(CH_2)_2(R_7)$ ;

$R_{29}$  is

- a)  $-NR_{27}R_{28}$ ,  
 b)  $-OR_{27}$ , or  
 c)  $-NHC(=O)R_{28}$ ;

25 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

- 30 a)  $NR_{39}$ ,  
 b)  $-S(=O)_i$ , or  
 c) O;

$R_{38}$  is

- 35 a) H,  
 b)  $C_{1-6}$  alkyl,  
 c)  $-(CH_2)_q$ -aryl, or

d) halo;

R<sub>39</sub> is

- 5 a) H,  
 b) C<sub>1-6</sub> alkyl optionally substituted with one or more OH, halo, or -CN,  
 c) -(CH<sub>2</sub>)<sub>q</sub>-aryl,  
 d) -CO<sub>2</sub>R<sub>40</sub>,  
 e) -COR<sub>41</sub>,  
 f) -C(=O)-(CH<sub>2</sub>)<sub>q</sub>-C(=O)R<sub>40</sub>,  
 g) -S(=O)<sub>2</sub>-C<sub>1-6</sub> alkyl,  
 10 h) -S(=O)<sub>2</sub>-(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
 i) -(C=O)<sub>j</sub>-Het;

R<sub>40</sub> is

- 15 a) H,  
 b) C<sub>1-6</sub> alkyl optionally substituted with one or more OH, halo, or -CN,  
 c) -(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
 d) -(CH<sub>2</sub>)<sub>q</sub>-OR<sub>42</sub>;

R<sub>41</sub> is

- 20 a) C<sub>1-6</sub> alkyl optionally substituted with one or more OH, halo, or -CN,  
 b) -(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
 c) -(CH<sub>2</sub>)<sub>q</sub>-OR<sub>42</sub>;

R<sub>42</sub> is

- 25 a) H,  
 b) C<sub>1-6</sub> alkyl,  
 c) -(CH<sub>2</sub>)<sub>q</sub>-aryl, or  
 d) -C(=O)-C<sub>1-6</sub> alkyl;

aryl is

- a) phenyl,  
 b) pyridyl, or  
 c) naphthyl; a to c optionally substituted with one or more halo, -CN, OH,  
 30 SH, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, or C<sub>1-6</sub> alkylthio;

wherein R<sub>43</sub> is

- a) H,  
 b) C<sub>1-2</sub> alkyl,  
 c) F, or  
 35 d) OH;

R<sub>44</sub> is

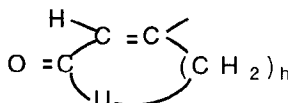
- a) H,  
 b) CF<sub>3</sub>,  
 c) C<sub>1-3</sub> alkyl optionally substituted with one or more halo,  
 d) phenyl optionally substituted with one or more halo,

5

- e) R<sub>44</sub> and R<sub>45</sub> taken together are a 5-, 6-, or 7-membered ring of the formula,

10

or



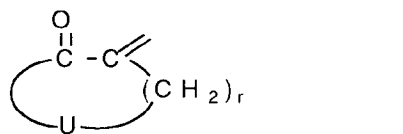
- f) R<sub>44</sub> and R<sub>45</sub> taken together are -(CH<sub>2</sub>)<sub>k</sub>-, when R<sub>46</sub> is an electron-withdrawing group;

15

R<sub>45</sub> and R<sub>46</sub> at each occurrence are the same or different and are

- a) an electron-withdrawing group,  
 b) H,  
 c) CF<sub>3</sub>,  
 d) C<sub>1-3</sub> alkyl optionally substituted with one halo,  
 e) phenyl, provided at least one of R<sub>45</sub> or R<sub>46</sub> is an electron-withdrawing group, or  
 f) R<sub>45</sub> and R<sub>46</sub> taken together are a 5-, 6-, 7-membered ring of the formula

25



U is

- a) CH<sub>2</sub>,  
 b) O,  
 c) S, or  
 d) NR<sub>47</sub>;

30

R<sub>47</sub> is

- a) H, or  
 b) C<sub>1-5</sub> alkyl;

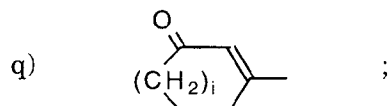
35

wherein R<sub>48</sub> is



- 5 a) carboxyl,  
 b) halo,  
 c) -CN,  
 d) mercapto,  
 e) formyl,  
 f) CF<sub>3</sub>,  
 g) -NO<sub>2</sub>,  
 h) C<sub>1-6</sub> alkoxy,  
 i) C<sub>1-6</sub> alkoxy carbonyl,  
 10 j) C<sub>1-6</sub> alkythio,  
 k) C<sub>1-6</sub> acyl,  
 l) -NR<sub>49</sub>R<sub>50</sub>,  
 m) C<sub>1-6</sub> alkyl optionally substituted with OH, C<sub>1-5</sub> alkoxy, C<sub>1-5</sub> acyl, or  
 -NR<sub>49</sub>R<sub>50</sub>,  
 15 n) C<sub>2-8</sub> alkenylphenyl optionally substituted with one or two R<sub>51</sub>,  
 o) phenyl optionally substituted with one or two R<sub>51</sub>,  
 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<sub>51</sub>, or

20



R<sub>49</sub> and R<sub>50</sub> at each occurrence are the same or different and are

- 25 a) H,  
 b) C<sub>1-4</sub> alkyl,  
 c) C<sub>5-6</sub> cycloalkyl, or  
 d) R<sub>49</sub> and R<sub>50</sub> 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,  
 30 and can in turn be optionally substituted with, including on the further nitrogen atom,  
 C<sub>1-3</sub> alkyl, or C<sub>1-3</sub> acyl;

R<sub>51</sub> is

- 35 a) carboxyl,  
 b) halo,  
 c) -CN,  
 d) mercapto,

- e) formyl,  
 f)  $\text{CF}_3$ ,  
 g)  $-\text{NO}_2$ ,  
 h)  $\text{C}_{1-6}$  alkoxy,  
 5 i)  $\text{C}_{1-6}$  alkoxy carbonyl,  
 j)  $\text{C}_{1-6}$  alkythio,  
 k)  $\text{C}_{1-6}$  acyl,  
 l)  $\text{C}_{1-6}$  alkyl optionally substituted with OH,  $\text{C}_{1-5}$  alkoxy,  $\text{C}_{1-5}$  acyl, or  $-\text{NR}_{49}\text{R}_{50}$ ,  
 10 m) phenyl,  
 n)  $-\text{C}(=\text{O})\text{NR}_{52}\text{R}_{53}$ ,  
 o)  $-\text{NR}_{49}\text{R}_{50}$ ,  
 p)  $-\text{N}(\text{R}_{52})(-\text{SO}_2\text{R}_{54})$ ,  
 q)  $-\text{SO}_2-\text{NR}_{52}\text{R}_{53}$ , or  
 15 r)  $-\text{S}(=\text{O})_i\text{R}_{54}$ ;

$\text{R}_{52}$  and  $\text{R}_{53}$  at each occurrence are the same or different and are

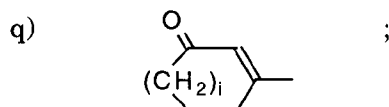
- a) H,  
 b)  $\text{C}_{1-6}$  alkyl, or  
 c) phenyl;  
 20  $\text{R}_{54}$  is  
 a)  $\text{C}_{1-4}$  alkyl, or  
 b) phenyl optionally substituted with  $\text{C}_{1-4}$  alkyl;

wherein  $\text{R}_{55}$  is

- a) carboxyl,  
 25 b) halo,  
 c)  $-\text{CN}$ ,  
 d) mercapto,  
 e) formyl,  
 f)  $\text{CF}_3$ ,  
 30 g)  $-\text{NO}_2$ ,  
 h)  $\text{C}_{1-6}$  alkoxy,  
 i)  $\text{C}_{1-6}$  alkoxy carbonyl,  
 j)  $\text{C}_{1-6}$  alkythio,  
 k)  $\text{C}_{1-6}$  acyl,  
 35 l)  $-\text{NR}_{56}\text{R}_{57}$ ,  
 m)  $\text{C}_{1-6}$  alkyl optionally substituted with OH,  $\text{C}_{1-5}$  alkoxy,  $\text{C}_{1-5}$  acyl, or

-NR<sub>56</sub>R<sub>57</sub>,

- n) C<sub>2-8</sub> alkenylphenyl optionally substituted with one or two R<sub>58</sub>,  
 o) phenyl optionally substituted with one or two R<sub>58</sub>,  
 p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to three  
 5 atoms selected from the group consisting of S, N, and O, optionally substituted with  
 one or two R<sub>58</sub>, or



10

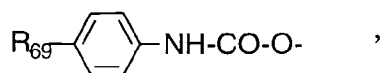
R<sub>56</sub> and R<sub>57</sub> at each occurrence are the same or different and are

- a) H,  
 b) formyl,  
 c) C<sub>1-4</sub> alkyl,  
 15 d) C<sub>1-4</sub> acyl,  
 e) phenyl,  
 f) C<sub>3-6</sub> cycloalkyl, or  
 g) R<sub>56</sub> and R<sub>57</sub> taken together with the nitrogen atom is a 5-, 6-  
 20 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<sub>1-3</sub> alkyl, or C<sub>1-3</sub> acyl;

R<sub>58</sub> is

- a) carboxyl,  
 25 b) halo,  
 c) -CN,  
 d) mercapto,  
 e) formyl,  
 f) CF<sub>3</sub>,  
 30 g) -NO<sub>2</sub>,  
 h) C<sub>1-6</sub> alkoxy,  
 i) C<sub>1-6</sub> alkoxy-carbonyl,  
 j) C<sub>1-6</sub> alkythio,  
 k) C<sub>1-6</sub> acyl,  
 35 l) phenyl,  
 m) C<sub>1-6</sub> alkyl optionally substituted with OH, azido, C<sub>1-5</sub> alkoxy, C<sub>1-5</sub> acyl,

$-\text{NR}_{65}\text{R}_{66}$ ,  $-\text{SR}_{67}$ ,  $-\text{O}-\text{SO}_2\text{R}_{68}$ , or



- 5 n)  $-\text{C}(=\text{O})\text{NR}_{59}\text{R}_{60}$ ,  
 o)  $-\text{NR}_{56}\text{R}_{57}$ ,  
 p)  $-\text{N}(\text{R}_{59})(-\text{SO}_2\text{R}_{54})$ ,  
 q)  $-\text{SO}_2-\text{NR}_{59}\text{R}_{60}$ ,  
 r)  $-\text{S}(=\text{O})_i\text{R}_{54}$ ,  
 10 s)  $-\text{CH}=\text{N}-\text{R}_{61}$ , or  
 t)  $-\text{CH}(\text{OH})-\text{SO}_3\text{R}_{64}$ ;

$\text{R}_{54}$  is the same as defined above;

$\text{R}_{59}$  and  $\text{R}_{60}$  at each occurrence are the same or different and are

- a) H,  
 15 b)  $\text{C}_{1-6}$  alkyl,  
 c) phenyl, or  
 d) tolyl;

$\text{R}_{61}$  is

- a) OH,  
 20 b) benzyloxy,  
 c)  $-\text{NH}-\text{C}(=\text{O})-\text{NH}_2$ ,  
 d)  $-\text{NH}-\text{C}(=\text{S})-\text{NH}_2$ , or  
 e)  $-\text{NH}-\text{C}(=\text{NH})-\text{NR}_{62}\text{R}_{63}$ ;

$\text{R}_{62}$  and  $\text{R}_{63}$  at each occurrence are the same or different and are

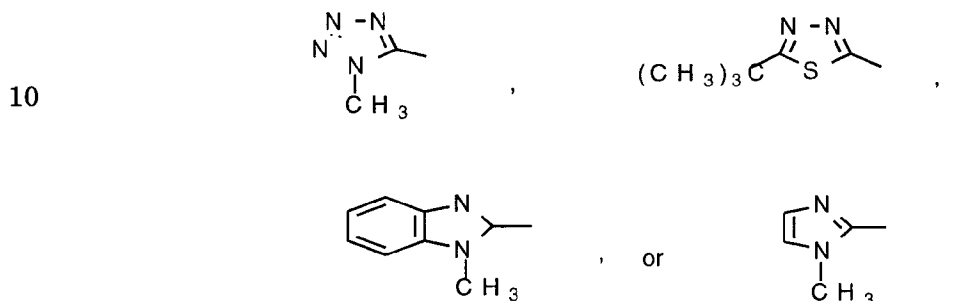
- 25 a) H, or  
 b)  $\text{C}_{1-4}$  alkyl optionally substituted with phenyl or pyridyl;

$\text{R}_{64}$  is

- a) H, or  
 b) a sodium ion;  
 30  $\text{R}_{65}$  and  $\text{R}_{66}$  at each occurrence are the same or different and are  
 a) H,  
 b) formyl,  
 c)  $\text{C}_{1-4}$  alkyl,  
 d)  $\text{C}_{1-4}$  acyl,  
 35 e) phenyl,  
 f)  $\text{C}_{3-6}$  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,
- 5 h)  $-P(O)(OR_{70})(OR_{71})$ , or
- i)  $-SO_2-R_{72}$ ;

$R_{67}$  is



15  $R_{68}$  is  $C_{1-3}$  alkyl;

$R_{69}$  is

- a)  $C_{1-6}$  alkoxy carbonyl, or  
 b) carboxyl;

$R_{70}$  and  $R_{71}$  at each occurrence are the same or different and are

- 20 a) H, or  
 b)  $C_{1-3}$  alkyl;

$R_{72}$  is

- a) methyl,  
 b) phenyl, or  
 25 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

- 30 a) H,  
 b) carboxyl,  
 c) halo,  
 d)  $-CN$ ,  
 e) mercapto,  
 35 f) formyl,  
 g)  $CF_3$ ,

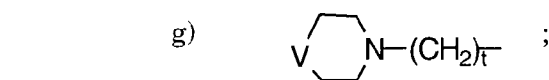
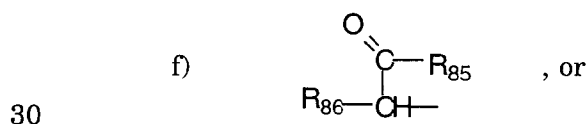
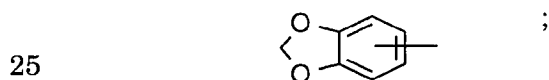
- h) -NO<sub>2</sub>,
- i) C<sub>1-6</sub> alkoxy,
- j) C<sub>1-6</sub> alkoxy carbonyl,
- k) C<sub>1-6</sub> alkythio,
- 5 l) C<sub>1-6</sub> acyl,
- m) -NR<sub>78</sub> R<sub>79</sub>,
- n) C<sub>1-6</sub> alkyl optionally substituted with OH, C<sub>1-5</sub> alkoxy, C<sub>1-5</sub> acyl, -NR<sub>78</sub>R<sub>79</sub>, -N(phenyl)(CH<sub>2</sub>-CH<sub>2</sub>-OH), -O-CH(CH<sub>3</sub>)(OCH<sub>2</sub>CH<sub>3</sub>), or -O-phenyl-[para-NHC(=O)CH<sub>3</sub>],
- 10 o) C<sub>2-8</sub> alkenylphenyl optionally substituted with R<sub>51</sub>,
- p) phenyl optionally substituted with R<sub>51</sub>, 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<sub>51</sub>;
- 15 R<sub>51</sub> is the same as defined above;
- R<sub>78</sub> and R<sub>79</sub> at each occurrence are the same or different and are
- a) H,
- b) C<sub>1-4</sub> alkyl,
- c) phenyl, or
- 20 d) R<sub>78</sub> and R<sub>79</sub> 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<sub>1-3</sub> alkyl, or C<sub>1-3</sub> acyl;
- 25 wherein T is
- a) O,
- b) S, or
- c) SO<sub>2</sub>;
- R<sub>75</sub>, R<sub>76</sub>, and R<sub>77</sub> are the same as defined above;
- 30 R<sub>80</sub> is
- a) H,
- b) formyl,
- c) carboxyl,
- d) C<sub>1-6</sub> alkoxy carbonyl,
- 35 e) C<sub>1-8</sub> alkyl,
- f) C<sub>2-8</sub> alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with OH, halo, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> acyl, C<sub>1-6</sub> alkylthio or C<sub>1-6</sub> alkoxy-carbonyl, or phenyl optionally substituted with halo,

- 5 g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF<sub>3</sub>, -NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> acyl, C<sub>1-6</sub> alkylthio, or C<sub>1-6</sub> alkoxy-carbonyl;
- h) -NR<sub>81</sub>R<sub>82</sub>,
- i) -OR<sub>90</sub>,
- 10 j) -S(=O)<sub>i</sub>-R<sub>91</sub>,
- k) -SO<sub>2</sub>-N(R<sub>92</sub>)(R<sub>93</sub>), or
- l) a radical of the following formulas:

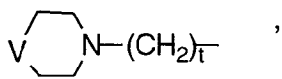
R<sub>81</sub> and R<sub>82</sub> at each occurrence are the same or different and are

- 15 a) H,
- b) C<sub>3-6</sub> cycloalkyl,
- c) phenyl,
- d) C<sub>1-6</sub> acyl,
- 20 e) C<sub>1-8</sub> alkyl optionally substituted with OH, C<sub>1-6</sub> 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<sub>3</sub>, halo, -NO<sub>2</sub>, C<sub>1-4</sub> alkoxy, -NR<sub>83</sub>R<sub>84</sub>, or



35 V is

- a) O,

- b) CH<sub>2</sub>, or  
 c) NR<sub>87</sub>;  
 R<sub>83</sub> and R<sub>84</sub> at each occurrence are the same or different and are
- 5 a) H, or  
 b) C<sub>1-4</sub> alkyl;  
 R<sub>85</sub> is
- a) OH,  
 b) C<sub>1-4</sub> alkoxy, or  
 c) -NR<sub>88</sub> R<sub>89</sub>;
- 10 R<sub>86</sub> is
- a) H, or  
 b) C<sub>1-7</sub> alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, -C(=O)-NH<sub>2</sub>, -CO<sub>2</sub>H, or -C(=NH)-NH<sub>2</sub>;
- 15 R<sub>87</sub> is
- a) H,  
 b) phenyl, or  
 c) C<sub>1-6</sub> alkyl optionally substituted by OH;
- 20 R<sub>88</sub> and R<sub>89</sub> at each occurrence are the same or different and are
- a) H,  
 b) C<sub>1-5</sub> alkyl  
 c) C<sub>3-6</sub> cycloalkyl, or  
 d) phenyl;
- 25 R<sub>90</sub> is
- a) C<sub>1-8</sub> alkyl optionally substituted with C<sub>1-6</sub> alkoxy or C<sub>1-6</sub> hydroxy, C<sub>3-6</sub> 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<sub>2</sub>, CF<sub>3</sub>, halo, -CN, OH, C<sub>1-5</sub> alkyl, C<sub>1-5</sub>
- 30 alkoxy, or C<sub>1-5</sub> acyl;
- b)  ,
- 35 c) phenyl, or  
 d) pyridyl;



R<sub>91</sub> is

- 5
- a) C<sub>1-16</sub> alkyl,
  - b) C<sub>2-16</sub> alkenyl,
- wherein the substituents (a) and (b) can be optionally substituted with C<sub>1-6</sub> alkoxy carbonyl, 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
- 10 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<sub>3</sub>, -NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> acyl, C<sub>1-6</sub> alkylthio, or C<sub>1-6</sub> alkoxy carbonyl;

R<sub>92</sub> and R<sub>93</sub> at each occurrence are the same or different and are

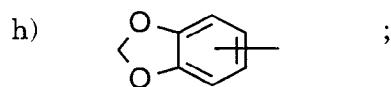
- 15
- a) H,
  - b) phenyl,
  - c) C<sub>1-6</sub> alkyl, or
  - d) benzyl;

R<sub>94</sub> and R<sub>95</sub> at each occurrence are the same or different and are

- 20
- a) H,
  - b) OH,
  - c) C<sub>1-6</sub> alkyl optionally substituted with -NR<sub>83</sub> R<sub>84</sub>, or
  - d) R<sub>94</sub> and R<sub>95</sub> taken together are =O;

R<sub>96</sub> is

- 25
- 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<sub>2</sub>, CF<sub>3</sub>, halo, -CN, OH, phenyl, C<sub>1-5</sub> alkyl, C<sub>1-5</sub> alkoxy, or C<sub>1-5</sub> acyl,
- 30
- c) morpholinyl,
  - d) OH,
  - e) C<sub>1-6</sub> alkoxy,
- 35
- f) -NR<sub>83</sub>R<sub>84</sub>,
  - g) -C(=O)-R<sub>97</sub>, or



R<sub>97</sub> is

- 5 a) morpholinyl,  
 b) OH, or  
 c) C<sub>1-6</sub> alkoxy;
- h is 1, 2, or 3;  
 i is 0, 1, or 2;
- 10 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;
- 15 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.

20

2. A compound of Claim 1 which is :

- a) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;
- 25 b) (S)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;
- c) (S)-N-[[3-[3-Fluoro-4-[2',5'-dioxospiro[piperidine-4,4'-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;
- d) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;
- 30 e) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;
- f) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N'-methylthiourea;
- g) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide;
- 35 h) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-

- oxazolidinyl)methyl]thiopropion-amide;
- i) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]-2-chlorothioacetamide;
- j) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]-  
5  $\alpha,\alpha,\alpha$ -trifluorothioacetamide;
- k) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]- $\alpha$ -fluorothioacetamide;
- l) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]- $\alpha,\alpha$ -difluorothioacetamide;
- 10 m) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]- $\alpha$ -cyanothioacetamide;
- n) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]- $\alpha,\alpha$ -dichlorothioacetamide;
- o) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]-  
15  $\alpha$ -(methoxycarbonyl)thioacetamide;
- p) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide;
- q) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide;
- 20 r)) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide;
- s) (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide;
- t) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-  
25 oxazolidinyl)methyl]thioacetamide;
- u) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide, thiomorpholine S-oxide;
- v) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide, thiomorpholine S, S-dioxide;
- 30 w) (S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl)methyl]thioacetamide;
- x) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl)methyl]thiourea;
- y) (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-  
35 oxazolidinyl)-methyl]thiourea;
- z) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-

oxazolidinyl)methyl]thiourea;

aa) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl]thiourea, thiomorpholine S-oxide;

bb) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl)methyl-S-  
5 methyldithiocarbamate;

3. 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.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/09889

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07D263/20 C07D417/12 C07D413/10 C07D413/04 A61K31/42  
 C07D261/04 C07D307/32 C07D471/10 //(C07D471/10,235:00,  
 221:00)

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 A61K

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	EP 0 127 902 A (E.I. DU PONT DE NEMOURS AND COMPANY) 12 December 1984 see claims ---	1-3
Y	EP 0 184 170 A (E.I. DU PONT DE NEMOURS AND COMPANY) 11 June 1986 see claims ---	1-3
Y	EP 0 359 418 A (THE UPJOHN COMPANY) 21 March 1990 see claims ---	1-3
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 see claims ---	1-3
Y	WO 97 14690 A (ZENECA LTD ) 24 April 1997 see claims ---	1-3
	-/--	

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

Date of the actual completion of the international search

14 August 1998

Date of mailing of the international search report

21/08/1998

Name and mailing address of the ISA

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Authorized officer

Henry, J

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/09889

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 0 789 025 A (BAYER AG) 13 August 1997 see page 33 - page 41; claims -----	1-3
P,Y	WO 98 07708 A (PHARMACIA & UPJOHN COMPANY) 26 February 1998 see claims -----	1-3
P,Y	DE 196 01 264 A (BAYER AG) 17 July 1997 see page 20 - page 23; claims -----	1-3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/09889

## 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.: 3  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 3  
is 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.: not applicable  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by the examples and the compounds of claim 2.

The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 98/09889

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		AU 2909984 A	13-12-1984
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/09889

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507271 A		AU 7557094 A CA 2168560 A CN 1130379 A EP 0717738 A JP 9502436 T ZA 9405894 A	27-03-1995 16-03-1995 04-09-1996 26-06-1996 11-03-1997 05-02-1996
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## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	4161720
<b>Application Number:</b>	11883218
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9960
<b>Title of Invention:</b>	Prevention and Treatment of Thromboembolic Disorders
<b>First Named Inventor/Applicant Name:</b>	Frank Misselwitz
<b>Customer Number:</b>	23416
<b>Filer:</b>	Christine Hansen/Kristen Clark
<b>Filer Authorized By:</b>	Christine Hansen
<b>Attorney Docket Number:</b>	BHC 051006
<b>Receipt Date:</b>	23-OCT-2008
<b>Filing Date:</b>	16-JUL-2008
<b>Time Stamp:</b>	09:30:46
<b>Application Type:</b>	U.S. National Stage under 35 USC 371

### Payment information:

Submitted with Payment	no
------------------------	----

### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement Letter	IDS_Letter.pdf	50541 <small>8f80a994f4f6a8977cad0e0ad4840e356f8085f8</small>	no	2

### Warnings:

### Information:

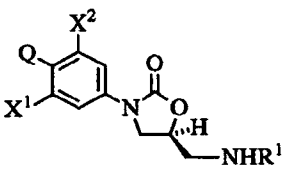
2	Information Disclosure Statement (IDS) Filed (SB/08)	IDS_Filed.pdf	202260	no	10
			0bb4716d262e0404c3ce911d7f848f86b2c39d8		
<b>Warnings:</b>					
<b>Information:</b>					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	DE_2836305.pdf	1505991	no	44
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<b>Warnings:</b>					
<b>Information:</b>					
4	Foreign Reference	GB_2140687.pdf	1821483	no	26
			7570732d14d59ec6e68296bc9a05bf2873d352c2		
<b>Warnings:</b>					
<b>Information:</b>					
5	Foreign Reference	EP_0127902.pdf	2628000	no	85
			55c313eb75982ff278e5325b648a3a57b8930ef2		
<b>Warnings:</b>					
<b>Information:</b>					
6	Foreign Reference	EP_0316594.pdf	1237979	no	37
			9b056e9d04fdd98b7d0050d794e060e7a34d8212		
<b>Warnings:</b>					
<b>Information:</b>					
7	Foreign Reference	EP_0350002.pdf	1184647	no	22
			67a4ae56c672e9ca4b1c843ae5da32610c65d94f		
<b>Warnings:</b>					
<b>Information:</b>					
8	Foreign Reference	EP_0352781.pdf	1885201	no	57
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<b>Warnings:</b>					
<b>Information:</b>					
9	Foreign Reference	WO_9309103.pdf	2327025	no	55
			e2b7277c0bf65723af113519be8f1fd0dbffa0aa1		
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<b>Information:</b>					
10	Foreign Reference	WO_9323384.pdf	2226361	no	45
			2c1327fd9f5db9dea48ccb3b43dbfb4ac52435c7		

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<b>Information:</b>					
11	Foreign Reference	EP_0623615.pdf	1328242 98aa6ecc908e4aaa90f218589b943d340994d1b2	no	18
<b>Warnings:</b>					
<b>Information:</b>					
12	Foreign Reference	EP_0645376.pdf	1390083 2dd498d16c86d75f961591a492f99caa8f69e141	no	20
<b>Warnings:</b>					
<b>Information:</b>					
13	Foreign Reference	EP_738726.pdf	2843607 efddea3de7b93f20e54c440915e661e3c18c4bf5	no	117
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<b>Information:</b>					
14	Foreign Reference	WO_9703072.pdf	2065176 4fc7214f0b4b8e4222fb6dd062a4f3d0747e372f	no	56
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<b>Information:</b>					
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<b>Information:</b>					
16	Foreign Reference	WO_9710223.pdf	1962537 70e5659006d37937ba59d52cc3810c7a4fb8a477	no	85
<b>Warnings:</b>					
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17	Foreign Reference	EP_0785200.pdf	1136723 9bede80a61332443165d566a157739c84c908681	no	36
<b>Warnings:</b>					
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18	Foreign Reference	DE_19604223.pdf	1633360 5ab256415915dab78f3edd71a93c9c1b55e19de0	no	34
<b>Warnings:</b>					
<b>Information:</b>					
19	Foreign Reference	WO_9801446.pdf	2746673 6b851dddfrdbd4ff7f9691ee876617682dedf77e7	no	68

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<b>Information:</b>					
20	Foreign Reference	WO_9854161.pdf	3591664	no	118
			67973d3caa82b38c89f3a46547471fdb7de22747		
<b>Warnings:</b>					
<b>Information:</b>					
<b>Total Files Size (in bytes):</b>				39832572	
<p><b>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b>  <b>If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</b></p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b>  <b>If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</b></p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b>  <b>If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</b></p>					



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>C07D 417/10, 413/10, A61K 31/42</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 99/02525</b> (43) International Publication Date: 21 January 1999 (21.01.99)</p>
<p>(21) International Application Number: PCT/US98/13437 (22) International Filing Date: 8 July 1998 (08.07.98) (30) Priority Data: 60/052,907 11 July 1997 (11.07.97) US 60/064,746 7 November 1997 (07.11.97) US (71) Applicant (for all designated States except US): PHARMACIA &amp; UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): THOMASCO, Lisa, Marie [US/US]; 953 Dobbin Drive, Kalamazoo, MI 49006 (US). GADWOOD, Robert, C. [US/US]; 5232 Stonchenge Drive, Kalamazoo, MI 49008 (US). ANDERSON, David, J. [GB/US]; 3809 Middlebury Drive, Kalamazoo, MI 49006 (US). (74) Agent: YANG, Lucy, X.; Pharmacia &amp; Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p>		<p>(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, 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, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>
<p>(54) Title: THIADIAZOLYL AND OXADIAZOLYL PHENYL OXAZOLIDINONE ANTIBACTERIAL AGENTS</p>		
<div style="text-align: center;">  <p>(I)</p> </div>		
<p>(57) Abstract</p> <p>The present invention provides thiadiazolyl and oxadiazolyl phenyl oxazolidinone compounds of formula (I) wherein Q is thiadiazolyl or oxadiazolyl; wherein X<sup>1</sup> and X<sup>2</sup> are independently hydrogen, fluorine, or chlorine; and wherein R<sup>1</sup> is, for example, -COCH<sub>3</sub> or -COCH<sub>2</sub>CH<sub>3</sub>. These compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive and gram-negative aerobic bacteria.</p>		

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THIADIAZOLYL AND OXADIAZOLYL PHENYL OXAZOLIDINONE  
ANTIBACTERIAL AGENTS

BACKGROUND OF THE INVENTION

5           The subject invention discloses thiadiazolyl and oxadiazolyl phenyl oxazolidinone derivatives. 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, streptococci and enterococci, as well as anaerobic organisms such as *Bacteroides spp.*, and acid-fast organisms such as *Mycobacterium*  
10 *tuberculosis*.

          Piperazine-containing oxazolidinones are disclosed in International Publication No. WO93/23384, November 25, 1987 (PCT/US93/03570). International Publication No. WO95/14684, June 1, 1995 (PCT/US94/10582) discloses esters of the oxazolidinone, piperazine ring structures disclosed in the above PCT application.  
15 International Publication No. WO95/07271, March 16, 1995 (PCT/US94/08904) discloses oxazolidinones although containing morpholine and thiomorpholine instead of the subject piperazine.

          Other earlier publications in the area of oxazolidinones are US Patent Nos. 4,801,600; 4,921,869; EPA 0352781 (January 31, 1989); and EPA 0316594 (May 24,  
20 1989) all assigned to E.I. DuPont De Nemours and Company, which are cited here to exemplify the state of the art.

INFORMATION DISCLOSURE

          International Publication No. WO 93/09103, published 13 May 1993, and corresponding US Patent No. 5,565,571, disclose substituted aryl- and heteroarylphenyl-  
25 oxazolidinones useful as antibacterial agents. Among the heteroaryl groups disclosed are groups such as imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl and triazolyl.

          International Publication No. WO96/23788, published 8 August 1996, discloses nitrogen-containing heteroaromatic ring substituted phenyloxazolidinone antimicrobials.  
30 This 5-member nitrogen-containing hetero-aromatic ring has from 1 to 4 nitrogen atoms and is attached to the phenyloxazolidinone through one of the nitrogen atoms.

          US Patent Nos. 4,948,801; 5,043,443; 5,130,316; and 5,254,577  
aminomethyloxooxazolidinyl aryl-substituted benzene derivatives useful as antibacterial

agents. Among the aromatic groups disclosed are groups such as diazinyl, triazinyl, thiazolyl, oxazolyl and unsubstituted 1,2,3-thiadiazol-4-yl. These compounds do not have flanking halogens on the benzene ring.

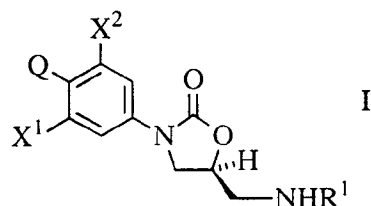
International Publication No. WO97/30981, published 28 August 1997, discloses  
 5 azolyl piperazinyl phenyl oxazolidinone antibacterials. Among the five-membered ring heterocycles (i.e., azolyl rings) disclosed are groups such as thiadiazolyl, oxazdiazolyl, thiazolyl, benzothiazolyl, thiatriazolyl, imidazolyl, benzimidazolyl, triazolyl, tetrazolyl, pyrazolynyl, pyrazolyl, indazolyl, benzoisothiazolyl, isoxazolyl and benisoxazolyl. In all cases, the piperazine nitrogen atom is attached at the carbon atom of the carbon-nitrogen  
 10 double bond of the heterocyclic ring.

US Serial No. 09/080,751, filed 18 May 1998 discloses oxazolidinone antibacterial agents having a thiocarbonyl functionality. It discloses the compound (S)-N-[[3-[3-fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide.

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## SUMMARY OF THE INVENTION

The present invention provides a compound of structural formula I:



or a pharmaceutically acceptable salt thereof.

wherein R<sup>1</sup> is

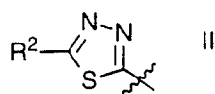
- 20 (a) -COR<sup>3</sup>,  
 (b) -COCH<sub>2</sub>Cl,  
 (c) -COCHCl<sub>2</sub>,  
 (d) -COCH<sub>2</sub>F,  
 (e) -COCHF<sub>2</sub>,  
 25 (f) -CO<sub>2</sub>CH<sub>3</sub>,  
 (g) -SO<sub>2</sub>CH<sub>3</sub>,  
 (h) -COCH<sub>2</sub>OH,  
 (i) -CSR<sup>3</sup>,  
 (j) -CSNH<sub>2</sub>, or

(k) -CSNHCH<sub>3</sub>;

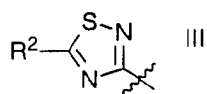
X<sup>1</sup> and X<sup>2</sup> are independently H, F, or Cl; and Q is an optionally substituted five membered ring heterocycle incorporating two nitrogen atoms and one sulfur or oxygen atom.

5 More specifically, in the present invention, Q is:

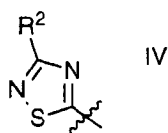
(a) 1,3,4-thiadiazol-2-yl:



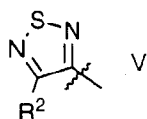
(b) 1,2,4-thiadiazol-3-yl:



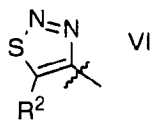
(c) 1,2,4-thiadiazol-5-yl:



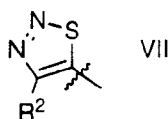
15 (d) 1,2,5-thiadiazol-3-yl:



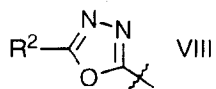
(e) 1,2,3-thiadiazol-4-yl:



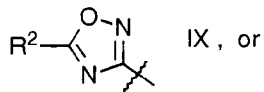
(f) 1,2,3-thiadiazol-5-yl:



(g) 1,3,4-oxadiazol-2-yl:

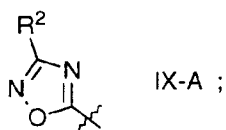


(h) 1,2,4-oxadiazol-3-yl:



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(i) 1,2,4-oxadiazol-5-yl

10 wherein R<sup>2</sup> is(a) R<sup>3</sup>-(b) R<sup>4</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-(c) NC(CH<sub>2</sub>)<sub>n</sub>-(d) R<sup>3</sup>OCO(CH<sub>2</sub>)<sub>n</sub>-15 (e) R<sup>3</sup>R<sup>5</sup>NCO(CH<sub>2</sub>)<sub>n</sub>-(f) R<sup>3</sup>R<sup>5</sup>N(CH<sub>2</sub>)<sub>n</sub>-(g) R<sup>4</sup>CONR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-(h) CF<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>-(i) CF<sub>2</sub>H(CH<sub>2</sub>)<sub>n</sub>-20 (j) R<sup>4</sup>CO(CH<sub>2</sub>)<sub>n</sub>-(k) F(CH<sub>2</sub>)<sub>n</sub>-(l) Cl(CH<sub>2</sub>)<sub>n</sub>-(m) Br(CH<sub>2</sub>)<sub>n</sub>-(n) R<sup>3</sup>O(CH<sub>2</sub>)<sub>n</sub>-25 (o) R<sup>3</sup>S(CH<sub>2</sub>)<sub>n</sub>-(p) R<sup>3</sup>SO(CH<sub>2</sub>)<sub>n</sub>-(q) R<sup>3</sup>SO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-(r) R<sup>3</sup>SO<sub>2</sub>NR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-

- (s)  $R^3R^4C(OH)(CH_2)_n-$ ,  
 (t)  $R^3R^4C(NHR^5)(CH_2)_n-$ ,  
 (u)  $HO_2C(CH_2)_n-$ ,  
 (v)  $O_2N(CH_2)_n-$ ,  
 5 (w) C<sub>2</sub>-C<sub>6</sub> alkenyl,  
 (x) C<sub>2</sub>-C<sub>6</sub> alkynyl,  
 (y) -CCl<sub>3</sub>,  
 (z)  $R^3ON=CR^3(CH_2)_n-$ ,  
 (aa)  $NCNR^5(CH_2)_n-$ ,  
 10 (bb)  $R^3ONR^5(CH_2)_n-$ , or  
 (cc)  $R^3OC(O)NR^5(CH_2)_n-$ ;

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

wherein p is 1, 2 or 3;

wherein R<sup>3</sup> is

- 15 (a) H,  
 (b) C<sub>1</sub>-C<sub>5</sub> alkyl, or  
 (c) cyclopropyl-;

wherein R<sup>4</sup> is

- (a) H,  
 20 (b) C<sub>1</sub>-C<sub>5</sub> alkyl-,  
 (c) cyclopropyl-,  
 (d)  $R^3O(CH_2)_p-$ , or  
 (e)  $R^3CO_2(CH_2)_p-$ ;

wherein R<sup>5</sup> is

- 25 (a) H, or  
 (b) C<sub>1</sub>-C<sub>3</sub> alkyl;

or a pharmaceutically acceptable salt thereof;

with the following proviso:

at least one of X<sup>1</sup> and X<sup>2</sup> is F or Cl.

- 30 More specifically, the present invention provides a compound of formula I

wherein R<sup>1</sup> is -COR<sup>3</sup>, or -CSR<sup>3</sup>;

wherein X<sup>1</sup> and X<sup>2</sup> are independently

- (a) H, or

(b) F:

wherein Q is the moiety of formula II or IV;

wherein R<sup>2</sup> is

- (a) R<sup>3</sup>.
- 5 (b) R<sup>4</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-,
- (c) NC(CH<sub>2</sub>)<sub>n</sub>-,
- (d) R<sup>3</sup>OCO(CH<sub>2</sub>)<sub>n</sub>-,
- (e) R<sup>3</sup>R<sup>5</sup>NCO(CH<sub>2</sub>)<sub>n</sub>-,
- (f) R<sup>3</sup>R<sup>5</sup>N(CH<sub>2</sub>)<sub>n</sub>-,
- 10 (g) R<sup>4</sup>CONR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-,
- (h) CF<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>-,
- (i) R<sup>4</sup>CO(CH<sub>2</sub>)<sub>n</sub>-,
- (j) F(CH<sub>2</sub>)<sub>n</sub>-,
- (k) Cl(CH<sub>2</sub>)<sub>n</sub>-,
- 15 (l) R<sup>3</sup>O(CH<sub>2</sub>)<sub>n</sub>-,
- (m) R<sup>3</sup>S(CH<sub>2</sub>)<sub>n</sub>-,
- (n) R<sup>3</sup>SO(CH<sub>2</sub>)<sub>n</sub>-,
- (o) R<sup>3</sup>SO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-,
- (p) R<sup>3</sup>SO<sub>2</sub>NR<sup>5</sup>CH<sub>2</sub>)<sub>n</sub>-,
- 20 (q) O<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>-, or
- (r) R<sup>3</sup>R<sup>4</sup>C(NHR<sup>5</sup>)(CH<sub>2</sub>)<sub>n</sub>-;

wherein n is 0, 1, or 2;

wherein R<sup>4</sup> is

- (a) H,
- 25 (b) C<sub>1</sub>-C<sub>3</sub> alkyl, or
- (c) cyclopropyl.

Even more specifically, the present invention provides the compound of formula I wherein R<sup>2</sup> is

- (a) R<sup>3</sup>,
- 30 (b) NC(CH<sub>2</sub>)<sub>n</sub>-,
- (c) R<sup>3</sup>NHCO(CH<sub>2</sub>)<sub>n</sub>-,
- (d) R<sup>4</sup>CO(CH<sub>2</sub>)<sub>n</sub>-,
- (e) F(CH<sub>2</sub>)<sub>n</sub>-,

(g)  $\text{Cl}(\text{CH}_2)_n-$ ,

(h)  $\text{R}^3\text{O}(\text{CH}_2)_n-$ ,

(i)  $\text{R}^3\text{S}(\text{CH}_2)_n-$ ,

(j)  $\text{R}^3\text{NH}(\text{CH}_2)_n-$ , or

5 (k)  $\text{R}^4\text{CONH}(\text{CH}_2)_n-$ .

Even more specifically, the present invention provides the above compounds wherein Q is the moiety of formula II.

In another aspect, the subject invention is directed toward 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 as described above. The compound may be administered in a pharmaceutical composition either orally, parenterally, transdermally, 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. Some of the compounds of the present invention, especially the 1,3,4-thiadiazol-2-yl-containing compounds, are also surprisingly effective antibacterial agents against fastidious gram-negative bacteria/organisms. The activity of several compounds of the present invention against a gram-negative bacterial strain is given in Table 2.

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

The carbon atoms 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  $\text{C}_i\text{-C}_j$  indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example,  $\text{C}_1\text{-C}_3$  alkyl refers to alkyl of one to three carbon atoms, inclusive, or ethyl, ethyl, propyl, and isopropyl.

Examples of alkyl of one to nine carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and nonyl, and all isomeric forms thereof, straight and branched.

Examples of alkenyl of one to five carbon atoms, inclusive, are ethenyl, propenyl, butenyl, pentenyl, and all isomeric forms thereof.

## DETAILED DESCRIPTION OF THE INVENTION

The X<sup>1</sup> and X<sup>2</sup> groups may be independently either hydrogen atoms or the defined halogen atoms in a variety of substitution patterns. The X<sup>1</sup> and X<sup>2</sup> substituents are preferably one fluorine and one H.

5           The preferred absolute configuration at C-5 of the oxazolidinone ring of compounds claimed in this invention is as represented in the structure of Formula I. This configuration is called (*S*) under the Cahn-Ingold-Prelog nomenclature system. It is this (*S*)-enantiomer which is antibacterially active. The racemic mixture is useful in the same way and for the same purpose as the pure (*S*)-enantiomer; the difference is that twice as  
10 much racemic material must be used to produce the same antibacterial effect. It will be apparent to one skilled in the art that selected azolyl ring systems may have additional chiral centers present to give diastereomers. These diastereomers, in racemic and enantiomerically enriched forms, are also within the scope of the compounds of Formula I.

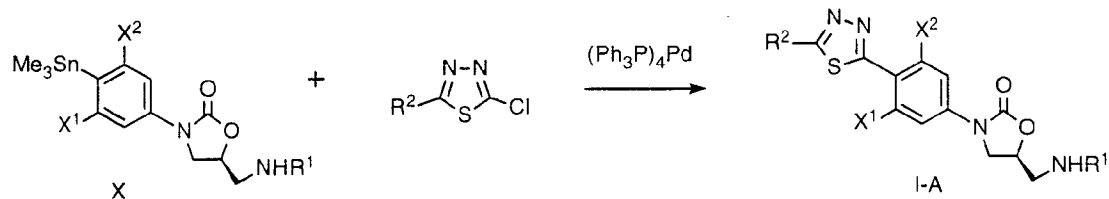
15           As is apparent to those of ordinary skill in the art, the compounds of the present invention can exist in several tautomeric forms, and all such tautomeric forms are included within the scope of the present invention. For instance, in the compound of Example 29 below, the 4,5-dihydro-5-oxo-1,3,4-thiadiazol-2-yl group, can exist as the 5-hydroxy-1,3,4-thiadiazol-2-yl group and both such tautomers are included within the  
20 scope of the present invention.

          Methods for preparing the oxazolidinones of Formula I are depicted in the following pages. It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative procedures are feasible and may be preferred in some cases.

25           1,3,4-Thiadiazoles (I-A) of the present invention (formula I wherein Q is moiety II) are made by the reaction of the trimethylstannylphenyl oxazolidinone, X, with 2-chloro-1,3,4-thiadiazoles as shown in Scheme I-A below. Oxazolidinone X is prepared as described in US Patent No. 5,565,571 (Preparation 19). The required 2-chloro-1,3,4-thiadiazoles are well known in the chemical literature and many methods exist for their  
30 preparation.

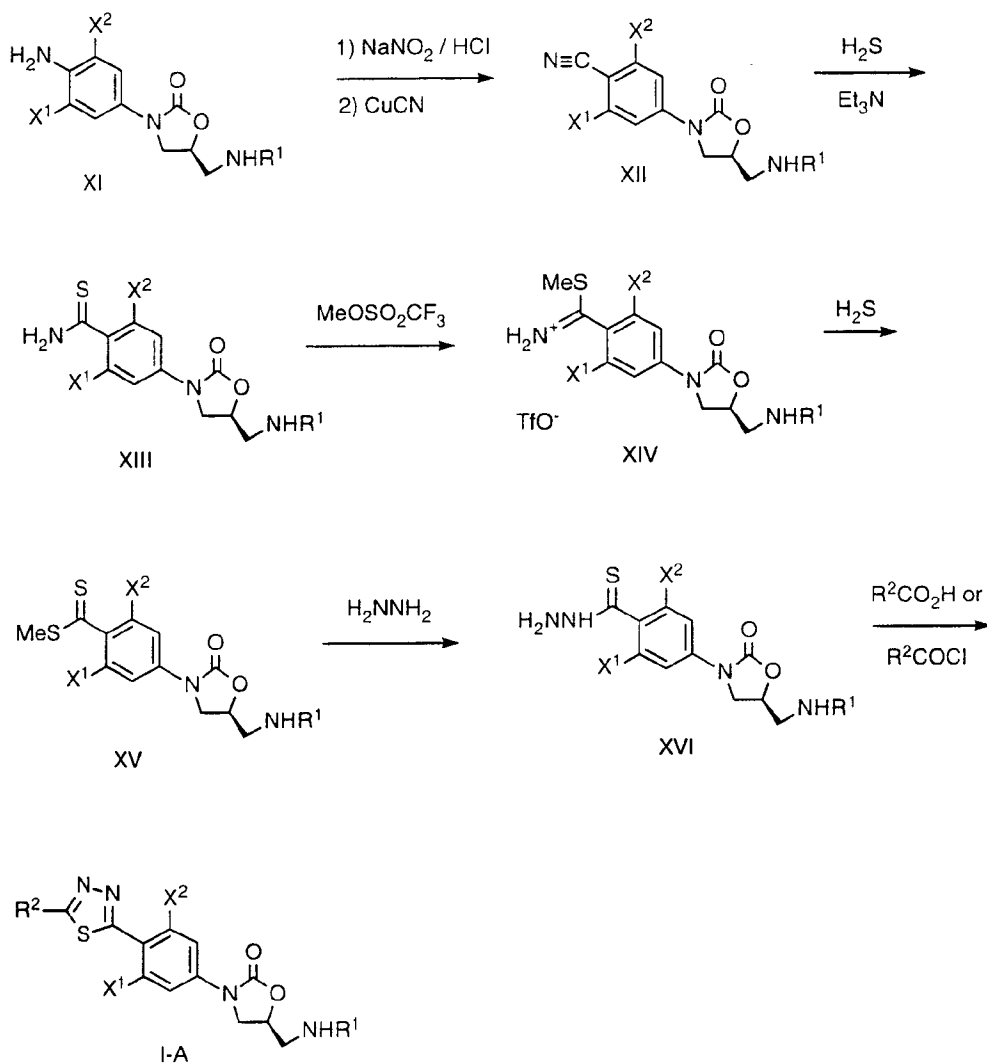


Scheme I-A



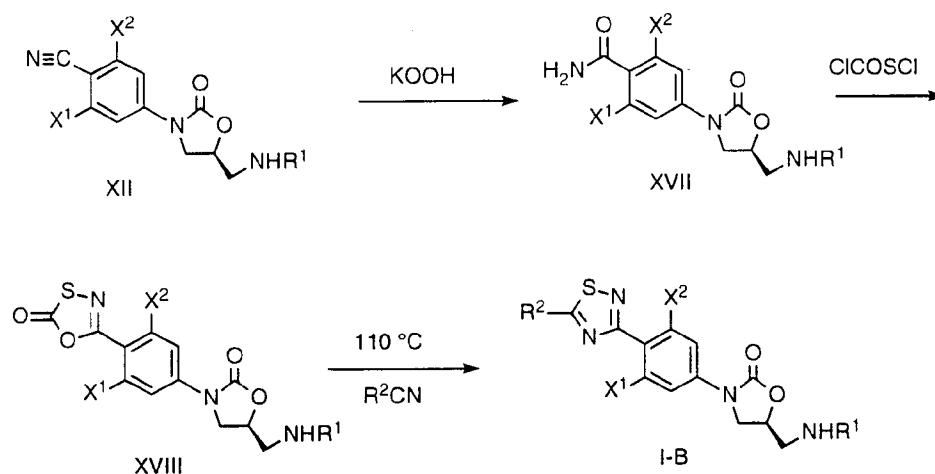
- 5 Alternatively, oxazolidinones I-A are preferably made by the sequence of steps shown in Scheme 1 below. Diazotization of aniline XI (prepared as described in International Publication No. WO 96/23788, published 8 August 1996, on page 33, lines 13-20) and reaction of the diazonium salt with cuprous cyanide gives the nitrile, XII. This nitrile is converted to the thioamide XIII by reaction with hydrogen sulfide.
- 10 Methylation of the thioamide is carried out by reaction with methyl triflate to produce the isothioamide XIV. Reaction of XIV with hydrogen sulfide gives the dithiobenzoate ester, XV. Addition of hydrazine to XV produces the thiobenzhydrazide XVI. Reaction of XVI with various carboxylic acids or acid chlorides affords the thiadiazoles I-A.

Scheme 1



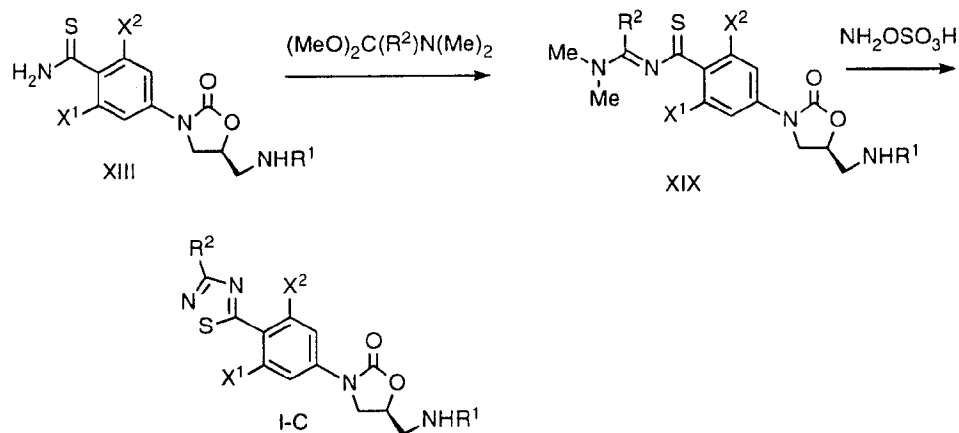
1,2,4-Thiadiazoles (I-B) of the present invention (formula I wherein Q is moiety III) are made by the reaction sequence shown in Scheme 2 below. Hydrolysis of the nitrile XII to the amide XVII is accomplished with potassium hydroperoxide. Reaction of XVII with chlorocarbonylsulfonylchloride produces the oxathiazolone, XVIII. Pyrolysis of XVIII in the presence of various nitriles leads to oxazolidinones I-B.

Scheme 2



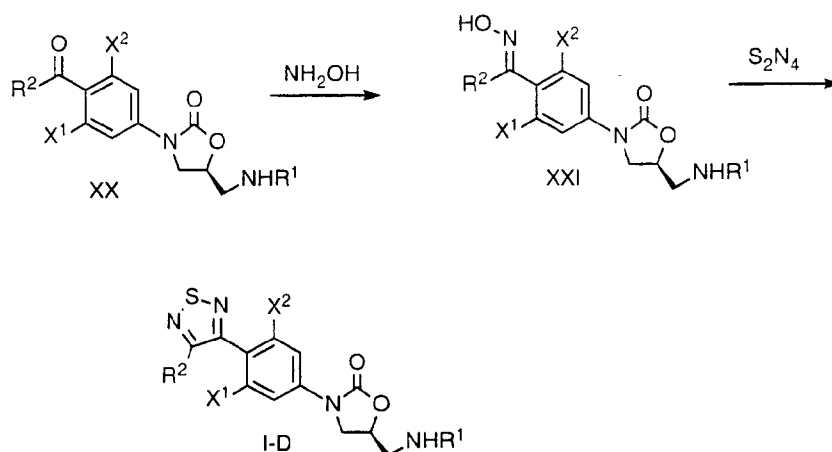
1,2,4-Thiadiazoles (I-C) of the present invention (formula I wherein Q is moiety IV) are made by procedures outlined by Y. Lin (*J. Org. Chem.* 1980, 45, 3750-3753) as shown in 5 Scheme 3 below. Thus, reaction of the thiobenzamide XIII with a dimethoxyalkylamine leads to the amidine, XIX. Treatment of this amidine with hydroxylamine sulfonic acid produces the oxazolidinone I-C.

Scheme 3



10 1,2,5-Thiadiazoles (I-D) of the present invention (formula I wherein Q is moiety V) are made by procedures outlined by J. Cho (*J. Chem. Soc. Perkin Trans. I*, 1993, 2345-2350). As shown in Scheme 4 below, reaction of the appropriate aryl ketone XX with hydroxylamine gives the oxime XXI. Treatment of XXI with S<sub>2</sub>N<sub>4</sub> produces oxazolidinone I-D. The required ketones are prepared by procedures disclosed by C-H. 15 Park (*J. Med. Chem.* 1992, 35, 1156-1165).

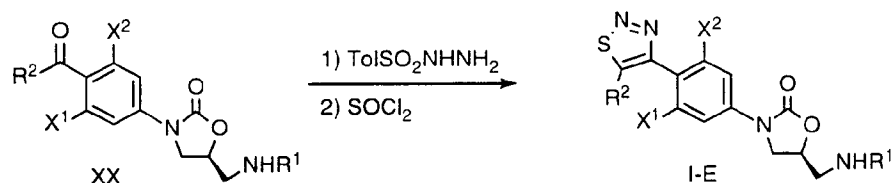
Scheme 4



1,2,3-Thiadiazoles (I-E) of the present invention (formula I wherein Q is moiety VI) are made from the appropriate ketone XX by procedures outlined by E. Thomas (*J. Med.*

5 *Chem.* 1985, 28, 2345-2350) and shown below in Scheme 5.

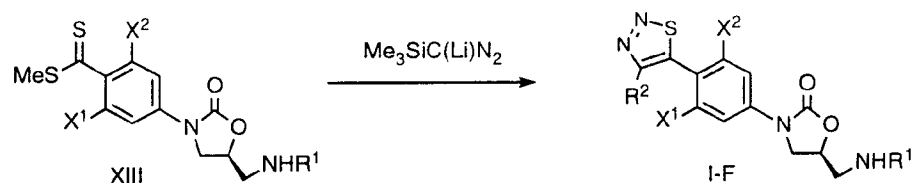
Scheme 5



1,2,3-Thiadiazoles (I-F) of the present invention (formula I wherein Q is moiety VII) are made from the dithiobenzoate XIII according to the method of T. Aoyama (*Heterocycles*,

10 1986, 24, 589-592), as shown in Scheme 6 below.

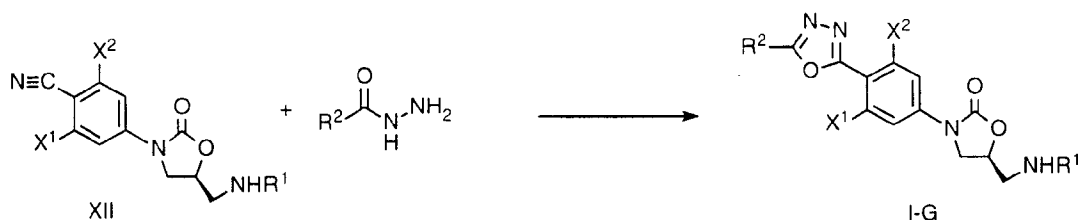
Scheme 6



1,3,4-oxadiazoles (I-G) of the present invention (formula I wherein Q is moiety VIII) are made from the nitrile XII using the appropriate acylhydrazide, following the procedures

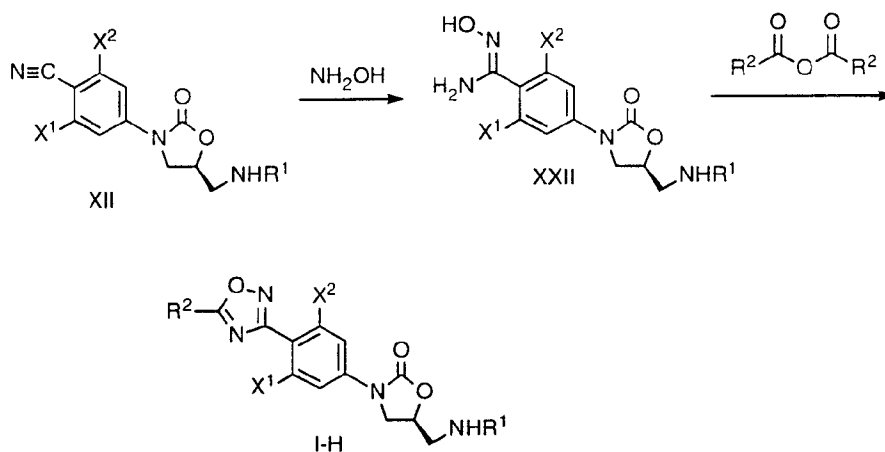
15 reported by R. L. Harris (*Aust.J.Chem.* 1977, 30, 2225-2240) as shown below in Scheme 7.

Scheme 7

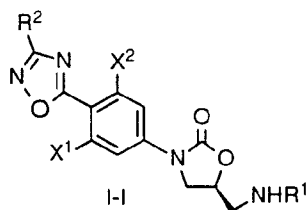


1,2,4-Oxadiazoles (I-H) of the present invention (formula I wherein Q is moiety IX) are made from the nitrile XII by conversion to the hydroxyamidine XXII and then cyclization with the appropriate anhydride, as shown in Scheme 8 below.

Scheme 8



The 1,2,4-Oxadiazoles (I-I) of the present invention (formula I wherein Q is moiety IX-A) are made as additional products from the reaction shown in Scheme 3.



The preparation of oxazolidinones having a thiocarbonyl functionality is disclosed in US Patent Application, Serial No. 60/048,342, filed 30 May 1997, which is hereby incorporated by reference herein.

The compounds of Formula I are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral, topical, transdermal, and oral administration.

The pharmaceutical compositions of this invention are 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 and 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, parenterally, transdermally, or topically 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. The therapeutic uses of these compounds include their use in treating ocular infections and other ophthalmic uses. 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  
5 for administration, e.g., two to four times per day.

The compounds of Formula I according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to  
10 Formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3-7. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few  
15 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  
20 I according to this invention, due to their aqueous solubility, are advantageously administered orally in solid and liquid dosage forms.

The oxazolidinone antibacterial agents of this invention have useful activity against a variety of microorganisms. The *in vitro* activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum  
25 inhibitory concentration (MIC) by agar dilution as described in "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically" (MFT) published Jan. 1983 by the National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The activity of selected compounds of this invention against *Staphylococcus aureus* and *Streptococcus*  
30 *pneumoniae* are shown in Table 1.

The following compounds of the present invention are preferred:

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

2. (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-carboxamide;
3. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
- 5 4. (S)-N-[[3-[4-(5-Ethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
5. (S)-N-[[3-[3-Fluoro-4-(5-propyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
6. (S)-N-[[3-[4-[5-(Aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
- 10 7. (S)-N-[[3-[3-Fluoro-4-[5-[[[(methylsulfonyl)amino]methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
8. (S)-N-[[3-[3-Fluoro-4-(5-fluoromethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
- 15 9. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
10. (S)-N-[[3-[4-(5-Acetoxyethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
11. (S)-N-[[3-[3-Fluoro-4-(5-hydroxymethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
- 20 12. (S)-N-[[3-[3-Fluoro-4-[5-(methoxymethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
13. (S)-N-[[3-[4-[5-(Cyanomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
- 25 14. (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetamide;
15. (S)-N-[[3-[3-Fluoro-4-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
16. (S)-N-[[3-[3-Fluoro-4-[5-(3-oxobutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;
- 30 17. (5S)-N-[[3-[3-Fluoro-4-[5-(3-hydroxybutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide;



18. (S)-Methyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-propanoate;
19. (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-propanamide;
- 5 20. (S)-N-[[3-[4-[5-(2-Cyanoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
21. (S)-N-[[3-[3-Fluoro-4-[5-[(methylthio)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
22. (S)-N-[[3-[3-Fluoro-4-[5-[(methylsulfinyl)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 23. (S)-N-[[3-[3-Fluoro-4-[5-[2-(methylthio)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
24. (S)-N-[[3-[3-Fluoro-4-[5-[2-(methylsulfinyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 25. (S)-Ethyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetate;
26. (S)-N-[[3-[3-Fluoro-4-[5-(2-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
27. (S)-Ethyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-carboxylate;
- 20 28. (5S)-N-[[3-[3-Fluoro-4-[5-(2-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
29. (S)-N-[[3-[4-(4,5-Dihydro-5-oxo-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 30. (S)-N-[[3-[4-(5-Amino-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
31. (S)-N-[[3-[3-Fluoro-4-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
32. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
- 30 33. (S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,2,4-thiadiazole-5-carboxamide;

34. (S)-N-[[3-[3-Fluoro-4-(1,2,4-thiadiazol-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
35. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 5 36. (S)-N-[[3-[3-Fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
37. (S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,2,4-oxadiazole-5-carboxamide;
38. (S)-N-[[3-[4-(5-Cyano-1,2,4-oxadiazol-3-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 39. (S)-N-[[3-[3-Fluoro-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
40. (S)-N-[[3-[3-Fluoro-4-(1,2,4-oxadiazol-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 41. (S)-N-[[3-[3-Fluoro-4-[5-(formylamino)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
42. (S)-N-[[3-[4-[5-(2-Chloroethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
43. (S)-N-[[3-[3-Fluoro-4-[5-(1-propenyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 44. (S)-N-[[3-[4-[5-(2-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
45. (S)-N-[[3-[4-[5-[2-(Acetylamino)ethyl]-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 46. (S)-N-[[3-[3-Fluoro-4-[5-[2-[(methylsulfonyl)amino]ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
47. (5S)-N-[[3-[3-Fluoro-4-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
48. (S)-N-[[3-[3-Fluoro-4-[5-(1-methylethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 30 49. (S)-N-[[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide;

50. (S)-N-[[3-[3-Fluoro-4-[5-(3-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
51. [S-(R\*,R\*)]-N-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 5 52. [S-(R\*,S\*)]-N-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
53. (S)-N-[[3-[3-Fluoro-4-[5-(2-nitroethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
54. (S)-N-[[3-[3-Fluoro-4-[5-(3-nitropropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 55. [S-(R\*,R\*)]-N-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
56. [S-(R\*,S\*)]-N-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 57. (S)-N-[[3-[4-[5-(3-Aminopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
58. (S)-N-[3-[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]propyl]acetamide;
59. (S)-N-[[3-[4-[5-(5-Acetyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 60. (S)-N-[[3-[4-[5-(3-Chloropropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
61. (S)-N-[[3-[4-[5-(3-Cyanopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 62. (S)-N-[[3-[3-Fluoro-4-[5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
63. (S)-N-[[3-[3-Fluoro-4-[5-[3-(hydroxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
64. (S)-N-[[3-[3-Fluoro-4-[5-[2-(hydroxyimino)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 30 65. (S)-N-[[3-[3-Fluoro-4-[5-[3-(methoxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

66. (S)-N-[[5-[4-[5-[(Acetyloxyacetyl amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide;
67. (S)-N-[[5-[4-[5-[(Hydroxyacetyl amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide;
- 5 68. (S)-N-[5-[4-[5-[(Acetyl amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]-2-(acetyloxy)acetamide;
69. (S)-N-[[3-[3-Fluoro-4-[5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
70. (S)-N-[[3-[3-Fluoro-4-[5-[2-(methylsulfonyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 71. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
72. (S)-N-[[3-[3-Fluoro-4-[5-(2-methoxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
- 15 73. (S)-N-[[3-[3-Fluoro-4-[5-(2-methoxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
74. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide;
75. (S)-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;
- 20 76. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanethioamide;
77. N-(((5S)-3-{4-[5-(aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)ethanethioamide;
- 25 78. 2-({[5-(4-((5S)-5-[(ethanethioyl amino)methyl]-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl}amino)-2-oxoethyl acetate; and
79. N-{[5-(4-((5S)-5-[(ethanethioyl amino)methyl]-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl}-2-hydroxyacetamide.
- The following compounds of the present invention are most preferred:
- 30 1. (S)-N-[[3-[4-(5-Cyano-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
2. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

3. (S)-N-[[3-[4-(5-Ethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
4. (S)-N-[[3-[4-[5-(Aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 5 5. (S)-N-[[3-[3-Fluoro-4-[5-[(methylsulfonyl)amino]methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
6. (S)-N-[[3-[3-Fluoro-4-(5-fluoromethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
7. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 8. (S)-N-[[3-[4-(5-Acetoxymethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
9. (S)-N-[[3-[3-Fluoro-4-(5-hydroxymethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 10. (S)-N-[[3-[4-[5-(Cyanomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
11. (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetamide;
12. (S)-N-[[3-[3-Fluoro-4-[5-(3-oxobutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 13. (S)-N-[[3-[4-[5-(2-Cyanoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
14. (S)-N-[[3-[3-Fluoro-4-[5-[2-(methylsulfinyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 15. (S)-N-[[3-[3-Fluoro-4-[5-(2-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
16. (S)-N-[[3-[4-(4,5-Dihydro-5-oxo-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
17. (S)-N-[[3-[3-Fluoro-4-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 30 18. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;

19. (5*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
20. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 5 21. [*S*-(*R*\*.*R*\*)]-*N*-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
22. [*S*-(*R*\*.*S*\*)]-*N*-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
23. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-nitroethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 24. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-nitropropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
25. [*S*-(*R*\*.*R*\*)]-*N*-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 26. [*S*-(*R*\*.*S*\*)]-*N*-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
27. (*S*)-*N*-[[3-[4-[5-(3-Cyanopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
28. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[3-(hydroxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 29. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(hydroxyimino)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
30. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylsulfonyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 31. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
32. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide;
33. (*S*)-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;
- 30 34. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanethioamide;

35. *N*-[[(*5S*)-3-{4-[5-(aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]ethanethioamide;
36. 2-([5-(4-[(*5S*)-5-[(ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl)amino)-2-oxoethyl acetate; or
- 5 37. *N*-{[5-(4-[(*5S*)-5-[(ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl)-1,3,4-thiadiazol-2-yl)methyl]-2-hydroxyacetamide.

Table 1.

*In Vitro* Activity of Examples Against Selected Gram-Positive Bacteria

Example No.	MIC ( $\mu\text{g/mL}$ )	
	<i>S. Aureus</i> UC <sup>®</sup> 9213	<i>S. pneumoniae</i> UC <sup>®</sup> 9912
1	0.5	<0.125
2	0.5	0.25
3	1	<0.125
4	1	0.25
5	1	0.25
6	8	<0.125
7	4	<0.125
8	1	0.25
9	1	0.25
10	1	<0.125
11	1	<0.125
12	2	0.25
13	2	0.25
14	4	<0.125
15	2	0.5
16	1	<0.125
17	2	0.25
18	2	0.25
19	8	<0.125
20	0.5	<0.125
21	1	0.25

Example No.	MIC ( $\mu\text{g/mL}$ )	
	<i>S. Aureus</i> UC <sup>b</sup> 9213	<i>S. pneumoniae</i> UC <sup>b</sup> 9912
22	8	0.25
23	1	0.25
24	4	0.25
25	2	0.25
26	2	<0.125
27	8	<0.125
28	2	0.25
29	1	0.25
30	4	0.25
31	0.5	<0.125
32	1	<0.125
33	16	2
34	1	0.25
35	16	4
36	4	1
37	>16	1
38	>16	2
39	16	8
40	2	0.5
41	4	0.5
42	1	<0.125
43	2	0.5
44	>16	0.25
45	16	0.5
46	16	0.5
47	2	0.25
48	1	0.25
49	16	0.25
50	2	0.25
51	2	0.25



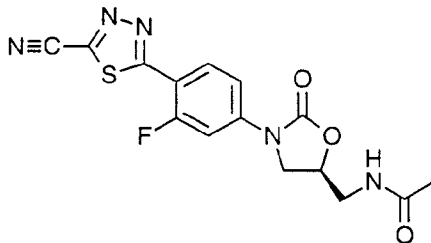
Example No.	MIC ( $\mu\text{g/mL}$ )	
	<i>S. Aureus</i> UC <sup>o</sup> 9213	<i>S. pneumoniae</i> UC <sup>o</sup> 9912
52	2	0.25
53	1	0.25
54	2	0.25
55	8	<0.125
56	4	<0.125
57	16	0.5
58	8	0.25
59	2	0.5
60	2	0.5
61	1	<0.125
62	2	0.5
63	2	<0.125
64	1	<0.125
65	8	2
66	16	<0.5
67	16	<0.5
68	8	2
69	4	<0.5
70	4	<0.5
71	1	0.25
72	4	0.25
73	2	<0.5
74	0.25	<0.125
75	0.25	<0.125
76	0.25	<0.125
77	<0.5	<0.5
78	2	<0.5

Table 2.  
MIC Data for a Gram Negative Bacterial Strain

Example No.	MIC (µg/mL) for HI 30063
1	2
3	2
4	4
6	2
7	2
8	4
9	4
10	4
11	4
13	4
14	4
16	4
20	2
24	4
26	2
29	4
31	4
32	4
47	4
50	4
51	4
52	4
53	4
54	4
55	4
56	4
61	4
63	4
64	2
70	4
71	4
74	1
75	1
76	1
77	<0.5
78	4

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1. (S)-N-[[3-[4-(5-Cyano-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CN). Refer to Scheme 1-A.



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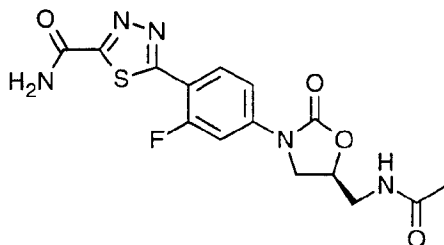
A mixture of the oxazolidinone X, prepared as described in US 5,565,571 (Preparation 19) (208.1 mg), 2-chloro-5-cyano-1,3,4-thiadiazole (72.9 mg), tris(dibenzylideneacetone)dipalladium(0) (9.1 mg) and triphenylarsine (12.2 mg) in 1-methyl-2-pyrrolidinone (3 mL) is evacuated and flushed with N<sub>2</sub> three times. The dark reaction mixture is stirred under N<sub>2</sub> for 6 days. The reaction mixture is partitioned between water (20 mL) and ethyl acetate (30 mL) and the phases are separated. The aqueous phase is extracted with ethyl acetate (2 x 25 mL). The combined organics are washed with water (20 mL), brine (20 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The dark residue is purified by flash chromatography using 5% methanol in ethyl acetate as the eluent to afford 25.2 mg of the desired thiadiazole.

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Physical characteristics are as follows: mp 210-211 °C. <sup>1</sup>H NMR (DMSO) δ 8.39, 8.24, 7.78, 7.60, 4.78, 4.19, 3.81, 3.43, 1.81; Anal. Found: C, 48.67; H, 3.57; N, 18.86; S, 8.33.

20

Example 2. (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-carboxamide (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H<sub>2</sub>NCO). Refer to Scheme 1.

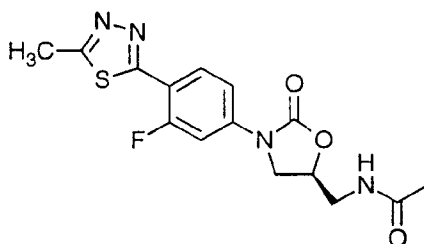


A solution of the title compound of Example 1 (58.6 mg) in 10:1 H<sub>2</sub>SO<sub>4</sub> / H<sub>2</sub>O (1 mL) is heated at 40 °C for 3.5 h. The cooled reaction mixture is treated with ice (15 mL)

and the mixture is adjusted to pH 7 with 50 % NaOH, resulting in formation of a solid precipitate. The reaction mixture is concentrated. The resulting solid is dissolved in methanol/chloroform, absorbed onto silica gel, and purified on 20 g of silica gel using 8% methanol in dichloromethane as the eluent to afford 37.1 mg of the title product as a tan solid.

Physical characteristics are as follows: mp 243-244 °C (dec). <sup>1</sup>H NMR (DMSO) δ 8.62, 8.32, 8.25, 8.18, 7.76, 7.59, 4.76, 4.18, 3.80, 3.42, 1.81.

Example 3. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>). Refer to Scheme 1.



Step 1. The aniline XI, prepared as described in International Publication No. WO 96/23788, published 8 August 1996 (5.2 g) is dissolved in 2 N HCl (23 mL) and cooled to 0 °C. Sodium nitrite (2.0 g) in water (12 mL) is added and the resulting yellow solution is stirred at 0 °C for 30 min. Solid sodium bicarbonate is carefully added until the solution reaches pH 7. In a separate flask, copper (I) cyanide (2.3 g) and potassium cyanide (1.9 g) are suspended in water (19 mL) and ethyl acetate (38 mL) at 0 °C. The neutralized diazonium salt is added to this solution via cannula over 35 min. The resulting mixture is stirred at 0 °C for 30 min (during which time the mixture becomes very dark in color) then at room temperature for 1 h. The dark heterogeneous reaction mixture is filtered through a pad of celite to remove copper salts. The filter cake is washed with ethyl acetate (2 x 50 mL) and water (1 x 50 mL). The phases of the filtrate are separated. The aqueous layer is extracted with ethyl acetate (100 mL). The combined organics are dried (MgSO<sub>4</sub>), filtered and concentrated. The orange residue is dissolved in 30% acetone in dichloromethane and filtered through a short column of silica gel using 30 % acetone in dichloromethane as the eluent. The filtrate is concentrated to afford 3.4 g of desired nitrile XII as a yellow solid.

Physical characteristics are as follows: mp 173-174 °C. <sup>1</sup>H NMR (DMSO) δ 8.22, 7.92, 7.74, 7.52, 4.76, 4.14, 3.76, 3.40, 1.80; Anal. Found: C, 56.16; H, 4.34; N, 14.83.

Step 2. To a stirred solution of the nitrile XII (prepared in Step 1, 3.06 g) in 30 mL of DMF is added triethylamine (3.8 mL) at room temperature. The reaction is heated to 100 °C and H<sub>2</sub>S is bubbled into the flask for 1 h. The reaction is then cooled to 60 °C over 30 min. A portion of the DMF (15 mL) is removed via bulb to bulb distillation. The reaction mixture is then poured onto 100 mL of ice and stirred until the ice melts. The mixture is filtered and the orange solid is dried overnight in a vacuum oven to afford 2.9 g of the thioamide XIII. An analytical sample of the thioamide is prepared by chromatography through a Biotage 40S column (1 % MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

Physical characteristics are as follows: mp 116-119 °C ; <sup>1</sup>H NMR (DMSO) δ 10.1, 9.4, 8.23, 7.12, 7.46, 7.29, 4.7, 4.12, 3.73, 3.4045, 1.81. Anal. Found: C, 50.54; H, 4.70; N, 13.04; S, 9.60.

Step 3. To a stirred solution of the thioamide XIII (prepared in step 2, 1.05 g) in 1:1 THF/CH<sub>2</sub>Cl<sub>2</sub> (37 mL) under N<sub>2</sub> is added methyl triflate (0.49 mL). The resulting orange solution is stirred at room temperature for 1 h, then pyridine (0.82 mL) is added. Hydrogen sulfide is bubbled through the reaction mixture for 1 h. The hydrogen sulfide is replaced with N<sub>2</sub> and nitrogen is bubbled through the reaction mixture for 30 min. The orange solution is concentrated. The resulting orange residue is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica, and purified using a Biotage 40 M column with a SIM using 2.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 640.2 mg of the methyl dithiobenzoate XV as an orange foam which is used immediately in the next reaction without further purification.

Physical characteristics are as follows: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.68, 7.47, 7.13, 6.81, 4.80, 4.04, 3.79, 3.64, 2.73, 2.00.

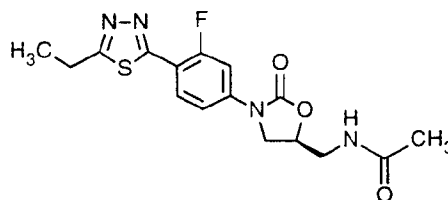
Step 4. To a stirred solution of the dithiobenzoate XV (prepared in step 3, 640.2 mg) in ethanol (18 mL) is added hydrazine monohydrate (0.33 mL). (The orange color of the dithiobenzoate dissipates within 5 min after addition of hydrazine). The reaction mixture is stirred at room temperature for 25 min, then concentrated. The yellow residue is dissolved in methanol/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica, and purified on a Biotage 40S column using a SIM and 7% methanol in dichloromethane as the eluent to afford 369.0 mg (60%) of the desired thiohydrazide XVI.

Physical characteristics are as follows: mp 207-208 °C (bubbles). <sup>1</sup>H NMR (DMSO) δ 12.4, 8.23, 7.54, 7.48, 7.29, 6.25, 4.73, 4.11, 3.72, 3.40, 1.81.

Step 5. To a stirred suspension of the thiohydrazide XVI (prepared as described in step 4, 200.0 mg) in dry THF (4 mL) is added acetyl chloride (52 μL). The reaction mixture is heated at reflux for 30 min, cooled and concentrated. The yellow solid is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica, and purified by flash chromatography using 7% methanol in dichloromethane as the eluent to afford 156.7 mg of the desired thiadiazole 1-A as an off-white solid.

Physical characteristics are as follows: mp 240-242 °C. <sup>1</sup>H NMR (DMSO) δ 8.22, 7.72, 7.53, 4.76, 4.16, 3.78, 3.42, 2.77, 1.81; Anal. Found: C, 51.30; H, 4.17; N, 15.97.

Example 4. (*S*)-*N*-[[3-[4-(5-Ethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CH<sub>2</sub>). Refer to Scheme 1.



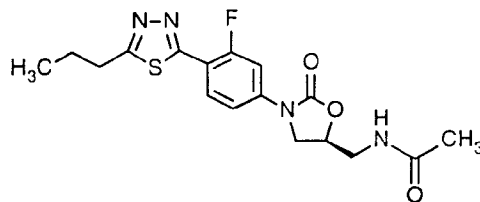
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The thiohydrazide XVI from Step 4 of Example 3 (200 mg) is reacted with propionyl chloride (107 μL) according to the procedure of Step 5 of Example 3 to afford 261 mg of the title compound.

Physical characteristics are as follows: mp 221-223 °C. <sup>1</sup>H-NMR (DMSO) δ 8.23, 7.70, 7.53, 4.76, 4.17, 3.80, 3.42, 3.15, 1.82, 1.35. Anal. Found: C, 52.69; H, 4.59; N, 15.39.

Example 5. (*S*)-*N*-[[3-[3-Fluoro-4-(5-propyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.

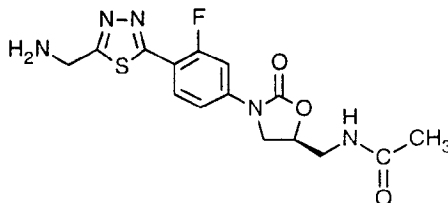
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The thiohydrazide XVI from Step 4 of Example 3 (300 mg) is reacted with butyryl chloride (190  $\mu$ L) according to the procedure of Step 5 of Example 3 to afford 205 mg of the title compound.

Physical characteristics are as follows: mp 210-212  $^{\circ}$ C.  $^1$ H-NMR (DMSO)  $\delta$  8.24, 7.70, 7.53, 4.76, 4.17, 3.80, 3.42, 3.09, 1.82, 1.79, 0.96. Anal. Found: C, 53.57; H, 5.02; N, 14.69.

Example 6. (*S*)-*N*-[[3-[4-[5-(Aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A,  $X^1 = H$ ,  $X^2 = F$ .  $R^1 = CH_3CO$ ,  $R^2 = NH_2CH_2$ ). Refer to Scheme 1.



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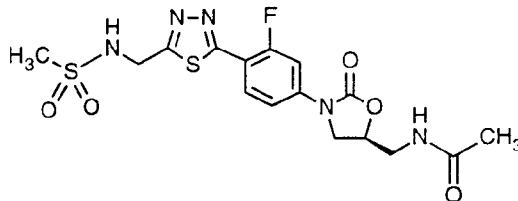
Step 1. The thiohydrazide XVI from Step 4 of Example 3 (532 mg) is reacted with Fmoc glycyl chloride (669 mg) according to the procedure of Step 5 of Example 3 to afford 631 mg of the Fmoc protected form of the title compound.

Step 2. The product from step 1 is stirred in 5 mL of piperidine at room temperature for 1 h. The desired product is collected by filtration. The mother liquor is absorbed onto silica gel and chromatographed using 2% MeOH (saturated with  $NH_3$ ) in  $CH_2Cl_2$  as eluent to afford 178 mg of the title compound.

Physical characteristics are as follows: mp 216-217  $^{\circ}$ C.  $^1$ H-NMR (DMSO)  $\delta$  8.22, 7.70, 7.52, 4.76, 4.17, 4.13, 3.80, 3.42, 1.82. %  $H_2O$ : 3.65. Anal. Found: C, 46.09; H, 4.45; N, 17.01.

20

Example 7. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[[[(methylsulfonyl)amino]methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A,  $X^1 = H$ ,  $X^2 = F$ ,  $R^1 = CH_3CO$ ,  $R^2 = CH_3SO_2NHCH_2$ ). Refer to Scheme 1.



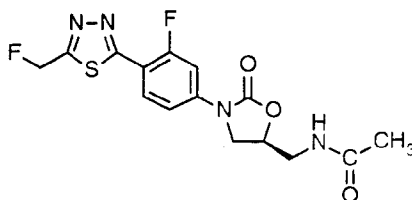
To a suspension of the amine prepared in Example 6 (300 mg) in  $CH_2Cl_2$  (10 mL) is added triethylamine (459  $\mu$ L) and methanesulfonyl chloride (127  $\mu$ L). The reaction is

25

heated to 100 °C for 2 h. The reaction mixture is then cooled to room temperature and concentrated. The residue is absorbed onto silica gel and chromatographed using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 161 mg of the title compound.

Physical characteristics are as follows: mp 160 °C. <sup>1</sup>H-NMR (DMSO) δ 8.22, 7.70, 7.52, 4.77, 4.17, 4.13, 3.81, 3.42, 3.29, 1.82. % H<sub>2</sub>O: 3.08. Anal. Found: C, 46.12; H, 4.47; N, 17.06.

Example 8. (S)-N-[[3-[3-Fluoro-4-(5-fluoromethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup>=FCH<sub>2</sub>). Refer to Scheme 1.



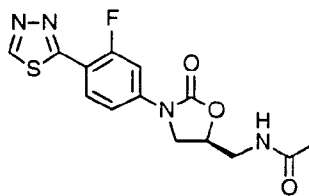
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Prepared from the thiohydrazide XVI according to the procedure of Step 5 of Example 3, substituting fluoroacetyl chloride for acetyl chloride. Purified by flash chromatography using 5% methanol in dichloromethane to give 107.0 mg of the desired fluoromethyl thiadiazole as a white solid.

Physical characteristics are as follows: mp 222-223 °C. <sup>1</sup>H NMR (DMSO) δ 8.30, 8.27, 7.76, 7.57, 6.01, 5.85, 4.77, 4.18, 3.80, 3.42, 1.81; Anal. Found: C, 48.64; H, 3.90; N, 15.09.

Example 9. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H). Refer to Scheme 1.

20



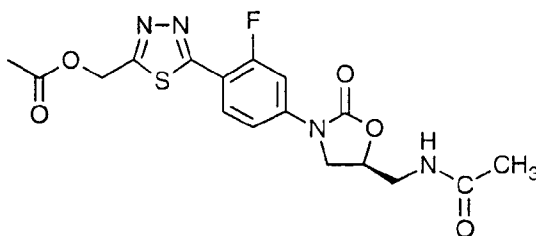
A mixture of thiohydrazide XVI from Step 4 of Example 3 (195 mg) and formic acid (2 mL) is heated at reflux for 45 min. The cooled reaction mixture is concentrated. The resulting residue is dissolved in methanol, absorbed onto silica gel and purified by flash chromatography using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to afford 134 mg of the title compound.

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Physical characteristics are as follows: mp 234-235 °C. <sup>1</sup>H-NMR (DMSO) δ 9.75, 8.27, 7.75, 7.55, 4.77, 4.17, 3.79, 3.42, 1.81. Anal. Found: C, 49.87; H, 3.79; N, 16.64; S, 9.43.

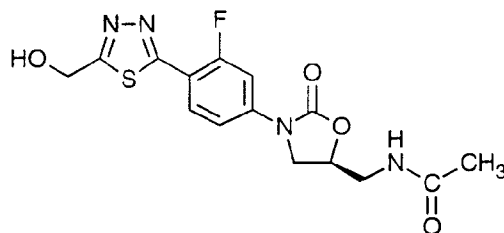
5 Example 10. (*S*)-*N*-[[3-[4-(5-Acetoxyethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.



10 Prepared from the thiohydrazide XVI according to the procedure of Step 5 of Example 3, substituting acetoxyacetyl chloride for acetyl chloride. Purified by flash chromatography using 5% methanol in dichloromethane as the eluent to afford 374.1 mg of the title thiadiazole as an off-white solid.

Physical characteristics are as follows: mp 181-182 °C. <sup>1</sup>H NMR (DMSO) δ 8.27, 7.75, 7.55, 5.53, 4.76, 4.17, 3.76, 3.42, 2.11, 1.81.

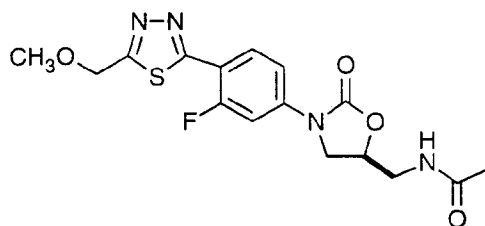
15 Example 11. (*S*)-*N*-[[3-[3-Fluoro-4-(5-hydroxymethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = HOCH<sub>2</sub>). Refer to Scheme 1.



20 Potassium carbonate (60.6 mg) is added to a stirred suspension of the title compound of Example 10 (128.0 mg) in methanol (3 mL). The heterogeneous reaction mixture is stirred at room temperature for 15 min. Dichloromethane (3 mL) is added and the homogenous reaction mixture is filtered through a plug of cotton to remove the solids. The filtrate is absorbed onto silica gel and purified by flash chromatography using 10% methanol in dichloromethane as the eluent to afford 93.6 mg of the desired hydroxymethyl thiadiazole as a white solid.

Physical characteristics as follows: mp 212-214 °C. <sup>1</sup>H NMR (DMSO) δ 8.24, 7.73, 7.54, 6.25, 4.90, 4.77, 4.17, 3.81, 3.42, 1.81; Anal. Found: C, 49.00; H, 4.20; N, 15.23; S, 8.55.

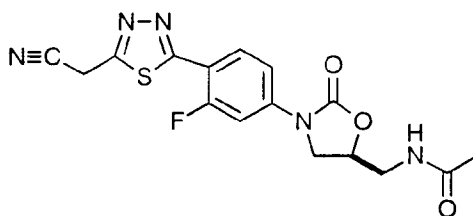
5 Example 12. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methoxymethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>OCH<sub>2</sub>). Refer to Scheme 1.



10 The thiohydrazide XVI from Step 4 of Example 3 (343 mg) is reacted with methoxyacetyl chloride (228 mg) according to the procedure of Step 5. Example 3 to afford 339 mg of the title compound.

Physical characteristics are as follows: mp 198-199 °C. <sup>1</sup>H-NMR (DMSO) δ 8.26, 7.73, 7.55, 4.90, 4.77, 4.17, 3.79, 3.42, 3.40, 1.81. % Water (KF) = 0.13. Anal. Found: C, 49.40; H, 4.44; N, 14.39; S, 8.24.

15 Example 13. (*S*)-*N*-[[3-[4-[5-(Cyanomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = NCCH<sub>2</sub>). Refer to Scheme 1.

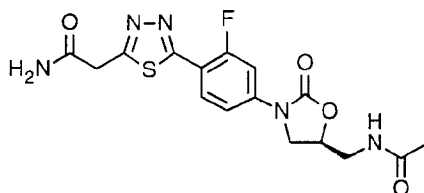


20 Step 1. To a stirred solution of cyanoacetic acid (10.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) is added oxalyl chloride (11.0 mmol) followed by 2 drops of DMF. The reaction mixture is stirred at RT for 1- 18 h, then concentrated. The cyanoacetyl chloride is isolated by distillation.

Step 2. The thiohydrazide XVI of Step 4 of Example 3 (216 mg) is reacted with cyanoacetyl chloride (82 mg) according to the procedure of Step 5 of Example 3 to afford 164 mg of the title compound.

Physical characteristics are as follows: mp 250-251 °C . <sup>1</sup>H-NMR (DMSO) δ 8.26, 7.76, 7.56, 4.75, 4.17, 3.79, 3.42, 1.81. % Water (KF) = 0.65. Anal. Found: C, 50.03; H, 3.91; N, 17.98; S, 8.33.

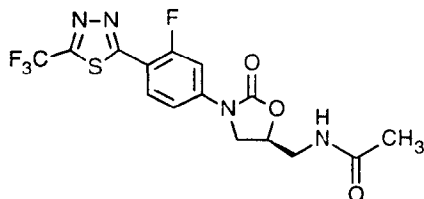
5 Example 14. (*S*)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H<sub>2</sub>NCOCH<sub>2</sub>). Refer to Scheme 1.



10 A solution of the nitrile of Example 13 (378 mg) in 7 mL of 10:1 H<sub>2</sub>SO<sub>4</sub>/H<sub>2</sub>O is heated at 40 °C for 3h. The cooled reaction mixture is poured onto 20 mL of ice and the pH is adjusted to 7 with 50% NaOH. A tan precipitate forms. The solid is isolated by filtration, washing with H<sub>2</sub>O and drying. The solid is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 227 mg of the title compound.

15 Physical characteristics are as follows: mp 248-249 °C. <sup>1</sup>H-NMR (DMSO) δ 8.24, 7.81, 7.72, 7.53, 7.31, 4.76, 4.17, 4.09, 3.80, 3.42, 1.81; % Water (KF) = 1.02; Anal. Found: C, 48.35; H, 4.17, N, 17.01, S, 7.80.

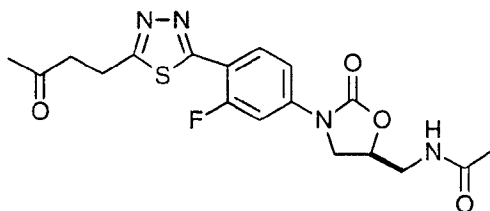
20 Example 15. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CF<sub>3</sub>). Refer to Scheme 1.



25 The thiohydrazide XVI from Step 4 of Example 3 (300 mg) is refluxed in neat trifluoroacetic acid (3 mL) for 8 h and then stirred overnight at rt. The reaction mixture is then concentrated in vacuo. The residue is triturated with CH<sub>3</sub>CN to afford 156 mg of the title compound.

Physical characteristics are as follows: mp 237-239 °C. <sup>1</sup>H-NMR (DMSO) δ 8.38, 8.26, 7.78, 7.61, 4.78, 4.19, 3.81, 3.43, 1.82. Anal. Found: C, 44.97; H, 3.12; N, 13.90.

5 Example 16. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-oxobutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>COCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.

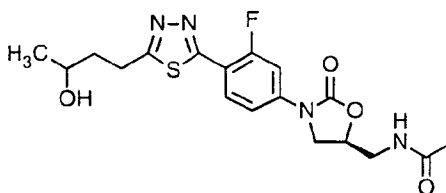


Step 1. Levulinyl chloride is prepared from levulinic acid and oxalyl chloride following the procedure of Step 1, Example 13.

10 Step 2. The thiohydrazide XVI of Step 4 of Example 3 (328 mg) is reacted with levulinyl chloride (268 mg) according to the procedure of Step 5, Example 3 to afford 323 mg of the title compound.

Physical characteristics are as follows: mp 209-210 °C. <sup>1</sup>H-NMR (DMSO) δ 8.23, 7.68, 7.52, 4.76, 4.16, 3.78, 3.42, 3.28, 3.03, 2.13, 1.81. Anal. Found: C, 52.86; H, 15 4.71; N, 13.79; S, 7.76.

Example 17. (*5S*)-*N*-[[3-[3-Fluoro-4-[5-(3-hydroxybutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CH(OH)CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.

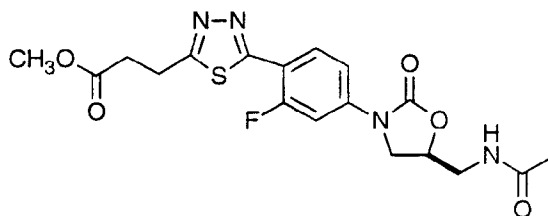


20 To a stirred suspension of the ketone of Example 16 (280 mg) in methanol, cooled to 0 °C, is added sodium borohydride (52 mg). The reaction mixture is stirred at room temperature for 1 h, then additional sodium borohydride (25 mg) is added. Stirring is continued for an additional 3 h, then the reaction mixture is treated with water. The  
25 reaction mixture is poured into CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the phases are separated. The aqueous phase is extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL) and the combined organic phases are dried (MgSO<sub>4</sub>), filtered and concentrated. The residue is dissolved in methanol, absorbed

onto silica gel and purified by flash chromatography using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 130.3 mg of the title compound as a white solid.

Physical characteristics are as follows: mp 200-201 °C. <sup>1</sup>H-NMR (DMSO) δ 8.23, 7.72, 7.53, 4.76, 4.62, 4.17, 3.78, 3.67, 3.42, 3.16, 1.81, 1.10. Anal. Found: C, 52.59; H, 5.16; N, 13.63; S, 7.78.

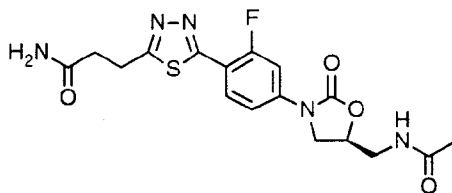
Example 18. (*S*)-Methyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-propanoate. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>OCOCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.



10 The thiohydrazide XVI of Example 3 (346 mg) is reacted with 3-carbomethoxypropionyl chloride (335 mg) according to the procedure of Step 5, Example 3 to afford 327 mg of the title compound.

Physical characteristics are as follows: mp 200-202 °C. <sup>1</sup>H-NMR (DMSO) δ 8.22, 7.70, 7.52, 4.76, 4.17, 3.78, 3.60, 3.40, 2.89, 1.81. Anal. Found: C, 51.06; H, 4.52; N, 13.23; S, 7.42.

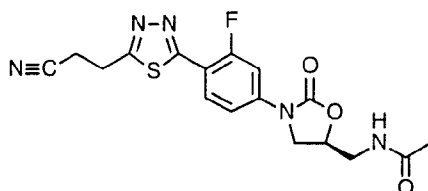
Example 19. (*S*)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-propanamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = NH<sub>2</sub>COCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.



20 The ester of Example 18 (156.7 mg) in methanolic ammonia (7 mL) is heated in a sealed tube at 100 °C for 12 h. A solid precipitate forms upon cooling. The solid is isolated by filtration, washed with ether and dried to afford 115.0 mg of the title compound as a white solid.

Physical characteristics are as follows: mp 254-255 °C. <sup>1</sup>H-NMR (DMSO) δ 8.22, 7.72, 7.53, 7.41, 6.90, 4.76, 4.17, 3.79, 3.42, 2.60, 1.81. Anal. Found: C, 49.71; H, 4.49; N, 17.13; S, 7.87.

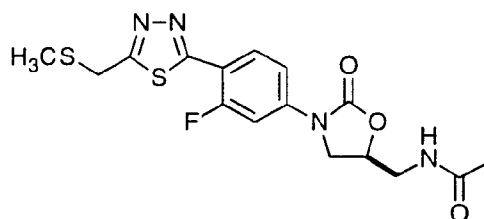
5 Example 20. (*S*)-*N*-[[3-[4-[5-(2-Cyanoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = NCCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.



To a stirred suspension of the amide of Example 19 (110 mg) in dry THF (1.4 mL) and pyridine (0.42 mL) cooled to 0 °C is added trifluoroacetic anhydride (96 μL). The reaction mixture is stirred at 0 °C, and then at RT for 2 h. The reaction mixture is concentrated and the residue is purified by flash chromatography using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 64 mg of the title compound.

Physical characteristics are as follows: mp 208-210 °C. <sup>1</sup>H-NMR (DMSO) δ 8.25, 7.72, 7.54, 4.77, 4.16, 3.81, 3.50, 3.48, 3.06, 1.81; % Water (KF) = 0.4; Anal. Found: C, 51.63; H, 4.18; N, 17.23; S, 7.92.

15 Example 21. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[(methylthio)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>SCH<sub>2</sub>). Refer to Scheme 1.



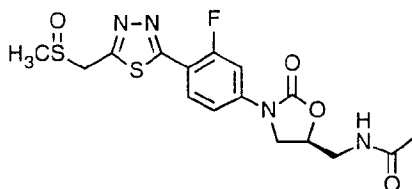
20

Step 1. (Methylthio)acetyl chloride is prepared as described in *J. Chem. Soc., Perkins Trans. I* 1996, 853.

Step 2. The thiohydrazide XVI of Example 3 (628 mg) is reacted with (methylthio)acetyl chloride (480 mg) according to the procedure of Step 5, Example 3 to afford 25 573 mg of the title compound.

Physical characteristics are as follows: mp 209-211 °C. <sup>1</sup>H-NMR (DMSO) δ 8.25, 7.70, 7.55, 4.76, 4.23, 4.17, 3.82, 3.42, 2.10, 1.81. Anal. Found: C, 48.36; H, 4.38; N, 14.05; S, 16.04.

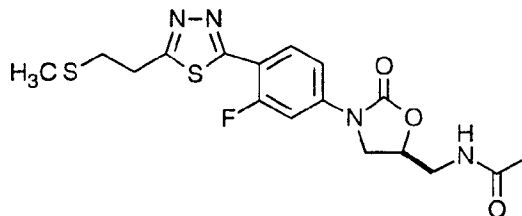
5 Example 22. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[(methylsulfinyl)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>S(O)CH<sub>2</sub>). Refer to Scheme 1.



To a stirred suspension of the sulfide of Example 21 (110 mg) in 1:1  
10 methanol/water (4.4 mL) is added sodium metaperiodate (65 mg). The reaction mixture is heated at reflux for 30 min, during which time the reaction mixture becomes homogeneous. The reaction mixture is cooled and a solid precipitate forms. The solid is removed by filtration and the filtrate is concentrated. The resulting residue is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 5%  
15 MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 89 mg of the title compound.

Physical characteristics are as follows: mp 200-201 °C. <sup>1</sup>H-NMR (DMSO) δ 8.29, 8.23, 7.74, 7.55, 4.84, 4.77, 4.64, 4.18, 3.80, 3.42, 2.56, 1.81; Anal. Found: C, 46.32; H, 4.18; N, 13.38; S, 15.44.

20 Example 23. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylthio)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.

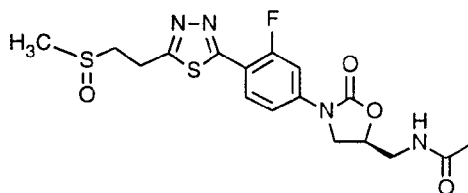


25 Step 1. 3-(Methylthio)propionyl chloride is prepared according to the procedure found in *Synthesis*, 1986, 1070.

Step 2. The thiohydrazide XVI of Example 3 (357 mg) is reacted with 3-(methylthio)propionyl chloride (299 mg) according to the procedure of Step 5, Example 3 to afford 404 mg of the title compound.

Physical characteristics are as follows: mp 211-213 °C. <sup>1</sup>H-NMR (DMSO) δ 8.24, 7.69, 7.53, 4.77, 4.17, 3.79, 3.42, 2.91, 2.10, 1.81. Anal. Found: C, 49.90; H, 4.79; N, 13.50; S, 15.37.

Example 24. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylsulfinyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>S(O)CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.



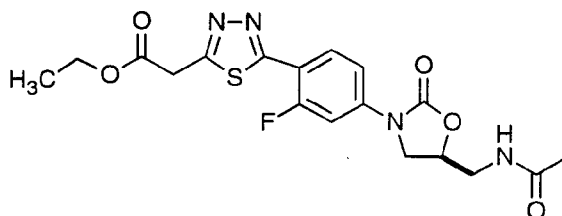
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To a stirred suspension of the sulfide of Example 23 (170 mg) in 6.4 mL MeOH/H<sub>2</sub>O (1:1) is added sodium metaperiodate (97 mg). The reaction is heated to reflux for 15 min. during which time the reaction mixture becomes homogeneous. The reaction mixture is cooled and a precipitate forms. The solid is removed by filtration and the filtrate is absorbed onto silica gel and purified by flash chromatography using 7% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 150 mg of the title compound as a white solid.

Physical characteristics are as follows: mp 193-914 °C. <sup>1</sup>H-NMR (DMSO) δ 8.24, 7.74, 7.54, 4.76, 4.17, 3.79, 3.55, 3.42, 3.16, 2.61, 1.81. Anal. Found: C, 47.70; H, 4.64; N, 13.02; S, 14.83.

20

Example 25. (*S*)-Ethyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetate. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CH<sub>2</sub>OCOCH<sub>2</sub>). Refer to Scheme 1.



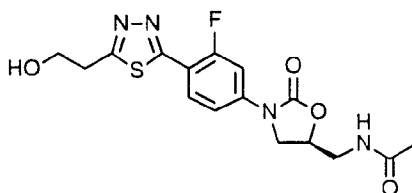
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The thiohydrazide XVI of Example 3 (587 mg) is reacted with ethyl malonyl chloride (352 mg) according to the procedure of Step 5, Example 3 to afford 539 mg of the title compound.

Physical characteristics are as follows: mp 158-159 °C. <sup>1</sup>H-NMR (DMSO) δ  
 5 8.26, 7.72, 7.52, 4.76, 4.38, 4.15, 3.79, 3.69, 3.42, 1.82, 1.21. Anal. Found: C, 50.94; H, 4.61; N, 13.22; S, 7.56.

Example 26. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = HOCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme 1.

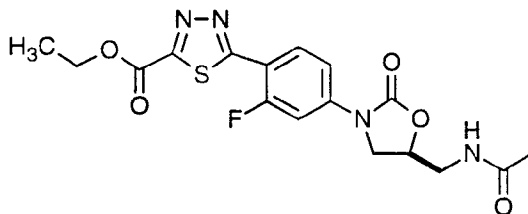


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To a stirred suspension of the ester of Example 25 (138 mg) in isopropanol (3 mL) is added a 2 M solution of lithium borohydride in THF (0.33 mL). The bright yellow reaction mixture is stirred at RT for 4 h, then quenched with water. The reaction  
 15 mixture is concentrated. The residue is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 7% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 54.0 mg of the title compound as a white solid.

Physical characteristics are as follows: mp 192-194 °C. <sup>1</sup>H-NMR (DMSO) δ  
 20 8.24, 7.70, 7.51, 5.08, 4.77, 4.17, 3.76, 3.42, 3.25, 1.81. Anal. Found: C, 50.09; H, 4.62; N, 14.71; S, 8.22.

Example 27. (*S*)-Ethyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-carboxylate. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CH<sub>2</sub>OCO). Refer to Scheme 1.

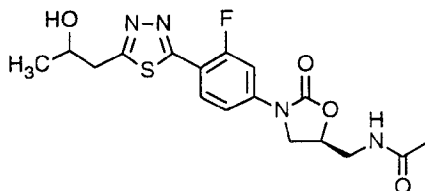


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The thiohydrazide XVI of Example 3 (364 mg) is reacted with ethyl oxalyl chloride (198 mg) according to the procedure of Step 5, Example 3 to afford 332 mg of the title compound.

Physical characteristics are as follows: mp 220-222 °C. <sup>1</sup>H-NMR (DMSO) δ  
 5 8.37, 8.23, 7.76, 7.59, 4.77, 4.43, 4.18, 3.81, 3.42, 3.29, 1.81, 1.35. Anal. Found: C, 49.53; H, 4.23; N, 13.53; S, 7.79.

Example 28. (5*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CH(OH)CH<sub>2</sub>). Refer to Scheme 1.



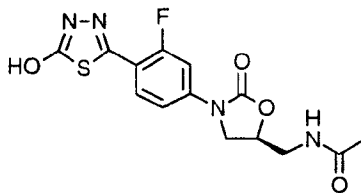
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Step 1. 3-(*tert*-Butyldimethylsiloxy)butyryl chloride is prepared according to the procedure found in *J. Org. Chem.* 1987, 52, 1780-1789.

Step 2. The thiohydrazide XVI of Example 3 (323 mg) is reacted with 3-(*tert*-  
 15 butyldimethylsiloxy) butyryl chloride (468 mg) according to the procedure of Step 5, Example 3 to afford 219 mg of the title compound.

Physical characteristics are as follows: mp 200-202 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ  
 4.35, 2.95, 1.23, 0.87. 0.07. Anal. Found: C, 51.42; h, 4.89; N, 14.03; S, 7.93.

Example 29. (*S*)-*N*-[[3-[4-(4,5-Dihydro-5-oxo-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-  
 20 oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = HO). Refer to Scheme 1.

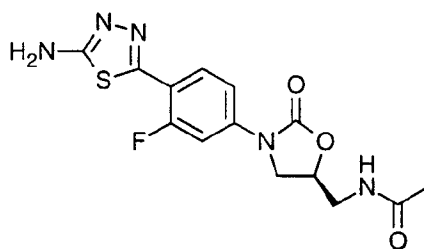


To a stirred suspension of the thiohydrazide XVI of Step 4 of Example 3 (339 mg)  
 25 in THF (10 mL) is added diphosgene (0.16 mL). The reaction is heated at reflux for 1 h. The cooled reaction is concentrated. The residue is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography to afford 54 mg of the title compound.

Physical characteristics are as follows: mp 230-232 °C. <sup>1</sup>H-NMR (DMSO) δ 8.22, 7.88, 7.50, 7.46, 4.74, 4.15, 3.76, 3.41, 1.81.

Example 30. (*S*)-*N*-[[3-[4-(5-Amino-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H<sub>2</sub>N).

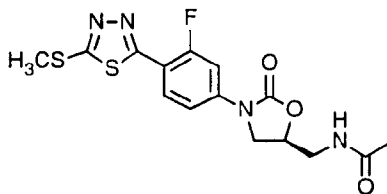
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Another method of making the compounds of formula I-A is as follows: A mixture of the nitrile XII (prepared in step 1 of Example 3, 1.22 g) and thiosemicarbazide (441.2 mg) in methane sulfonic acid (5 mL) is heated at 70 °C for 45 min. The cooled reaction mixture is treated with 1 N NH<sub>4</sub>OH, until precipitation occurs. The yellow precipitate is isolated by filtration and dried. This solid is dissolved in hot ethanol and water and the solution is made alkaline (pH 8) with 1 N NH<sub>4</sub>OH. Upon cooling, a solid is deposited. The solid is isolated by filtration, washed with water and dried in a vacuum oven at 40 °C overnight to afford 982.7 mg of the title thiadiazole.

Physical characteristics are as follows: mp 261-262 °C (dec). <sup>1</sup>H NMR (DMSO) δ 8.24, 8.06, 7.62, 7.45, 4.74, 4.14, 3.76, 3.41, 1.81; % Water (KF) = 0.35%. Anal. Found: C, 47.42; H, 4.09; N, 19.75; S, 9.14.

Example 31. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>S). Refer to Scheme 1.

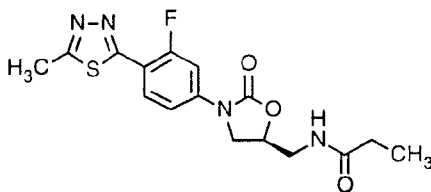


Step 1. Methyl hydrazinecarbodithioate is prepared according to the procedure in *J. Med. Chem.* 1979, 22, 855-862).

Step 2. A mixture of the nitrile XII prepared in Step 1, Example 3 (266 mg) and methyl hydrazinecarbodithioate (293 mg) in methane sulfonic acid (4 mL) is heated at 65 °C for 18 h. The cooled reaction mixture is cooled and treated with 1 M aqueous NH<sub>4</sub>OH after which a solid precipitate forms. The solid is isolated by filtration. The solid is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified using a Biotage 40 S column using 3% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 124.5 mg of the title compound as a white solid.

Physical characteristics are as follows: mp 196-198 °C. <sup>1</sup>H-NMR (DMSO) δ 8.23, 7.75, 7.54, 4.77, 4.16, 3.78, 3.42, 2.80, 1.81. % Water (KF) 2.50; Anal. Found: C, 45.51; H, 3.88; N, 14.15; S, 16.22.

Example 32. (*S*)-*N*-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide. (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F. R<sup>1</sup> = CH<sub>3</sub>CH<sub>2</sub>CO, R<sup>2</sup> = CH<sub>3</sub>). Refer to Scheme 1.

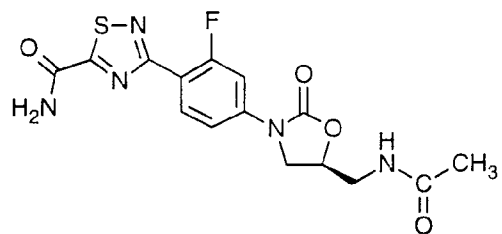


Step 1. To a solution of hydroxylamine hydrochloride (732 mg) in pyridine (25 mL) is added the title compound of Example 3 (693 mg). The mixture turns homogenous with the addition of EtOH (2.5 mL). The reaction mixture is heated to reflux for 4 hours. The reaction is cooled to room temperature and the precipitated product is collected by filtration to afford 124 mg of the aminomethyl oxazolidinone.

Step 2. To a suspension of the compound prepared in Step 1 (200 mg) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> is added propionyl chloride (113 μL) and triethylamine (362 μL). The reaction is heated to 70 °C for 2 hours. The reaction is concentrated and the residue is triturated with Et<sub>2</sub>O. Further purification by chromatography using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent gives 189 mg of the title compound.

Physical characteristics are as follows: mp 249-251 °C. <sup>1</sup>H-NMR (DMSO) δ 8.20, 7.69, 7.51, 4.78, 4.17, 3.82, 3.43, 2.77, 2.08, 0.93. Anal. Found: C, 52.78; H, 4.66; N, 15.32.

Example 33. (S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,2,4-thiadiazole-5-carboxamide (I-B, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = NH<sub>2</sub>CO). Refer to Scheme 2.



5 Step 1. The nitrile XII (prepared in step 1 of Example 3, 1.11g) is dissolved in warm DMSO (3.0 mL) and powdered potassium carbonate (100 mg) is added. The mixture is cooled to 15 °C and 30% hydrogen peroxide (900 uL) is added. A vigorous exothermic reaction begins and after it subsides, the cooling bath is removed and the reaction stirred 15 minutes at 20 °C. The reaction is diluted with ethanol (100 mL) and  
10 toluene (200 mL) and filtered, then concentrated *in vacuo* to an orange oil. The oil is chromatographed over silica gel, eluting with 10% methanol in methylene chloride. The product is recrystallized from ethyl acetate to give 840 mg of the product XVII as white crystals.

Physical characteristics as follows: mp 219-20°C; <sup>1</sup>H NMR (300 MHz, DMSO)  
15 δ 8.27, 7.71, 7.56, 7.53, 7.34, 4.72, 4.12, 3.74, 3.40, 1.80; Anal. Found: C, 52.55; H, 4.90; N, 14.12.

Step 2. The amide XVII prepared in step 1 (100mg) is dispersed in acetonitrile (4 mL) and chlorocarbonyl sulfonyl chloride (70 uL) is added. The reaction is warmed to 80 °C for 1.5 hours. The solvent is evaporated and the residue is chromatographed over  
20 silica gel, eluting with 5% methanol in methylene chloride to give the product XVIII (47 mg) as a tan solid.

Physical characteristics are as follows: mp 175 °C, dec. <sup>1</sup>H NMR (300 MHz, DMSO) δ 8.24, 7.92, 7.65, 7.51, 4.75, 4.16, 3.78, 3.41, 1.81;

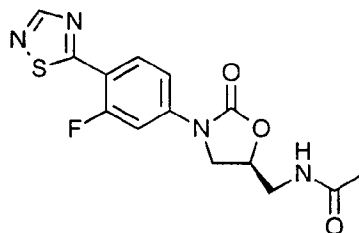
Step 3. The 1,3,4-oxathiazole-2-one XVIII prepared in step 2 (40 mg) is mixed  
25 with ethylcyanoformate (1.5 mL) in toluene (3.0 mL) and heated to reflux (130 °C) for 17 hours. The solvent is evaporated under a stream of dry nitrogen and the residue is chromatographed over silica gel, eluting with 5 % methanol in methylene chloride to afford 21 mg of the ethyl thiadiazolecarboxylate (I-B, R<sup>2</sup> = CH<sub>3</sub>CH<sub>2</sub>CO) as a yellow solid.

Physical characteristics are as follows: mp 115-117 °C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.25, 7.60, 7.28, 6.43, 4.83, 4.53, 4.11, 3.84, 3.69, 2.03, 1.46.

Step 4. The ethyl thiadiazolecarboxylate prepared in Step 3 (175 mg) is dissolved in methanol (10 mL) and methanol saturated with ammonia (5 mL) is added. The reaction is stirred at 20 °C for 2 hours. A tan precipitate forms. The solution is diluted with warm methanol (10 mL) and treated with decolorizing carbon and filtered. The solution is concentrated and the residue is recrystallized from ethyl acetate/ methanol, to give 120 mg of the title compound as tan crystals.

Physical characteristics are as follows: mp = 238-240 °C. <sup>1</sup>H NMR (300 MHz, DMSO) δ 8.53, 8.26, 8.24, 7.67, 7.49, 4.77, 4.18, 3.80, 3.42, 1.82. HRMS (FAB) found for C<sub>15</sub>H<sub>14</sub>FN<sub>5</sub>O<sub>4</sub>S+H<sup>+</sup>, 380.0822.

Example 34. (*S*)-*N*-[[3-[3-Fluoro-4-(1,2,4-thiadiazol-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-C, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = H). Refer to Scheme 3.



15

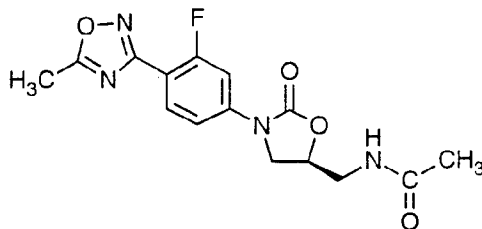
Step 1: A mixture of thioamide XIII, prepared as described in Step 2 of Example 3 (0.500 g) and *N,N*-dimethylformamide dimethyl acetal (257 μL) in dry methylene chloride (3.2 mL) is stirred under nitrogen for 1 hr. The reaction mixture is then triturated with diethyl ether and the orange precipitate filtered and dried under reduced pressure to give the amidine which is not further purified but is used directly in the next step. mp 163 - 165 °C (decomp.).

Step 2: A mixture of the amidine prepared in step 1 (0.250 g) in absolute ethanol (1.7 mL) and pyridine (0.11 mL) under nitrogen is treated with a solution of hydroxylamine-*O*-sulfonic acid (85 mg) in methanol (1.0 mL). The resulting mixture is stirred at ambient temperature for 45 mins, concentrated under reduced pressure, rediluted with water (25 mL) and extracted with methanol/chloroform (10/90, 4 x 50 mL). The combined organic phases are then washed with aqueous sodium hydroxide (0.1 M, 50 mL), water (50 mL) and saline (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product. Purification by reverse

phase HPLC (Zorbax SB-18 column, 20 - 60% acetonitrile/water eluent) gives 21 mg of the title compound.

Physical characteristics are as follows: mp 199-200°C. <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ. 8.71, 8.34, 7.76, 7.32, 6.17, 4.85, 4.13, 3.86, 3.72, 2.05.

- 5 Example 35. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I -H where X<sup>1</sup> is H, X<sup>2</sup> is F, R<sup>1</sup> is COCH<sub>3</sub> and R<sup>2</sup> is CH<sub>3</sub>). Refer to Scheme 8.



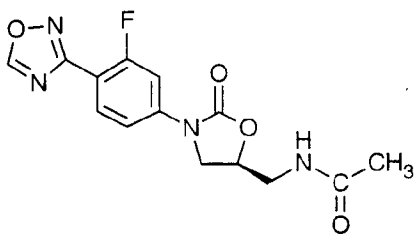
- Step 1. The nitrile XII (prepared in step 1 of Example 3, 2.77g), hydroxylamine  
 10 hydrochloride (2.08g) and powdered sodium carbonate (4.23g) are dissolved in methanol (30 mL). The reaction is warmed to reflux for 2.5 hours and turns very dark in color. The reaction is diluted with 1:1 methylene chloride and methanol (50 mL) and filtered through celite. The celite is washed with another aliquot of solvent (50 mL) and the combined filtrates are concentrated in vacuo. The residue is chromatographed over silica  
 15 gel, eluting with 10% methanol in methylene chloride to give a yellow foam which is crystallized from methanol/ethyl acetate to give 2.2 g of the hydroxyamidine XXII as a yellow crystalline solid.

- Physical characteristics are as follows: mp 196-7 °C dec.; <sup>1</sup>H NMR (300 MHz, DMSO) δ 9.63, 8.26, 7.50, 7.31, 5.78, 4.75, 4.13, 3.75, 3.42, 1.83; Anal.  
 20 Found: C, 50.23; H, 4.89; N, 17.96.

- Step 2. The hydroxyamidine XXII prepared in step 1 (310 mg) is dissolved in acetic anhydride (3 mL) and heated at 120 °C for 3 hours. The solvent is evaporated under a stream of dry nitrogen and the residue is chromatographed over silica gel, eluting with 10 % methanol in methylene chloride to give a white solid. The product is  
 25 recrystallized from ethyl acetate / hexane as white needles to afford 145 mg of title product.

Physical characteristics are as follows: mp 177-9 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.02, 7.62, 7.31, 6.13, 4.82, 4.10, 3.83, 3.68, 2.66, 2.03; Anal. Found: C, 53.55; H, 4.64; N, 16.41.

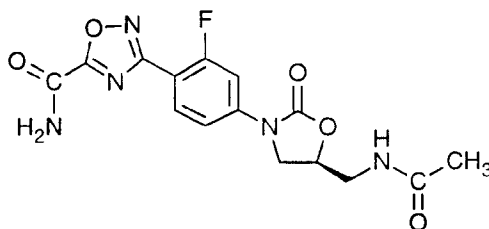
Example 36. (*S*)-*N*-[[3-[3-Fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-H where X<sup>1</sup> is H, X<sup>2</sup> is F, R<sup>1</sup> is COCH<sub>3</sub> and R<sup>2</sup> is H). Refer to Scheme 8.



5 The hydroxyamidine XXII (prepared in step 1 of Example 35, 200 mg) is dispersed in triethyl orthoformate (3 mL) and heated at reflux until all starting material is gone by TLC. Triethylamine (3 equivalents) and methanol (2 mL) are added and the mixture is stirred at 50 °C for 17 hours. The solvent is evaporated and the residue is chromatographed over silica gel to give 47 mg of the desired product as a white solid.

10 Physical characteristics are as follows: mp 197-9 °C. <sup>1</sup>H NMR (300 MHz, DMSO) δ 9.77, 8.27, 8.08, 7.75, 7.56, 4.78, 4.19, 3.81, 3.44, 1.83; Anal. Found: C, 52.51; H, 4.45; N, 16.37.

Example 37. (*S*)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,2,4-oxadiazole-5-carboxamide (I-H where X<sup>1</sup> is H, X<sup>2</sup> is F, R<sup>1</sup> is COCH<sub>3</sub> and R<sup>2</sup> is H<sub>2</sub>NCO). Refer to Scheme 8.



Step 1. The hydroxyamidine XXII (prepared in step 1 of example 35, 930 mg), is dissolved in pyridine (1.0 mL) and methylene chloride (10mL) and the solution is stirred at 20 °C. Ethyl oxalyl chloride (285 uL) is added dropwise and the reaction is stirred for 20 1 hour. The solvent is evaporated under a stream of nitrogen and the residue is chromatographed over silica gel, eluting with 10% methanol in methylene chloride, to give 700 mg of crude oxadiazole ester.

Step 2. The crude ester prepared in step 1 (700 mg) is dissolved in methanol (15 mL) and methanol saturated with ammonia (10 mL) is added. The reaction is stirred 25 hours at ambient temperature and then cooled in a refrigerator for 2 hours. The product

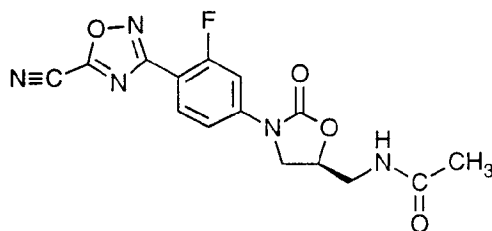


crystallizes from the reaction mixture and is collected by filtration to afford 315 mg of title product.

Physical characteristics are as follows: mp 218-20 °C; <sup>1</sup>H NMR (300 MHz, DMSO) δ 8.80, 8.48, 8.27, 8.08, 7.74, 7.58, 4.80, 4.20, 3.82, 3.45, 1.84; Anal.

5 Found: C, 48.35; H, 4.13; N, 18.48.

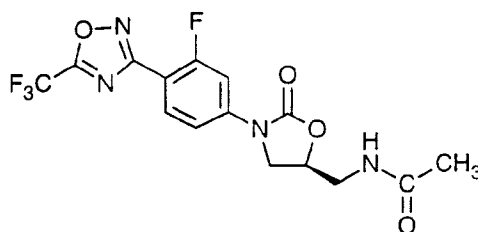
Example 38. (*S*)-*N*-[[3-[4-(5-Cyano-1,2,4-oxadiazol-3-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I -H where X<sup>1</sup> is H, X<sup>2</sup> is F, R<sup>1</sup> is COCH<sub>3</sub> and R<sup>2</sup> is CN).



10 The title amide of Example 37 (150 mg) is dissolved in pyridine (1.0 mL) and THF (2.0 mL) and cooled to 0 °C. Trifluoroacetic anhydride (170 uL) is added. The reaction is stirred for 20 minutes, then allowed to warm to ambient temperature and stirred for 17 hours. The solvent is evaporated under dry nitrogen and the residue is chromatographed over silica gel, eluting with 10% methanol in methylene chloride to  
15 give a white solid. Recrystallization from ethyl acetate/hexane gives 110 mg of the title product as white needles.

Physical characteristics are as follows: mp 200-2 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.98, 7.67, 7.31, 7.26, 4.78, 4.04, 3.83, 3.58, 1.93; Anal. Found: C, 51.98; H, 3.72; N, 20.00.

20 Example 39. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I -H where X<sup>1</sup> is H, X<sup>2</sup> is F, R<sup>1</sup> is COCH<sub>3</sub> and R<sup>2</sup> is CF<sub>3</sub>). Refer to Scheme 8.

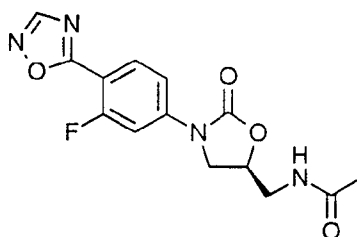


The hydroxyamidine XXII prepared in step 1 of Example 35 (310 mg) is  
25 dissolved in pyridine (3.0 mL) and trifluoroacetic anhydride (282 uL) is added at 20 °C.

The reaction is stirred for 10 minutes, and then warmed to reflux for 30 minutes. The reaction is allowed to slowly cool and then the solvent is evaporated under a stream of dry nitrogen. The residue is chromatographed over silica gel, eluting with 10% methanol in methylene chloride to give a white solid which is recrystallized from ethyl acetate/hexane to afford 295 mg of the title product.

Physical characteristics are as follows: mp 192-3 °C. <sup>1</sup>H NMR (300 MHz, DMSO) δ 8.27, 8.10, 7.74, 7.60, 4.80, 4.20, 3.81, 3.44, 1.83. Anal. Found: C, 46.21; H, 3.25; N, 14.29.

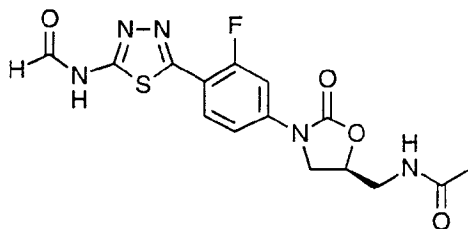
Example 40. (*S*)-*N*-[[3-[3-Fluoro-4-(1,2,4-oxadiazol-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-I, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = H).



The title compound (57 mg) is obtained as a byproduct from the procedure of example 34.

Physical characteristics are as follows: mp 199-200°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.12, 8.24, 8.17, 7.73, 7.59, 4.79, 4.20, 3.82, 3.44, 1.83. Anal. Found: C, 52.16; H, 4.13; N, 17.34.

Example 41. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(formylamino)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = H, X<sup>2</sup> = F, R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = HC(O)NH).



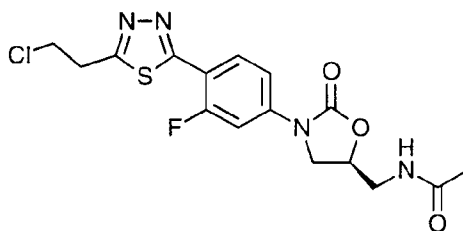
To a stirred suspension of the compound of Example 30 (184 mg) in dry THF (5 mL) is added 1H-benzotriazole-1-carboxaldehyde (168 mg). The reaction mixture is heated at reflux for 48 hours, cooled and concentrated. The residue is dissolved in

EtOH/CH<sub>3</sub>CN, absorbed onto silica gel and purified by flash chromatography using 7% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to yield 155 mg of the title compound as a white solid.

Physical characteristics are as follows: mp 259-260 °C (dec). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 12.9, 8.53, 8.25, 7.71, 7.53, 4.76, 4.17, 3.79, 3.42, 1.81. % Water (KF) = 3.65.

5 Anal. Found: C, 46.29; H, 3.92; N, 17.65; S, 8.04.

Example 42. (*S*)-*N*-[[3-[4-[5-(2-Chloroethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = ClCH<sub>2</sub>CH<sub>2</sub>).



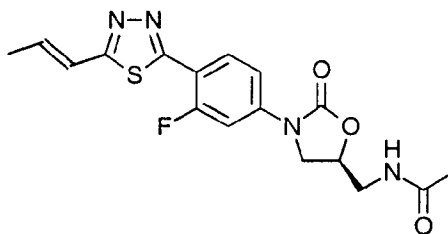
10

The thiohydrazide XVI of Example 3 (250 mg) is reacted with acryloyl chloride (125 μL) according to the procedure of Step 5, Example 3 to afford 196 mg of the title compound.

Physical characteristics are as follows: mp 178-180 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.26, 7.73, 7.53, 4.76, 4.18, 4.05, 3.80, 3.63, 3.43, 1.82. Anal. Found: C, 48.94; H, 4.08; N, 13.96.

15

Example 43. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(1-propenyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = CH<sub>3</sub>CH=CH).

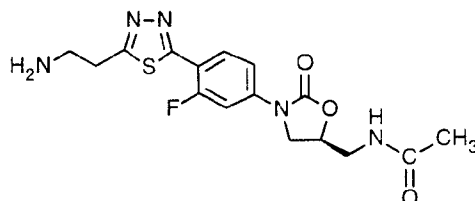


20

The thiohydrazide XVI from Step 4 of Example 3 (200 mg) is reacted with 3-butenoyl chloride (127 mg) according to the procedure of Step 5, Example 3 to afford 120 mg of the title compound.

Physical characteristics are as follows: mp 242-244 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.27, 7.71, 7.53, 6.88, 6.76, 4.77, 3.80, 3.42, 1.94, 1.82. HRMS (EI) Found for C<sub>17</sub>H<sub>17</sub>FN<sub>4</sub>O<sub>3</sub>S, 377.1075.

5 Example 44. (*S*)-*N*-[[3-[4-[5-(2-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



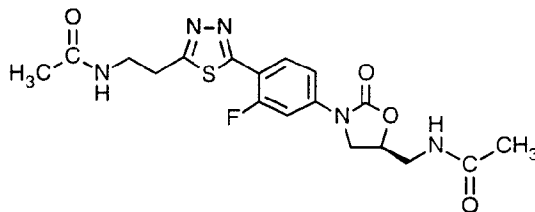
Step 1. Fmoc-β-Ala-OH (1.0 g) is suspended in methylene chloride at room temperature under nitrogen. Oxalyl chloride (298 μL) is added followed by two drops of  
10 DMF. After stirring overnight at room temperature, the reaction is concentrated to afford 0.75 g of the acid chloride (Fmoc-β-Ala-Cl).

Step 2. The thiohydrazide XVI of Example 3 (210 mg) is reacted with Fmoc-β-Ala-Cl (275 mg, from Step 1) according to the procedure of Step 5, Example 3 to afford 358 mg of the Fmoc-protected title compound.

15 Step 3. The Fmoc-protected amine prepared in Step 2 (1.3 g) is dissolved in piperidine (30 mL) and stirred for 1 hour at room temperature. The reaction is concentrated and the residue is purified by flash chromatography using 5% MeOH (saturated with NH<sub>3</sub>) in CH<sub>2</sub>Cl<sub>2</sub> to afford 0.59 g of the title compound.

Physical characteristics are as follows: mp 195-197 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.22,  
20 7.70, 7.52, 4.76, 4.17, 3.80, 3.42, 3.32, 3.15, 2.91, 1.82. Anal. Found: C, 50.19; H, 5.07; N, 17.92; S, 8.02.

Example 45. (*S*)-*N*-[[3-[4-[5-[2-(Acetylamino)ethyl]-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>C(O)NHCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.

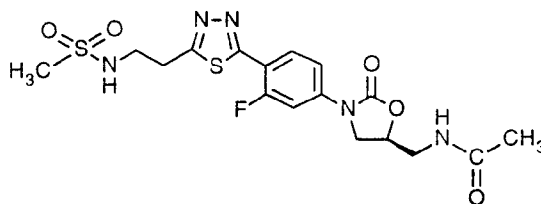


25

The thiadiazole prepared in Example 44, Step 3 (300 mg) is combined with acetic anhydride (97  $\mu$ L) and pyridine (199  $\mu$ L) in 20 mL of  $\text{CH}_2\text{Cl}_2$ . The reaction is heated overnight and then concentrated in vacuo. The residue is dissolved in  $\text{CH}_2\text{Cl}_2$  and  
 5 MeOH, absorbed onto silica, and purified by flash chromatography using 5% MeOH in  $\text{CH}_2\text{Cl}_2$  as eluent to afford 251 mg of the title compound.

Physical characteristics are as follows: mp 259-261  $^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  8.25, 8.08, 7.70, 7.53, 4.77, 4.17, 3.79, 3.42, 3.26, 1.82, 1.78. Anal. Found: C, 51.25; H, 4.83; N, 16.59; S, 7.46.

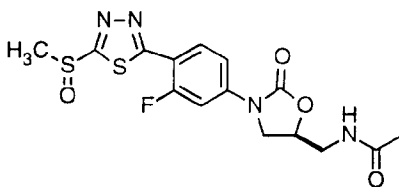
10 Example 46. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-[(methylsulfonyl)amino]ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A,  $\text{X}^1 = \text{F}$ ,  $\text{X}^2 = \text{H}$ ,  $\text{R}^1 = \text{CH}_3\text{CO}$ ,  $\text{R}^2 = \text{CH}_3\text{SO}_2\text{NHCH}_2\text{CH}_2$ ). Refer to Scheme I.



The thiadiazole prepared in Example 44, Step 3 (300 mg) is suspended in  $\text{CH}_2\text{Cl}_2$   
 15 (10 mL) and methanesulfonyl chloride (127  $\mu$ L) and triethylamine (458  $\mu$ L) are added. The reaction is heated to 60  $^\circ\text{C}$  for 3 hours and then concentrated to dryness. The residue is taken up in  $\text{CH}_2\text{Cl}_2$  and MeOH, absorbed onto silica gel, and purified by flash chromatography using 5% MeOH in  $\text{CHCl}_3$  as eluent to afford 145 mg of the title compound.

20 Physical characteristics are as follows: mp 213-214.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  8.25, 7.71, 7.53, 7.30, 4.77, 4.17, 3.81, 3.35, 2.92, 1.82. Anal. Found: C, 44.19; H, 4.57; N, 15.08; S, 13.57.

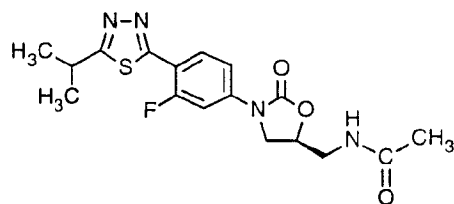
Example 47. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A,  $\text{X}^1 = \text{F}$ ,  $\text{X}^2 = \text{H}$ ,  $\text{R}^1 = \text{CH}_3\text{CO}$ ,  
 25  $\text{R}^2 = \text{CH}_3\text{SO}$ ). Refer to Scheme I.



The sulfide prepared in Step 2 of Example 31 (252 mg) is suspended in CH<sub>3</sub>OH (5 mL) and water (5 mL). Sodium metaperiodate (155 mg) is added with stirring. The reaction mixture is heated at reflux for 18 hours and then cooled and concentrated. The residue is dissolved in CH<sub>3</sub>OH and CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 20% CH<sub>3</sub>CN in ethyl acetate to 5 % CH<sub>3</sub>OH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 104 mg of the title compound.

Physical characteristics are as follows: mp 213-215 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.31, 7.76, 7.59, 4.77, 4.18, 3.81, 3.42, 3.17, 1.81. Anal. Found: C, 44.87; H, 3.72; N, 13.88; S, 15.61.

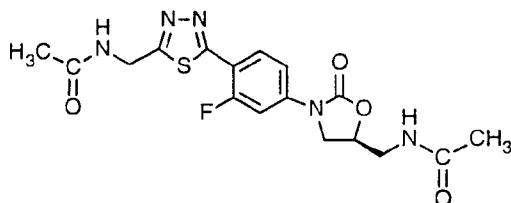
Example 48. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(1-methylethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = (CH<sub>3</sub>)<sub>2</sub>CH). Refer to Scheme I.



The thiohydrazide XVI prepared in Example 3, Step 4 (300 mg) is reacted with isobutyryl chloride (125 μL) according to the procedure of Step 5, Example 3 to afford 150 mg of the title compound.

Physical characteristics are as follows: mp 158 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.22, 7.70, 7.52, 4.73, 3.79, 3.79, 3.50, 3.42, 1.82, 1.39. Anal. Found: C, 53.63; H, 5.18; N, 14.81; S, 8.43.

Example 49. (*S*)-*N*-[[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>C(O)NHCH<sub>2</sub>). Refer to Scheme I.

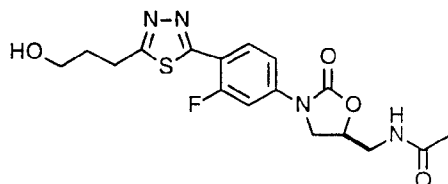


The amine of Example 6, Step 2 (300 mg) is mixed with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and triethylamine (457 μL). The temperature is lowered to 0 °C and acetyl chloride (117 μL)

is added. The reaction is warmed to RT and then concentrated in vacuo. The solid is dissolved in CH<sub>2</sub>Cl<sub>2</sub> and MeOH, absorbed onto silica gel, and flash chromatographed using 6% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 301 mg of the title compound.

Physical characteristics are as follows: mp 233-235 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ  
 5 8.90, 8.25, 7.70, 7.51, 4.77, 4.65, 4.17, 3.81, 3.41, 1.89, 1.82. Anal. Found: C, 49.98; H, 4.45; N, 16.95.

Example 50. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = HOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



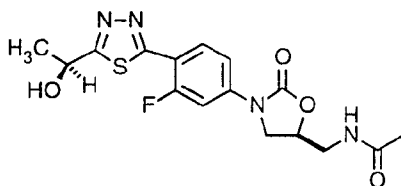
10

Step 1. 4-[(*tert*-Butyldiphenylsilyl)oxy]butyryl chloride is prepared as described in *J. Org. Chem.*, 1996, 61, 2413-2427.

Step 2. The thiohydrazide XVI prepared in Example 3, Step 4 (352 mg) is reacted  
 15 with the acid chloride prepared in Step 1 of this example (776 mg) according to the procedure of Example 3, Step 5. The residue is treated with methanol to afford 363 mg of the title compound.

Physical characteristics are as follows: mp 195-197 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ  
 20 8.23, 7.70, 7.51, 4.76, 4.62, 4.16, 3.79, 3.42, 3.16, 1.89, 1.81; Anal. Found: C, 51.33; H, 4.97; N, 14.06; S, 7.42.

Example 51. [*S*-(*R*\*,*R*\*)]-*N*-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = *S*-CH<sub>3</sub>CH(OH)). Refer to Scheme I.

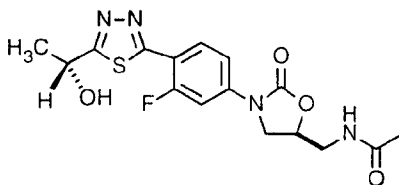


Step 1. The *t*-butyldimethylsilyl ether of L-lactic acid chloride is prepared as  
 25 described in *Tetrahedron Letters*, 1996, 37, 3515-3518.

Step 2. The thiohydrazide XVI prepared in Example 3, Step 4 (414 mg) is reacted with the acid chloride prepared in Step 1 of this example (563 mg) according to the procedure of Example 3, Step 5. The residue is treated with methanol to afford 383 mg of the title compound.

- 5 Physical characteristics are as follows: mp 202-203 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.25, 7.70, 7.52, 6.39, 5.15, 4.76, 4.17, 3.79, 3.42, 1.81, 1.53. Anal. Found: C, 50.28; H, 4.44; N, 14.73; S, 8.42.

- Example 52. [*S*-(*R*<sup>\*</sup>,*S*<sup>\*</sup>)]-*N*-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = *R*-CH<sub>3</sub>CH(OH)). Refer to Scheme I.
- 10

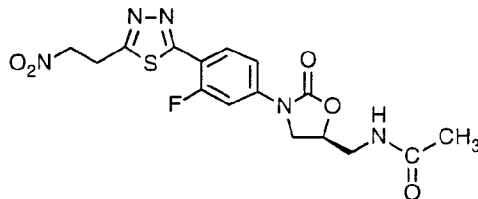


Step 1. The *t*-butyldimethylsilyl ether of *R*-lactic acid chloride is prepared as described in *Tetrahedron Letters*, 1996, 37, 3515-3518.

- 15 Step 2. The thiohydrazide XVI of Example 3, Step 4 (414 mg) is reacted with the acid chloride prepared in Step 1 of this example (563 mg) according to the procedure of Example 3, Step 5. The residue is treated with methanol to afford 383 mg of the title compound.

- Physical characteristics are as follows: mp 209-210 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.23, 7.70, 7.51, 6.41, 5.15, 4.76, 4.17, 3.79, 3.42, 1.81, 1.50; Anal. Found: C, 50.32; H, 4.66; N, 14.56; S, 8.27.
- 20

- Example 53. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-nitroethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = O<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



25

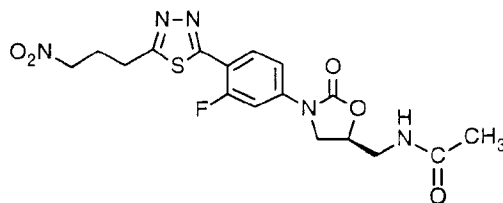


Step 1. 3-Nitropropionyl chloride is prepared according to the procedure of *J. Pharm. Sci.* 1978, 67, 421-3.

Step 2. The thiohydrazide XVI of Example 3, Step 4 (300 mg) is reacted with the acid chloride prepared in Step 1 of this example (164 mg) according to the procedure of Example 3, Step 5.

Physical characteristics are as follows: mp 195-197 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.23, 7.71, 7.53, 5.09, 4.76, 4.17, 3.81, 3.42, 1.82. Anal. Found: C, 46.87; H, 4.19; N, 16.79; S, 7.70.

Example 54. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-nitropropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = O<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.

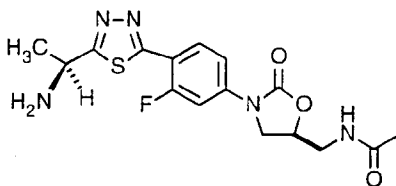


Step 1. 4-Nitrobutyryl chloride is prepared according to the procedure of *Chem. Pharm. Bull.* 1992, 40, 2338-2343.

Step 2. The thiohydrazide XVI of Example 3, step 4 (1.44 g) is reacted with the acid chloride prepared in Step 1 of this example (868 mg) according to the procedure of Example 3, Step 5.

Physical characteristics are as follows: mp 183-185 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.26, 7.71, 7.53, 4.76, 4.69, 4.17, 3.80, 3.42, 3.24, 2.40, 1.82. Anal. Found: C, 48.50; H, 4.44; N, 16.10; S, 7.45.

Example 55. [*S*-(*R*<sup>\*</sup>,*R*<sup>\*</sup>)]-*N*-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = *S*-CH<sub>3</sub>CHNH<sub>2</sub>). Refer to Scheme I.

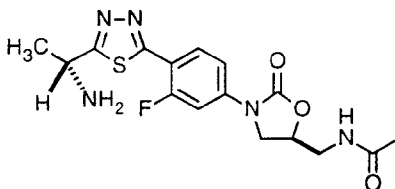


Step 1. The thiohydrazide XVI of Example 3, Step 4 (383 mg) is reacted with Fmoc-Ala-Cl (503 mg) according to the procedure of Example 3, Step 5 to afford a protected aminoethyl thiadiazole.

Step 2. The protected thiadiazole prepared in step 1 (355 mg) is stirred in  
 5 piperidine (8.4 mL) at room temperature for 1 hour and then concentrated. The residue is triturated with ether and the solid is isolated by filtration and dried. The solid is dissolved in methanol/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 7% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 211 mg of the title compound.

10 Physical characteristics are as follows: mp 184-186 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.24, 7.70, 7.50, 4.76, 4.40, 4.17, 3.78, 3.42, 2.57, 1.81, 1.44. Anal. Found: C, 49.49; H, 5.10; N, 17.93; S, 8.11.

Example 56. [*S*-(*R*<sup>\*</sup>,*S*<sup>\*</sup>)]-N-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> =  
 15 H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = R-CH<sub>3</sub>CHNH<sub>2</sub>). Refer to Scheme I.

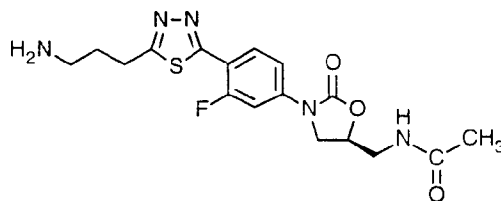


Step 1. The thiohydrazide XVI of Example 3, Step 4 (359 mg) is reacted with Fmoc-D-Ala-Cl (472 μL) according to the procedure of Example 3, Step 5 to afford a protected aminoethyl thiadiazole.

20 Step 2. A suspension of the thiadiazole prepared in Step 1 of this example (390 mg) in piperidine (9 mL) is stirred at room temperature for 1 hour and then concentrated. The residue is triturated with ether and the solid is isolated by filtration and dried. The solid is dissolved in methanol/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 7% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 229 mg of the title  
 25 compound.

Physical characteristics are as follows: mp 201-203 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.24, 7.70, 7.51, 4.76, 4.40, 4.16, 3.79, 3.42, 3.33, 2.63, 1.81, 1.44. Anal. Found: C, 49.27; H, 5.03; N, 17.90; S, 8.07.

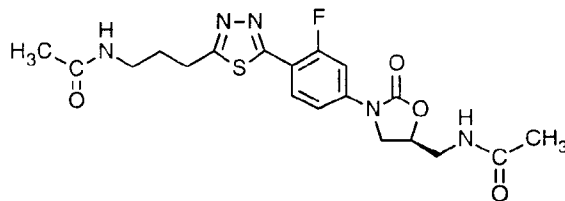
Example 57. (*S*)-*N*-[[3-[4-[5-(3-Aminopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



5 The 3-nitropropylthiadiazole prepared in Example 54, Step 2 (400 mg) is dissolved in MeOH (100 mL) and DMF (25 mL). Raney Nickel (approx. 1.0 g) is added and the reaction is placed on a Parr apparatus under H<sub>2</sub> (45 psi) overnight. The reaction is filtered and concentrated. The residue is taken up in CHCl<sub>3</sub> and MeOH, absorbed onto silica gel, and purified by flash chromatography using 1.5% MeOH (saturated with NH<sub>3</sub>)  
 10 in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 193 mg of the title compound.

Physical characteristics are as follows: mp 181-183 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.23, 7.70, 7.52, 4.77, 4.16, 3.81, 3.42, 3.17, 2.61, 1.82. Anal. Found: C, 51.36; H, 5.04; N, 17.23; S, 7.85.

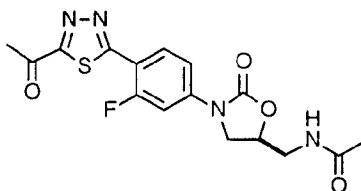
Example 58. (*S*)-*N*-[3-[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]propyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H,  
 15 R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



The 3-aminopropylthiadiazole prepared in Example 57 (300 mg) is dissolved in  
 20 CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at room temperature under nitrogen. Acetic anhydride (90 μL) and pyridine (185 μL) are added, and the reaction is heated to reflux for 1 hour. The reaction is then cooled and concentrated. The residue is dissolved in MeOH and CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel, and purified by flash chromatography using 3% MeOH (saturated with NH<sub>3</sub>) in CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 287 mg of the title compound.

Physical characteristics follow: mp 229-230 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.23, 7.93, 7.71, 7.53, 4.77, 4.17, 3.82, 3.42, 3.13, 1.88, 1.82, 1.79. Anal. Found: C, 52.04; H, 5.10; N, 15.89; S, 7.27.

5 Example 59. (*S*)-*N*-[[3-[4-(5-Acetyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CO). Refer to Scheme I.

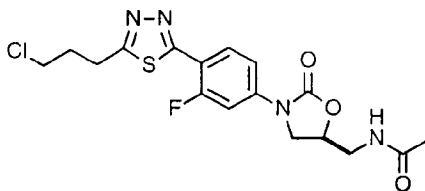


Step 1. Pyruvyl chloride is prepared as described in *Synthesis*, 1975, 163-164.

10 Step 2. The thiohydrazide XVI of Example 3, Step 4 (959 mg) is reacted with the acid chloride prepared in Step 1 of this example (655 mg) according to the procedure of Example 3, Step 5 to give 442 mg of the title compound.

Physical characteristics are as follows: mp 242-244 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.35, 8.27, 7.75, 7.56, 4.78, 4.18, 3.81, 3.43, 2.74, 1.81. Anal. Found: C, 50.43; H, 4.03; N, 14.75; S, 8.35.

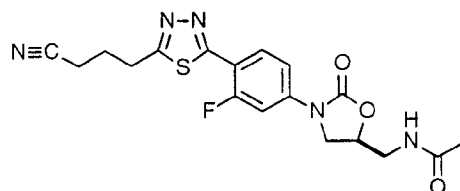
15 Example 60. (*S*)-*N*-[[3-[4-[5-(3-Chloropropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = ClCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



20 The thiohydrazide XVI of Example 3, Step 4 (322 mg) is reacted with 4-chlorobutryl chloride (140 μL) according to the procedure of Example 3, Step 5 to give the title compound (306 mg).

Physical characteristics are as follows: mp 199-200 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.23, 7.73, 7.52, 4.77, 4.17, 3.79, 3.74, 3.42, 3.29, 2.27, 1.8. Anal. Found: C, 49.08; H, 4.50; N, 13.45; Cl, 8.52; S, 7.62.

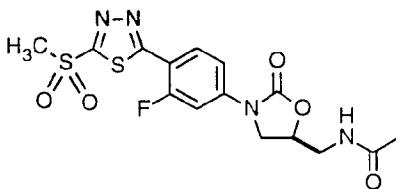
Example 61. (*S*)-*N*-[[3-[4-[5-(3-Cyanopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = NCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



5 A mixture of the chloride prepared in Example 60 (145 mg) and tetrabutylammonium cyanide (189 mg) in dry DMF (3.5 mL) is heated at 80°C for 30 minutes. The DMF is removed under vacuum and the residue is dissolved in methanol/CH<sub>2</sub>Cl<sub>2</sub>. The solid that forms is isolated by filtration and dried to afford 81 mg of the title compound.

10 Physical characteristics are as follows: mp 186-187 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.24, 7.73, 7.55, 4.77, 4.17, 3.79, 3.42, 3.24, 2.63, 2.08, 1.81. Anal. Found: C, 51.05; H, 4.74; N, 16.47; S, 7.59.

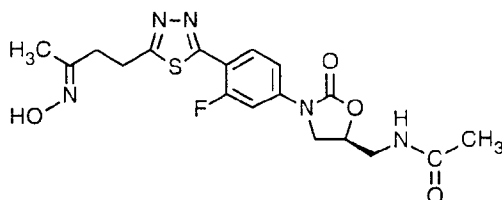
Example 62. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, 15 R<sup>2</sup> = CH<sub>3</sub>SO<sub>2</sub>). Refer to Scheme I.



The sulfide prepared in Example 31, Step 2 (206 mg) is dissolved in methanol (2 mL) and water (2 mL). Oxone (431 mg) is added and the reaction mixture is heated at reflux for 4 hours. The reaction mixture is cooled and the solid is separated by filtration 20 and then washed with water. The solid is dissolved in methanol/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 6% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 166 mg of the title compound.

Physical characteristics are as follows: mp 244-245 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.36, 8.24, 7.80, 7.62, 4.78, 4.19, 3.81, 3.65, 3.43, 1.81. Anal. Found: C, 43.08; H, 3.90; 25 N, 13.28; S, 14.92.

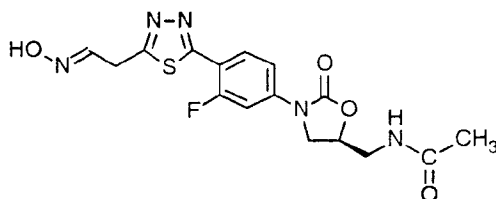
Example 63. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[3-(hydroxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>C(NO<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



5 The ketone prepared in Example 16, Step 2 (330 mg) is dissolved in EtOH (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (15 mL). Hydroxylamine hydrochloride (169 mg) is added and the reaction is heated to 60 °C overnight under a nitrogen atmosphere. The reaction is then concentrated and the residue is dissolved in MeOH and CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica, and purified by flash chromatography using 3% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 304 mg  
10 of the title compound.

Physical characteristics are as follows: mp 218-220 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.23, 7.70, 7.50, 4.76, 4.17, 3.79, 3.42, 3.29, 2.64, 1.82, 1.78. Anal. Found: C, 50.58; H, 4.78; N, 16.36; S, 8.07.

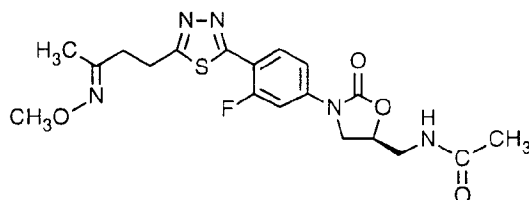
Example 64. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(hydroxyimino)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H,  
15 R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = HC(NO<sub>2</sub>)CH<sub>2</sub>). Refer to Scheme I.



A mixture of stannous chloride (407 mg), thiophenol (462 mg), and triethylamine (0.98 mL) is prepared in CH<sub>3</sub>CN (5 mL) at room temperature. The nitroethyl thiadiazole prepared in Example 53, Step 2 (585 mg) is added to this mixture as a solution in 5 mL of  
20 1:1 MeOH and CH<sub>2</sub>Cl<sub>2</sub>. The reaction is stirred for 2 hours and then concentrated to dryness. The residue is absorbed onto silica gel purified by flash chromatography using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 205 mg of the title compound.

Physical characteristics are as follows: mp 228-230 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ  
25 8.25, 7.70, 7.55, 7.08, 4.80, 4.16, 3.79, 3.42, 1.81. Anal. Found: C, 48.51; H, 4.17; N, 17.39; S, 7.88.

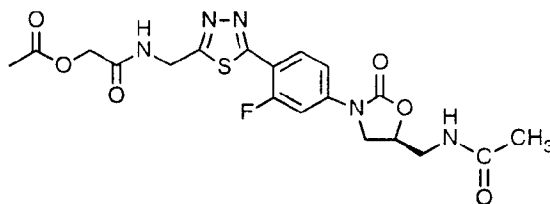
Example 65. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[3-(methoxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>C(NOCH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



5 The ketone prepared in Example 16, Step 2 (200 mg) is dissolved in MeOH (2 mL) and H<sub>2</sub>O (6 mL). To this solution is added methoxylamine hydrochloride (45 mg), Na<sub>2</sub>CO<sub>3</sub> (28 mg), and one drop of acetic acid. The reaction is heated at 100 °C for 2 hours. The reaction is cooled and the solids are removed by filtration. The filtrate is flash chromatographed using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 104 mg of the title  
10 compound.

Physical characteristics are as follows: mp 220-221 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.26, 7.73, 7.55, 4.78, 4.19, 3.80, 3.73, 3.44, 3.33, 2.67, 1.85, 1.83. Anal. Found: C, 52.13; H, 5.03; N, 15.78; S, 7.20.

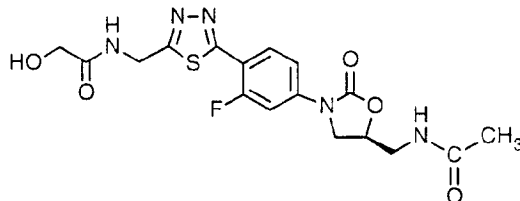
Example 66. (*S*)-*N*-[[5-[4-[5-[(Acetyloxyacetyl)amino]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>C(O)NHCH<sub>2</sub>). Refer to Scheme I.



20 The amine prepared in Example 6, Step 2 (605 mg) is dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL). To this solution is added acetoxyacetylchloride (348 μL) and pyridine (541 μL). The reaction is heated at reflux for 1 hour. The solvent is removed and the residue is absorbed onto silica gel and purified by flash chromatography using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 445 mg of the title compound.

25 Physical characteristics are as follows: mp 210-211 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.00, 8.27, 7.74, 7.55, 4.75, 4.54, 4.20, 3.82, 3.44, 2.11, 1.84. Anal. Found: C, 48.41; H, 4.24; N, 14.63; S, 6.58.

Example 67. (*S*)-*N*-[[5-[4-[5-[(Hydroxyacetyl)amino]methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = HOCH<sub>2</sub>C(O)NHCH<sub>2</sub>). Refer to Scheme I.

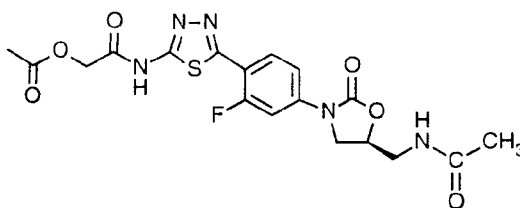


5

The thiadiazole prepared in Example 66 (250 mg) is suspended in MeOH (8 mL) at room temperature and K<sub>2</sub>CO<sub>3</sub> (104 mg) is added. The reaction is stirred at room temperature for 30 minutes and then diluted with CH<sub>2</sub>Cl<sub>2</sub> until homogeneous. The solids are removed by filtration and the reaction is concentrated. The residue is dissolved in MeOH and CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel and purified by flash chromatography using 8% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 108 mg of the title compound.

Physical characteristics are as follows: mp 202-5 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.80, 8.26, 7.73, 7.55, 5.26, 4.76, 4.19, 3.89, 3.82, 3.44, 1.84. Anal. Found: C, 47.76; H, 4.39; N, 15.97; S, 7.28.

Example 68. (*S*)-*N*-[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]-2-(acetyloxy)acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>C(O)NH). Refer to Scheme I.



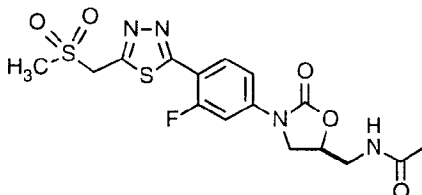
The aminothiadiazole prepared in Example 30 (100 mg) is dissolved in pyridine (5 mL) and chilled in an ice bath. Acetoxyacetyl chloride (184 μL) is added and the ice bath is removed. The reaction is stirred for 30 minutes and then concentrated in vacuo. The residue is dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel, and flash chromatographed using 4% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 89 mg of the title compound.

25



Physical characteristics are as follows: mp 245-246 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 13.0, 8.26, 7.71, 7.55, 4.85, 4.78, 4.19, 3.82, 3.44, 2.14, 1.84. Anal. Found: C, 47.66; H, 4.14; N, 14.94; S, 6.74.

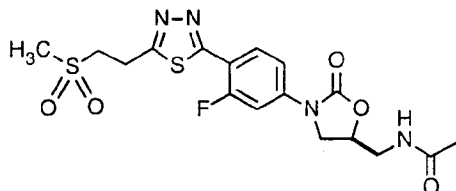
5 Example 69. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A. X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



10 The sulfide prepared in Example 21. Step 2 (177 mg) is suspended in 1:1 methanol/water (4.0 mL) and oxone (359 mg) is added. The reaction mixture is heated at reflux for 2 hours and then cooled. The solid is isolated by filtration, washed with water and dried. The solid is dissolved in THF/acetone, absorbed onto silica gel and purified by flash chromatography using 5 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 136 mg of the  
15 title compound.

Physical characteristics are as follows: mp 216-217 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.32, 8.25, 7.74, 7.59, 5.32, 4.79, 4.20, 3.83, 3.45, 3.16, 1.84. Anal. Found: C, 44.68; H, 4.06; N, 12.95; S, 14.65.

20 Example 70. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylsulfonyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A. X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.



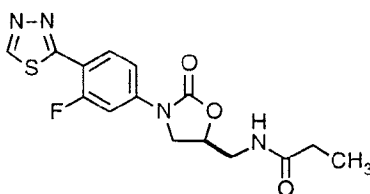
25 The sulfide prepared in Example 23, Step 2 (303 mg) is suspended in 1:1 methanol/water (8.0 mL). Oxone (590 mg) is added and the reaction mixture is heated at

reflux for 3 hours and then cooled. The solid is isolated by filtration, washed with water and dried. The solid is dissolved in THF/acetone, absorbed onto silica gel and purified by flash chromatography using 5 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent to afford 213 mg of the title compound.

5 Physical characteristics are as follows: mp 217-218 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.26, 7.76, 7.56, 4.78, 4.19, 3.81, 3.69, 3.63, 3.44, 3.08, 1.83. Anal. Found: C, 45.61; H, 4.41; N, 12.52; S, 14.32.

Example 71. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CH<sub>2</sub>CO, R<sup>2</sup> = H). Refer to Scheme I.

10



Step 1. The thiadiazole prepared in Example 9 (1.65 g) is dissolved in MeOH (130 mL) and 6M HCl (42 mL) is added. The reaction is heated at reflux for 24 hours and then cooled and diluted with ether (20 mL). The precipitate is filtered, washed with ether and dried to afford 1.60 g of the aminomethyl oxazolidinone as an HCl salt.

15

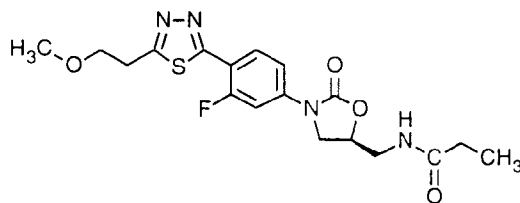
Step 2. The aminomethyl oxazolidinone prepared in Step 1 (249 mg) is dissolved in THF (10 mL) and saturated, aqueous Na<sub>2</sub>CO<sub>3</sub> (10 mL) is added. The solution is chilled in an ice bath and propionyl chloride (98 μL) is added. The ice bath is removed, and the reaction is stirred for 1 hour. The liquid phases are separated and the aqueous phase is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases are diluted with MeOH (10 mL) in order to dissolve the suspended solids. This organic solution is dried with MgSO<sub>4</sub>, filtered, and concentrated. The residue is triturated with *t*-butyl methyl ether and a few drops of MeOH to afford a solid which is filtered and dried to give 234 mg of the title compound.

20

25

Physical characteristics are as follows: mp 232-234 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.70, 8.31, 8.17, 7.73, 7.54, 4.79, 4.18, 3.82, 3.44, 2.08, 0.93. Anal. Found: C, 50.77; H, 4.27; N, 15.75; S, 9.15.

Example 72. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-methoxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CH<sub>2</sub>CO, R<sup>2</sup> = CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.

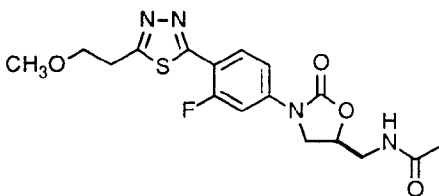


5 Step 1. The 2-chloroethyl thiadiazole prepared in Example 42 (760 mg) is dissolved in MeOH (60 mL) and 6M HCl (22 mL) is added. This solution is refluxed for 24 hours and then cooled and diluted with ether (20 mL). The precipitate is filtered, washed with ether and dried to afford 800 mg of the 2-methoxyethyl thiadiazole intermediate amine as an HCl salt.

10 Step 2. The amine salt prepared in step 1 (700 mg) is dissolved in a mixture of 15 mL of THF and 15 mL of saturated, aqueous Na<sub>2</sub>CO<sub>3</sub> at 0 °C. Propionyl chloride (170 μL) is added and the reaction mixture is stirred at room temperature for 3 hours. The reaction is concentrated and the residue is dissolved in MeOH and CH<sub>2</sub>Cl<sub>2</sub> and absorbed onto silica gel. The product is purified by flash chromatography using 2.5% MeOH  
15 (saturated with NH<sub>3</sub>) in CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 175 mg of the title compound.

Physical characteristics are as follows: mp 189-190 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.24, 8.16, 7.70, 7.52, 4.78, 4.16, 3.81, 3.69, 3.44, 3.37, 3.29, 2.08, 0.93. Anal. Found: C, 52.78; H, 5.21; N, 13.65; S, 7.78.

Example 73. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-methoxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CO, R<sup>2</sup> = CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>). Refer to Scheme I.

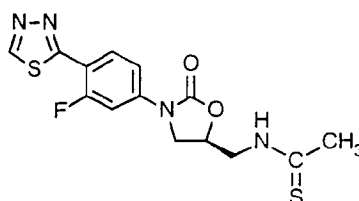


The amine salt prepared in Step 1 of Example 72 (150 mg) is dissolved in a mixture of THF (5 mL) and saturated, aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL) at 0 °C. To this solution  
25 is added acetyl chloride (30 μL), the reaction is allowed to warm to room temperature, and stirred for one hour. The reaction is diluted with water (5 mL) and extracted with

CH<sub>2</sub>Cl<sub>2</sub>. The organic phases are combined, dried over MgSO<sub>4</sub>, filtered, and concentrated to give 142 mg of the title compound.

Physical characteristics are as follows: mp 187-188°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.26, 7.73, 7.53, 4.78, 4.20, 3.85, 3.71, 3.45, 3.40, 3.31, 1.84. Anal. Found: C, 51.43; H, 4.97; N, 13.95; S, 8.03.

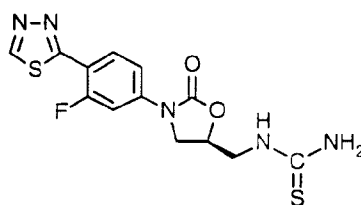
Example 74. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CS, R<sup>2</sup> = H). Refer to Scheme I.



The amine hydrochloride salt prepared in Step 1 of Example 71 (300 mg) is dissolved in THF (10 mL). Triethylamine (507 μL) and ethyldithioacetate (210 μL) are added to the solution. The reaction mixture is stirred at room temperature for 1.5 hours and then concentrated to dryness. The residue is taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with 10% KHSO<sub>4</sub> solution, H<sub>2</sub>O, and brine. The aqueous portions are back washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers are dried over MgSO<sub>4</sub>, filtered and absorbed onto silica for purification by flash chromatography using 2.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 175 mg of the title compound.

Physical characteristics are as follows: mp 195-196 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.4, 9.7, 8.31, 7.74, 7.56, 5.00, 4.23, 3.90, 2.43. Anal. Found: C, 47.53; H, 3.89; N, 15.70; S, 18.08.

Example 75. (*S*)-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = H<sub>2</sub>NCS, R<sup>2</sup> = H). Refer to Scheme I.



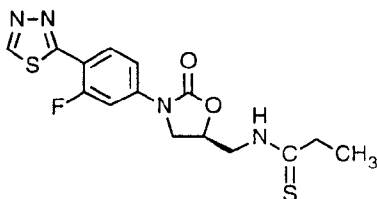
Step 1. The amine hydrochloride salt prepared in Step 1 of Example 71 (500 mg) is dissolved in 60 mL of CH<sub>2</sub>Cl<sub>2</sub>. This solution is added at 0 °C to a stirred solution of

1,1'-thiocarbonyl-di-2-(1H)-pyridone (422 mg) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL). The reaction is warmed to room temperature and stirred overnight. Triethylamine (315 μL) is added and the reaction is stirred for an additional hour. The reaction is then washed with H<sub>2</sub>O and brine and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue is absorbed onto silica and purified by flash chromatography using 20% CH<sub>3</sub>CN in CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 250 mg of an isothiocyanate which is used immediately in the next reaction.

Step 2. The isothiocyanate (240 mg) prepared in Step 1 is dissolved in THF (20 mL) and the resulting solution cooled to 0 °C. Ammonia gas is bubbled into the reaction for 6 minutes. The reaction is capped and allowed to stand for 45 minutes. The reaction is then concentrated and triturated with Et<sub>2</sub>O and a few drops of MeOH to give 230 mg of the title compound.

Physical characteristics are as follows: mp 215-217 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.85, 8.31, 7.93, 7.74, 7.55, 7.20, 4.90, 4.20, 3.85. Anal. Found: C, 43.91; H, 3.59; N, 19.40; S, 17.92.

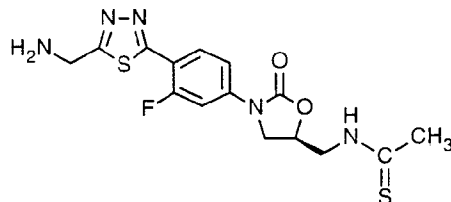
Example 76. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanethioamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CH<sub>2</sub>CS, R<sup>2</sup> = H). Refer to Scheme I.



The thiadiazole propanamide prepared in Example 71, Step 2 (238 mg) is dissolved in 1,4-dioxane (7 mL) and Lawesson's reagent (286 mg) is added to this solution. The reaction is heated at 100 °C for 18 hours. The dioxane is removed in vacuo and the residue is dissolved in MeOH and CH<sub>2</sub>Cl<sub>2</sub>, absorbed onto silica gel, and purified by flash chromatography using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 225 mg of the title compound.

Physical characteristics are as follows: mp 179-181 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.3, 9.80, 8.31, 7.73, 7.55, 5.02, 4.23, 3.92, 2.58, 1.13. Anal. Found: C, 48.94; H, 4.36; N, 14.84; S, 17.21.

Example 77. *N*-[[(5*S*)-3-{4-[5-(aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]ethanethioamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CS, R<sub>2</sub> = H<sub>2</sub>NCH<sub>2</sub>). Refer to Scheme I.



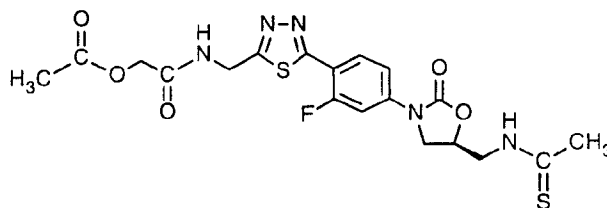
5

Step 1. The Fmoc-protected amine prepared in Example 6, Step 1 (3.0 g) is dissolved in 60 mL of *p*-dioxane at room temperature. Lawesson's reagent (2.13 g) is added and the reaction is heated at 100 °C for 2 hours. The reaction is cooled to room temperature and diluted with Et<sub>2</sub>O. The resulting precipitate is triturated with MeOH to give 2.6 g of the thioamide.

Step 2. The thioamide prepared in Step 1 (2.4 g) is stirred in 41 mL of piperidine at room temperature for 30 minutes. The reaction mixture is then concentrated. Purification by flash chromatography using 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent gives 1.17 g of the title compound.

Physical characteristics are as follows: mp 205-206 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.35, 8.25, 7.73, 7.55, 5.00, 4.24, 4.16, 3.90, 2.58, 2.50. Anal. Found: C, 47.12; H, 4.26; N, 18.16; S, 16.48.

Example 78. 2-([5-(4-{(5*S*)-5-[(ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl)amino)-2-oxoethyl acetate. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CS, R<sub>2</sub> = CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>CONHCH<sub>2</sub>). Refer to Scheme I.



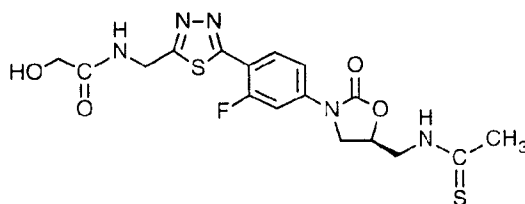
The amine prepared in Example 77, Step 2 (850 mg) is stirred in 35 mL of CH<sub>2</sub>Cl<sub>2</sub>. To this is added acetoxyacetylchloride (480 μL) and pyridine (730 μL). The reaction is heated to reflux for 1 hour. The reaction is cooled to room temperature and concentrated. Purification by flash chromatography using 1% NH<sub>4</sub>OH, 10% isopropanol,

and 89 % CHCl<sub>3</sub> as eluent results in partial hydrolysis of the acetoxycetamide and gives a mixture of compounds. Further purification of this mixture by flash chromatography using 5% MeOH in CHCl<sub>3</sub> as eluent affords 157 mg of the title compound.

Physical characteristics are as follows: mp 145-146 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ  
5 10.35, 9.00, 8.28, 7.74, 7.54, 5.00, 4.75, 4.55, 4.25, 3.94, 2.50, 2.11. Anal Found: C, 47.18; H, 4.28; N, 14.21; S, 12.82.

Example 79. *N*-{[5-(4-{(5*S*)-5-[(ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl}-2-hydroxyacetamide. (I-A, X<sup>1</sup> = F, X<sup>2</sup> = H, R<sup>1</sup> = CH<sub>3</sub>CS, R<sub>2</sub> = HOCH<sub>2</sub>CONHCH<sub>2</sub>). Refer to Scheme I.

10



15

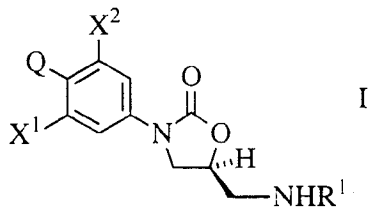
The mixture produced in the first chromatography of Example 78 is further purified by flash chromatography using 5% MeOH in CHCl<sub>3</sub> to afford 319 mg of the title compound.

Physical characteristics are as follows: mp 182-184 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ  
10.40, 8.80, 8.27, 7.73, 7.57, 5.62, 5.00, 4.74, 4.24, 3.90, 2.50. Anal. Found: C, 46.28; H, 4.15; N, 15.88; S, 14.31.

20

## CLAIMS

1. A compound of formula I:



wherein R<sup>1</sup> is

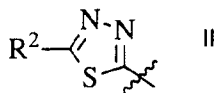
- 5           (a) -COR<sup>3</sup>,
- (b) -COCH<sub>2</sub>Cl,
- (c) -COCHCl<sub>2</sub>,
- (d) -COCH<sub>2</sub>F,
- (e) -COCHF<sub>2</sub>,
- 10           (f) -CO<sub>2</sub>CH<sub>3</sub>,
- (g) -SO<sub>2</sub>CH<sub>3</sub>,
- (h) -COCH<sub>2</sub>OH,
- (i) -CSR<sup>3</sup>,
- (j) -CSNH<sub>2</sub>, or
- 15           (k) -CSNHCH<sub>3</sub>;

wherein X<sup>1</sup> and X<sup>2</sup> are independently

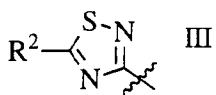
- (a) H,
- (b) F, or
- (c) Cl;

20 wherein Q is

(a) 1,3,4-thiadiazol-2-yl:



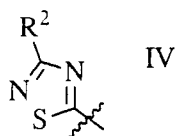
(b) 1,2,4-thiadiazol-3-yl:



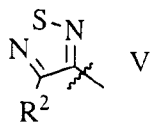
25



(c) 1,2,4-thiadiazol-5-yl:

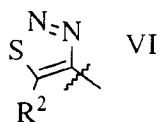


(d) 1,2,5-thiadiazol-3-yl:

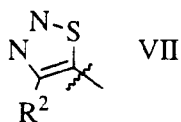


5

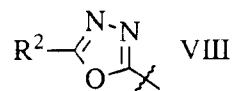
(e) 1,2,3-thiadiazol-4-yl:



10 (f) 1,2,3-thiadiazol-5-yl:

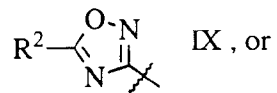


(g) 1,3,4-oxadiazol-2-yl:

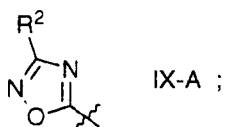


15

(h) 1,2,4-oxadiazol-3-yl:



(i) 1,2,4-oxadiazol-5-yl



20

wherein R<sup>2</sup> is

- (a) R<sup>3</sup>-  
 (b) R<sup>4</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-,  
 5 (c) NC(CH<sub>2</sub>)<sub>n</sub>-,  
 (d) R<sup>3</sup>OCO(CH<sub>2</sub>)<sub>n</sub>-,  
 (e) R<sup>3</sup>R<sup>5</sup>NCO(CH<sub>2</sub>)<sub>n</sub>-,  
 (f) R<sup>3</sup>R<sup>5</sup>N(CH<sub>2</sub>)<sub>n</sub>-,  
 (g) R<sup>4</sup>CONR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-,  
 10 (h) CF<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>-,  
 (i) CF<sub>2</sub>H(CH<sub>2</sub>)<sub>n</sub>-,  
 (j) R<sup>4</sup>CO(CH<sub>2</sub>)<sub>n</sub>-,  
 (k) F(CH<sub>2</sub>)<sub>n</sub>-,  
 (l) Cl(CH<sub>2</sub>)<sub>n</sub>-,  
 15 (m) Br(CH<sub>2</sub>)<sub>n</sub>-,  
 (n) R<sup>3</sup>O(CH<sub>2</sub>)<sub>n</sub>-,  
 (o) R<sup>3</sup>S(CH<sub>2</sub>)<sub>n</sub>-,  
 (p) R<sup>3</sup>SO(CH<sub>2</sub>)<sub>n</sub>-,  
 (q) R<sup>3</sup>SO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-,  
 20 (r) R<sup>3</sup>SO<sub>2</sub>NR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-,  
 (s) R<sup>3</sup>R<sup>4</sup>C(OH)(CH<sub>2</sub>)<sub>n</sub>-,  
 (t) R<sup>3</sup>R<sup>4</sup>C(NHR<sup>5</sup>)(CH<sub>2</sub>)<sub>n</sub>-,  
 (u) HO<sub>2</sub>C(CH<sub>2</sub>)<sub>n</sub>-,  
 (v) O<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>-,  
 25 (w) C<sub>2</sub>-C<sub>6</sub> alkenyl,  
 (x) C<sub>2</sub>-C<sub>6</sub> alkynyl,  
 (y) -CCl<sub>3</sub>,  
 (z) R<sup>3</sup>ON=CR<sup>3</sup>(CH<sub>2</sub>)<sub>n</sub>-,  
 (aa) NCNR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-,  
 30 (bb) R<sup>3</sup>ONR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-, or  
 (cc) R<sup>3</sup>OC(O)NR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-;

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

wherein p is 1, 2 or 3;

wherein R<sup>3</sup> is

- (a) H,
- (b) C<sub>1</sub>-C<sub>5</sub> alkyl, or
- (c) cyclopropyl-;

5 wherein R<sup>4</sup> is

- (a) H,
- (b) C<sub>1</sub>-C<sub>5</sub> alkyl-,
- (c) cyclopropyl-,
- (d) R<sup>3</sup>O(CH<sub>2</sub>)<sub>p</sub>-, or
- 10 (e) R<sup>3</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>p</sub>-;

wherein R<sup>5</sup> is

- (a) H, or
- (b) C<sub>1</sub>-C<sub>3</sub> alkyl;

or a pharmaceutically acceptable salt thereof;

15 with the following proviso:

at least one of X<sup>1</sup> and X<sup>2</sup> is F or Cl.

2. The compound of claim 1

wherein R<sup>1</sup> is

- 20 (a) -COR<sup>3</sup>, or
- (b) -CSR<sup>3</sup>;

wherein X<sup>1</sup> and X<sup>2</sup> are independently

- (a) H, or
- (b) F;

25 wherein Q is the moiety of formula II or IV;

wherein R<sup>2</sup> is

- (a) R<sup>3</sup>,
- (b) R<sup>3</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>-,
- (c) NC(CH<sub>2</sub>)<sub>n</sub>-,
- 30 (d) R<sup>3</sup>OCO(CH<sub>2</sub>)<sub>n</sub>-,
- (e) R<sup>3</sup>R<sup>5</sup>NCO(CH<sub>2</sub>)<sub>n</sub>-,
- (f) R<sup>3</sup>R<sup>5</sup>N(CH<sub>2</sub>)<sub>n</sub>-,
- (g) R<sup>4</sup>CONR<sup>5</sup>(CH<sub>2</sub>)<sub>n</sub>-,

- (h)  $\text{CF}_3(\text{CH}_2)_{n-}$ ,  
 (i)  $\text{R}^4\text{CO}(\text{CH}_2)_{n-}$ ,  
 (j)  $\text{F}(\text{CH}_2)_{n-}$ ,  
 (k)  $\text{Cl}(\text{CH}_2)_{n-}$ ,  
 5 (l)  $\text{R}^3\text{O}(\text{CH}_2)_{n-}$ ,  
 (m)  $\text{R}^3\text{S}(\text{CH}_2)_{n-}$ ,  
 (n)  $\text{R}^3\text{SO}(\text{CH}_2)_{n-}$ ,  
 (o)  $\text{R}^3\text{SO}_2(\text{CH}_2)_{n-}$ ,  
 (p)  $\text{R}^3\text{SO}_2\text{NR}^5(\text{CH}_2)_{n-}$ ,  
 10 (q)  $\text{O}_2\text{N}(\text{CH}_2)_{n-}$ , or  
 (r)  $\text{R}^3\text{R}^4\text{C}(\text{NHR}^5)(\text{CH}_2)_{n-}$ ;  
 (o)  $\text{R}^3\text{SO}_2\text{NR}^3(\text{CH}_2)_{n-}$ ,  
 (p)  $\text{R}^3\text{R}^4\text{C}(\text{OH})(\text{CH}_2)_{n-}$ , or  
 (q)  $\text{C}_2\text{-C}_6$  alkenyl;
- 15 wherein n is 0, 1, or 2;  
 wherein  $\text{R}^4$  is  
 (a) H,  
 (b)  $\text{C}_1\text{-C}_3$  alkyl, or  
 (c) cyclopropyl.

20

3. The compound of claim 2

wherein  $\text{R}^2$  is

- (a)  $\text{R}^3$ ,  
 (b)  $\text{NC}(\text{CH}_2)_{n-}$ ,  
 25 (c)  $\text{R}^3\text{NHCO}(\text{CH}_2)_{n-}$ ,  
 (d)  $\text{R}^4\text{CO}(\text{CH}_2)_{n-}$ ,  
 (e)  $\text{F}(\text{CH}_2)_{n-}$ ,  
 (g)  $\text{Cl}(\text{CH}_2)_{n-}$ ,  
 (h)  $\text{R}^3\text{O}(\text{CH}_2)_{n-}$ ,  
 30 (i)  $\text{R}^3\text{S}(\text{CH}_2)_{n-}$ ,  
 (j)  $\text{R}^3\text{NH}(\text{CH}_2)_{n-}$ , or  
 (k)  $\text{R}^4\text{CONH}(\text{CH}_2)_{n-}$ .

4. The compound of claim 3 wherein Q is the moiety of formula II.
5. The compound of claim 1 selected from the group consisting of:
  1. (*S*)-*N*-[[3-[4-(5-Cyano-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  2. (*S*)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-carboxamide;
  3. (*S*)-*N*-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 10 4. (*S*)-*N*-[[3-[4-(5-Ethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  5. (*S*)-*N*-[[3-[3-Fluoro-4-(5-propyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  6. (*S*)-*N*-[[3-[4-[5-(Aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 15 7. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[[[(methylsulfonyl)amino]methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  8. (*S*)-*N*-[[3-[3-Fluoro-4-(5-fluoromethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 20 9. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  10. (*S*)-*N*-[[3-[4-(5-Acetoxymethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  11. (*S*)-*N*-[[3-[3-Fluoro-4-(5-hydroxymethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 25 12. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methoxymethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  13. (*S*)-*N*-[[3-[4-[5-(Cyanomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 30 14. (*S*)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetamide;
  15. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

16. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-oxobutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
17. (*5S*)-*N*-[[3-[3-Fluoro-4-[5-(3-hydroxybutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 5 18. (*S*)-Methyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-propanoate;
19. (*S*)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-propanamide;
20. (*S*)-*N*-[[3-[4-[5-(2-Cyanoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 21. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[(methylthio)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
22. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[(methylsulfinyl)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 23. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylthio)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
24. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylsulfinyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
25. (*S*)-Ethyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetate;
- 20 26. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
27. (*S*)-Ethyl 5-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-carboxylate;
- 25 28. (*5S*)-*N*-[[3-[3-Fluoro-4-[5-(2-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
29. (*S*)-*N*-[[3-[4-(4,5-Dihydro-5-oxo-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
30. (*S*)-*N*-[[3-[4-(5-Amino-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 30 31. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

32. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
33. (S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,2,4-thiadiazole-5-carboxamide;
- 5 34. (S)-N-[[3-[3-Fluoro-4-(1,2,4-thiadiazol-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
35. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
36. (S)-N-[[3-[3-Fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 37. (S)-3-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,2,4-oxadiazole-5-carboxamide;
38. (S)-N-[[3-[4-(5-Cyano-1,2,4-oxadiazol-3-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 39. (S)-N-[[3-[3-Fluoro-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
40. (S)-N-[[3-[3-Fluoro-4-(1,2,4-oxadiazol-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
41. (S)-N-[[3-[3-Fluoro-4-[5-(formylamino)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 42. (S)-N-[[3-[4-[5-(2-Chloroethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
43. (S)-N-[[3-[3-Fluoro-4-[5-(1-propenyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 44. (S)-N-[[3-[4-[5-(2-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
45. (S)-N-[[3-[4-[5-[2-(Acetylamino)ethyl]-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
46. (S)-N-[[3-[3-Fluoro-4-[5-[2-[(methylsulfonyl)amino]ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 30 47. (5S)-N-[[3-[3-Fluoro-4-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

48. (S)-N-[[3-[3-Fluoro-4-[5-(1-methylethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
49. (S)-N-[[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide;
- 5 50. (S)-N-[[3-[3-Fluoro-4-[5-(3-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
51. [S-(R\*,R\*)]-N-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
52. [S-(R\*,S\*)]-N-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 53. (S)-N-[[3-[3-Fluoro-4-[5-(2-nitroethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
54. (S)-N-[[3-[3-Fluoro-4-[5-(3-nitropropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 55. [S-(R\*,R\*)]-N-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
56. [S-(R\*,S\*)]-N-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
57. (S)-N-[[3-[4-[5-(3-Aminopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 58. (S)-N-[3-[5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]propyl]acetamide;
59. (S)-N-[[3-[4-(5-Acetyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 60. (S)-N-[[3-[4-[5-(3-Chloropropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
61. (S)-N-[[3-[4-[5-(3-Cyanopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
62. (S)-N-[[3-[3-Fluoro-4-[5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 30 63. (S)-N-[[3-[3-Fluoro-4-[5-[3-(hydroxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;



64. (S)-N-[[3-[3-Fluoro-4-[5-[2-(hydroxyimino)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
65. (S)-N-[[3-[3-Fluoro-4-[5-[3-(methoxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 5 66. (S)-N-[[5-[4-[5-[(Acetyloxyacetyl amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide;
67. (S)-N-[[5-[4-[5-[(Hydroxyacetyl amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl]acetamide;
68. (S)-N-[5-[4-[5-[(Acetyl amino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]-2-(acetyloxy)acetamide;
- 10 69. (S)-N-[[3-[3-Fluoro-4-[5-[(methylsulfonyl)methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
70. (S)-N-[[3-[3-Fluoro-4-[5-[2-(methylsulfonyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 71. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
72. (S)-N-[[3-[3-Fluoro-4-[5-(2-methoxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
73. (S)-N-[[3-[3-Fluoro-4-[5-(2-methoxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 74. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide;
75. (S)-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;
- 25 76. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanethioamide;
77. N-(((5S)-3-{4-[5-(aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]ethanethioamide;
78. 2-({[5-(4-{(5S)-5-[(ethanethioyl amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl} amino)-2-oxoethyl acetate; and
- 30 79. N-{[5-(4-{(5S)-5-[(ethanethioyl amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl}-2-hydroxyacetamide.

6. The compound of claim 5 which is
1. (S)-N-[[3-[4-(5-Cyano-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  2. (S)-N-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 5 3. (S)-N-[[3-[4-(5-Ethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  4. (S)-N-[[3-[4-[5-(Aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 10 5. (S)-N-[[3-[3-Fluoro-4-[5-[[[(methylsulfonyl)amino]methyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  6. (S)-N-[[3-[3-Fluoro-4-(5-fluoromethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  7. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 15 8. (S)-N-[[3-[4-(5-Acetoxymethyl-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  9. (S)-N-[[3-[3-Fluoro-4-(5-hydroxymethyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 20 10. (S)-N-[[3-[4-[5-(Cyanomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  11. (S)-5-[4-[5-[(Acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1,3,4-thiadiazole-2-acetamide;
  12. (S)-N-[[3-[3-Fluoro-4-[5-(3-oxobutyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 25 13. (S)-N-[[3-[4-[5-(2-Cyanoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  14. (S)-N-[[3-[3-Fluoro-4-[5-[2-(methylsulfinyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  - 30 15. (S)-N-[[3-[3-Fluoro-4-[5-(2-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
  16. (S)-N-[[3-[4-(4,5-Dihydro-5-oxo-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

17. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
18. (*S*)-*N*-[[3-[3-Fluoro-4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
- 5 19. (5*S*)-*N*-[[3-[3-Fluoro-4-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
20. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-hydroxypropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
21. [*S*-(*R*\*,*R*\*)]-*N*-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
- 10 22. [*S*-(*R*\*,*S*\*)]-*N*-[[3-[3-Fluoro-4-[5-(1-hydroxyethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
23. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(2-nitroethyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 24. (*S*)-*N*-[[3-[3-Fluoro-4-[5-(3-nitropropyl)-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
25. [*S*-(*R*\*,*R*\*)]-*N*-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
26. [*S*-(*R*\*,*S*\*)]-*N*-[[3-[4-[5-(1-Aminoethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 27. (*S*)-*N*-[[3-[4-[5-(3-Cyanopropyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
28. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[3-(hydroxyimino)butyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 25 29. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(hydroxyimino)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
30. (*S*)-*N*-[[3-[3-Fluoro-4-[5-[2-(methylsulfonyl)ethyl]-1,3,4-thiadiazol-2-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
31. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanamide;
- 30 32. (*S*)-*N*-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide;

33. (S)-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;
34. (S)-N-[[3-[3-Fluoro-4-(1,3,4-thiadiazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanethioamide;
- 5 35. N-(((5S)-3-{4-[5-(aminomethyl)-1,3,4-thiadiazol-2-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)ethanethioamide;
36. 2-({[5-(4-{(5S)-5-[(ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-1,3,4-thiadiazol-2-yl]methyl}amino)-2-oxoethyl acetate; or
37. N-{{5-(4-{(5S)-5-[(ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl)-1,3,4-thiadiazol-2-yl]methyl}-2-hydroxyacetamide.
- 10

# INTERNATIONAL SEARCH REPORT

Internat. Application No  
PCT/US 98/13437

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D417/10 C07D413/10 A61K31/42

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 A61K

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	WO 97 09328 A (PHARMACIA & UPJOHN COMPANY) 13 March 1997 see claims; examples 87,88 ---	1-4
A	WO 96 23788 A (PHARMACIA & UPJOHN COMPANY) 8 August 1996 cited in the application see claims ---	1-4
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A	WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 cited in the application see claims ---	1-4
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

7 October 1998

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/13437

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International Application No

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<b>(51) Internationale Patentklassifikation <sup>6</sup> :</b> <b>C07D 263/24, 263/20, A61K 31/42, C07D 413/04, 413/10, 491/04 // (C07D 491/04, 307:00, 221:00)</b>	<b>A1</b>	<b>(11) Internationale Veröffentlichungsnummer: WO 99/03846</b>  <b>(43) Internationales Veröffentlichungsdatum:</b> 28. Januar 1999 (28.01.99)
<b>(21) Internationales Aktenzeichen:</b> PCT/EP98/04252  <b>(22) Internationales Anmeldedatum:</b> 8. Juli 1998 (08.07.98)  <b>(30) Prioritätsdaten:</b> 197 30 847.3      18. Juli 1997 (18.07.97)      DE  <b>(71) Anmelder (für alle Bestimmungsstaaten ausser US):</b> BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE).  <b>(72) Erfinder; und</b> <b>(75) Erfinder/Anmelder (nur für US):</b> BARTEL, Stephan [DE/DE]; Margaretenhöle 7, D-51465 Bergisch Gladbach (DE). GUARNIERI, Walter [IT/DE]; Wiesenstrasse 3, D-53909 Zülpich (DE). RIEDL, Bernd [DE/DE]; Claudiusweg 7, D-42115 Wuppertal (DE). HÄBICH, Dieter [DE/DE]; Krummacherstrasse 82, D-42115 Wuppertal (DE). STOLLE, Andreas [DE/DE]; Pahlkestrasse 80, D-42115 Wuppertal (DE). RUPPELT, Martin [DE/DE]; Von-der-Goltz-Strasse 7, D-42329 Wuppertal (DE). RADDATZ, Siegfried [DE/DE]; Jakob-Böhme-Strasse 21, D-51065 Köln (DE). ROSENRETER, Ulrich [DE/DE]; Obere Rutenbeck 6, D-42349 Wuppertal (DE). WILD, Hanno [DE/DE]; Ausblick 128, D-42113 Wuppertal (DE).	<b>(74) Gemeinsamer Vertreter:</b> BAYER AKTIENGESELLSCHAFT; D-51368 Leverkusen (DE).  <b>(81) Bestimmungsstaaten:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, 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), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches 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, GW, ML, MR, NE, SN, TD, TG).  <b>Veröffentlicht</b> <i>Mit internationalem Recherchenbericht.</i>	

**(54) Title:** TRICYCLICALLY SUBSTITUTED OXAZOLIDINONES

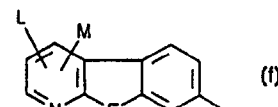
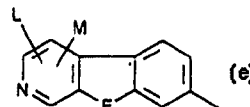
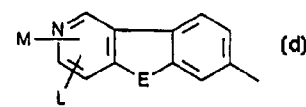
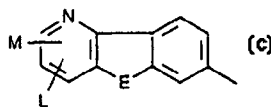
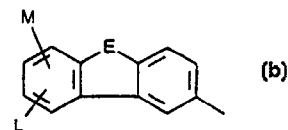
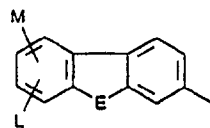
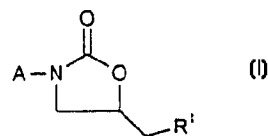
**(54) Bezeichnung:** TRICYCLISCH SUBSTITUIERTE OXAZOLIDINONE

**(57) Abstract**

The invention relates to tricyclically substituted oxazolidinones of general formula (I), wherein R<sup>1</sup> represents azido, hydroxy or a group of formula -OR<sup>2</sup>, O-SO<sub>2</sub>RO<sup>3</sup>, -(CO)<sub>a</sub>NR<sup>4</sup>R<sup>5</sup>, D-R<sup>6</sup> or -CO-R<sup>7</sup> and A represents a radical of formula (a), (b), (c), (d), (e), or (f) wherein E represents an oxygen or a sulphur atom, or the CO-, CH<sub>2</sub>-, SO- or SO<sub>2</sub> group, or a group of formula -NR<sup>14</sup>, C=NR<sup>15</sup> or -C=N-NR<sup>16</sup>R<sup>17</sup>. The invention also relates to a method for producing the tricyclically substituted oxazolidinones, and to their use as medicaments, especially as antibacterial medicaments.

**(57) Zusammenfassung**

Die vorliegende Erfindung betrifft tricyclisch substituierte Oxazolidinone der allgemeinen Formel (I) in welcher R<sup>1</sup> für Azido, Hydroxy oder für eine Gruppe der Formel -OR<sup>2</sup>, O-SO<sub>2</sub>R<sup>3</sup>, -(CO)<sub>a</sub>NR<sup>4</sup>R<sup>5</sup>, D-R<sup>6</sup> oder -CO-R<sup>7</sup> steht, A für einen Rest der Formel (a), (b), (c), (d), (e) oder (f) steht, worin E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet. Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.



### LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	ES	Spanien	LS	Lesotho	SI	Slowenien
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AZ	Aserbaidschan	GB	Vereinigtes Königreich	MC	Monaco	TD	Tschad
BA	Bosnien-Herzegowina	GE	Georgien	MD	Republik Moldau	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagaskar	TJ	Tadschikistan
BE	Belgien	GN	Guinea	MK	Die ehemalige jugoslawische Republik Mazedonien	TM	Turkmenistan
BF	Burkina Faso	GR	Griechenland			TR	Türkei
BG	Bulgarien	HU	Ungarn	ML	Mali	TT	Trinidad und Tobago
BJ	Benin	IE	Irland	MN	Mongolei	UA	Ukraine
BR	Brasilien	IL	Israel	MR	Mauretanien	UG	Uganda
BY	Belarus	IS	Island	MW	Malawi	US	Vereinigte Staaten von Amerika
CA	Kanada	IT	Italien	MX	Mexiko		
CF	Zentralafrikanische Republik	JP	Japan	NE	Niger	UZ	Usbekistan
CG	Kongo	KE	Kenia	NL	Niederlande	VN	Vietnam
CH	Schweiz	KG	Kirgisistan	NO	Norwegen	YU	Jugoslawien
CI	Côte d'Ivoire	KP	Demokratische Volksrepublik Korea	NZ	Neuseeland	ZW	Zimbabwe
CM	Kamerun			PL	Polen		
CN	China	KR	Republik Korea	PT	Portugal		
CU	Kuba	KZ	Kasachstan	RO	Rumänien		
CZ	Tschechische Republik	LC	St. Lucia	RU	Russische Föderation		
DE	Deutschland	LI	Liechtenstein	SD	Sudan		
DK	Dänemark	LK	Sri Lanka	SE	Schweden		
EE	Estland	LR	Liberia	SG	Singapur		

**Tricyclisch substituierte Oxazolidinone**

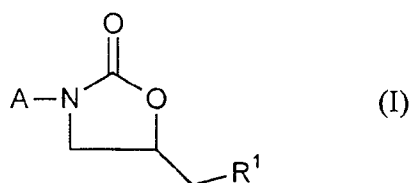
Die vorliegende Erfindung betrifft tricyclisch substituierte Oxazolidinone,  
 5 Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

Aus den Publikationen US 5 254 577, US 4 705 799, EP 311 090, US 4 801 600,  
 US 4 921 869, US 4 965 268, EP 312 000 und C.H. Park et al., J. Med. Chem.  
 35, 1156 (1992) sind N-Aryloxazolidinone mit antibakterieller Wirkung bekannt.  
 10 Außerdem sind 3-(Stickstoff-substituierte)phenyl-5-beta-amidomethyloxazolidin-2-one aus der EP 609 905 A1 bekannt.

Ferner werden in der PCT 93 08 179 A Oxazolidinonderivate mit einer Monoaminoxidase inhibitorischen Wirkung beschrieben.

Weitere bicyclisch substituierte Oxazolidinone mit antibakterieller Wirkung werden in unseren Anmeldungen EP 694 543, EP 694 544, EP 697 412 und EP  
 15 694 544, EP 697 412 und EP 738 726 beschrieben.

Die vorliegende Erfindung betrifft tricyclisch substituierte Oxazolidinone der allgemeinen Formel (I)



20 in welcher

R<sup>1</sup> für Azido, Hydroxy oder für eine Gruppe der Formel -OR<sup>2</sup>, O-SO<sub>2</sub>R<sup>3</sup>, -(CO)<sub>a</sub>NR<sup>4</sup>R<sup>5</sup>, D-R<sup>6</sup> oder -CO-R<sup>7</sup> steht,

worin

- R<sup>2</sup> geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet,
- R<sup>3</sup> 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,
- 5 a eine Zahl 0 oder 1 bedeutet,
- R<sup>4</sup> und R<sup>5</sup> 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,
- 10 oder
- R<sup>4</sup> oder R<sup>5</sup> eine Gruppe der Formel -CO-R<sup>8</sup> P(O)(OR<sup>9</sup>)(OR<sup>10</sup>) oder -SO<sub>2</sub>-R<sup>11</sup> bedeutet,
- 15 worin
- R<sup>8</sup> Cycloalkyl mit 3 bis 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Halogen substituiert ist, oder Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl oder Wasserstoff bedeutet,
- 20 oder
- geradkettiges oder verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert ist,
- 25 oder
- geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeutet,

oder

eine Gruppe der Formel  $-NR^{12}R^{13}$  bedeutet,

worin

5  $R^{12}$  und  $R^{13}$  gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,

oder

$R^8$  einen 5- bis 6-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeutet,

10  $R^9$  und  $R^{10}$  gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,

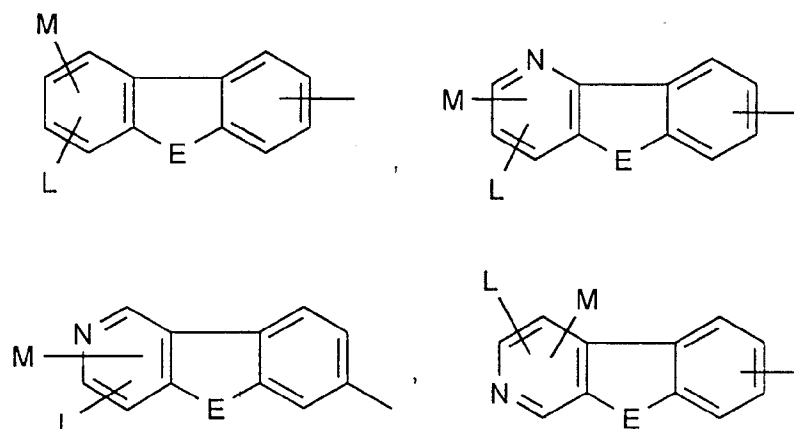
$R^{11}$  geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet,

15 D die Gruppe  $\begin{array}{c} \text{O} \\ || \\ -\text{C}-\text{O}- \end{array}$  oder  $\begin{array}{c} \text{O} \\ || \\ -\text{S}- \\ || \\ \text{O} \end{array}$  bedeutet,

$R^6$  Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen bedeutet,

20  $R^7$  Trifluormethyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet, das durch Halogen oder Trifluormethyl substituiert ist,

A für einen Rest der Formel



steht,

worin

5 E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet,

worin

10 R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> und R<sup>17</sup> gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeuten,

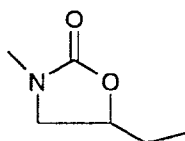
15 L und M gleich oder verschieden sind und Wasserstoff, Hydroxy, Carboxyl, Cyano, Halogen, Nitro, Formyl, Pyridyl, geradkettiges oder verzweigtes Alkyl, Acyl, Alkenyl, Alkoxy oder Alkoxy-carbonyl mit jeweils bis zu 8 Kohlenstoffatomen oder einen Rest der Formel -NR<sup>18</sup>R<sup>19</sup> bedeuten,

worin

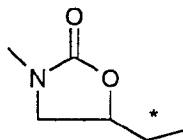
20 R<sup>18</sup> und R<sup>19</sup> gleich oder verschieden sind und die oben angegebene Bedeutung von R<sup>16</sup> und R<sup>17</sup> haben und mit dieser gleich oder verschieden sind,

und deren Salze.

Folgendes Formelschema veranschaulicht die entsprechend gekennzeichneten Schreibweisen für enantiomerenreine und racemische Formen:

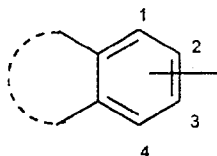


(A) (Racemat)



(B) (Enantiomer)

- 5 Im Rahmen der Erfindung kann das Oxazolidinongerüst an den heterocyclischen Rest über folgende Positionen angebunden werden:



Bevorzugt wird das Oxazolidinongerüst in den Positionen 2 und 3 angebunden. Besonders bevorzugt wird das Oxazolidinongerüst in der Position 3 angebunden.

- 10 Physiologisch unbedenkliche Salze der tricyclisch 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.
- 15

- 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, Ethyldiisopropyl-
- 20

amin, Prokain, Dibenzylamin, N-Methylmorpholin, Dihydroabietylamin, 1-Ephenamin oder Methyl-piperidin.

Als Salze können außerdem Reaktionsprodukte mit C<sub>1</sub>-C<sub>4</sub>-Alkylhalogeniden, insbesondere C<sub>1</sub>-C<sub>4</sub>-Alkyljodiden, fungieren.

- 5 Heterocyclus steht im allgemeinen für einen aromatischen 5- bis 6-gliedrigen 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.
- 10 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.

- 20 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.
- 25

- 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 als auch deren jeweilige Mischungen. Die
- 30



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

- 5      $R^1$    für Azido, Hydroxy oder für eine Gruppe der Formel  $-OR^2$ ,  $O-SO_2R^3$ ,  $-(CO)_aNR^4R^5$ ,  $D-R^6$  oder  $-CO-R^7$  steht,

worin

$R^2$    geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,

- 10      $R^3$    geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Phenyl oder TolyI bedeutet,

a     eine Zahl 0 oder 1 bedeutet,

$R^4$  und  $R^5$  gleich oder verschieden sind und

- 15     Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen oder tert.Butoxycarbonyl bedeuten,

oder

- 20      $R^4$  oder  $R^5$  eine Gruppe der Formel  $-CO-R^8$ ,  $P(O)(OR^9)(OR^{10})$  oder  $-SO_2-R^{11}$  bedeutet,

worin

$R^8$    Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl bedeutet, die gegebenenfalls durch Fluor, Chlor oder Brom substituiert sind, oder

Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl oder Wasserstoff bedeutet,

oder

5 geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder geradkettiges oder verzweigtes Thioalkyl oder Acyl mit  
 10 jeweils bis zu 5 Kohlenstoffatomen bedeutet, oder eine Gruppe der Formel  $-NR^{12}R^{13}$  bedeutet,

worin

$R^{12}$  und  $R^{13}$  gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,

15 oder

$R^8$  Isoxazolyl, Furyl, Thienyl, Pyrrol, Oxazolyl oder Imidazolyl bedeutet,

20  $R^9$  und  $R^{10}$  gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

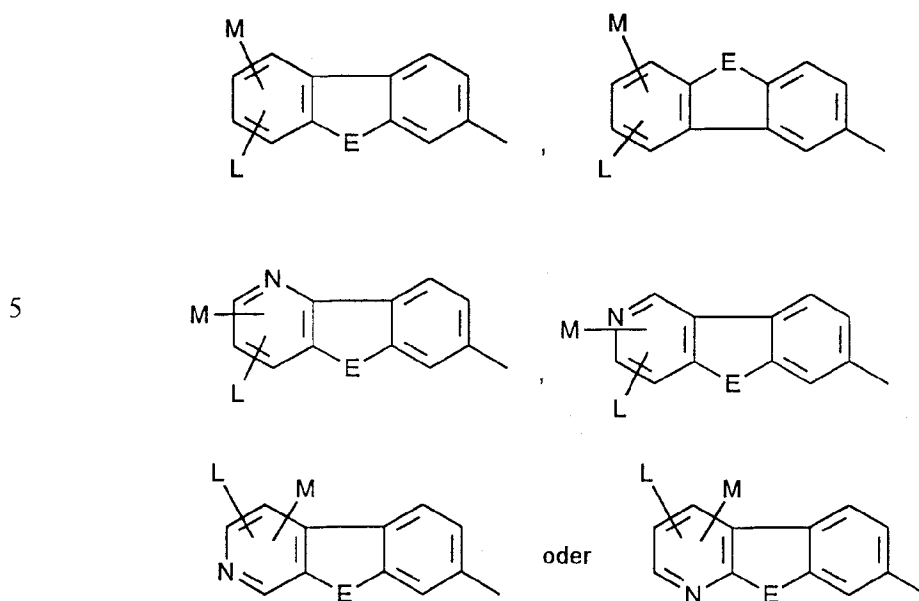
$R^{11}$  geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet,

D die Gruppe  $\begin{array}{c} \text{O} \\ || \\ -\text{C}-\text{O}- \end{array}$  oder  $\begin{array}{c} \text{O} \\ || \\ -\text{S}- \\ || \\ \text{O} \end{array}$  bedeutet,

25  $R^6$  Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,

R<sup>7</sup> Trifluormethyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet, das durch Fluor, Chlor, Brom oder Trifluormethyl substituiert ist,

A für einen Rest der Formel



E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet,

10

worin

R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> und R<sup>17</sup> gleich oder verschieden sind und Wasserstoff, oder geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeuten,

15

L und M gleich oder verschieden sind und Wasserstoff,

Carboxyl, Cyano, Fluor, Chlor, Brom, Nitro, Formyl, Pyridyl, geradkettiges oder verzweigtes Alkyl, Acyl, Alkenyl oder Alkoxy-carbonyl mit jeweils bis zu 7 Kohlenstoffatomen oder einen Rest der Formel  $-NR^{18}R^{19}$  bedeuten,

5 worin

$R^{18}$  und  $R^{19}$  gleich oder verschieden sind und die oben angegebene Bedeutung von  $R^{16}$  und  $R^{17}$  haben und mit dieser gleich oder verschieden sind,

und deren Salze.

10 Besonders bevorzugt sind Verbindungen der allgemeinen Formel (I),

in welcher

$R^1$  für Azido, Hydroxy oder für eine Gruppe der Formel  $-OR^2$ ,  $O-SO_2R^3$ ,  $-(CO)_aNR^4R^5$  oder  $-CO-R^7$  steht,

worin

15  $R^2$  geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet,

$R^3$  Methyl, Ethyl, Phenyl oder TolyI bedeutet,

a eine Zahl 0 oder 1 bedeutet,

20  $R^4$  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 oder tert.Butoxycarbonyl bedeuten,

oder

R<sup>4</sup> oder R<sup>5</sup> eine Gruppe der Formel -CO-R<sup>8</sup>, P(O)(OR<sup>9</sup>)(OR<sup>10</sup>) oder -SO<sub>2</sub>R<sup>11</sup> bedeutet,

worin

5 R<sup>8</sup> Cyclopropyl bedeutet, das gegebenenfalls durch Fluor substituiert ist, oder  
Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl oder Wasserstoff bedeutet,

oder

10 geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder  
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit  
15 jeweils bis zu 4 Kohlenstoffatomen bedeutet, oder  
eine Gruppe der Formel -NR<sup>12</sup>R<sup>13</sup> bedeutet,

worin

R<sup>12</sup> und R<sup>13</sup> gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

20 oder

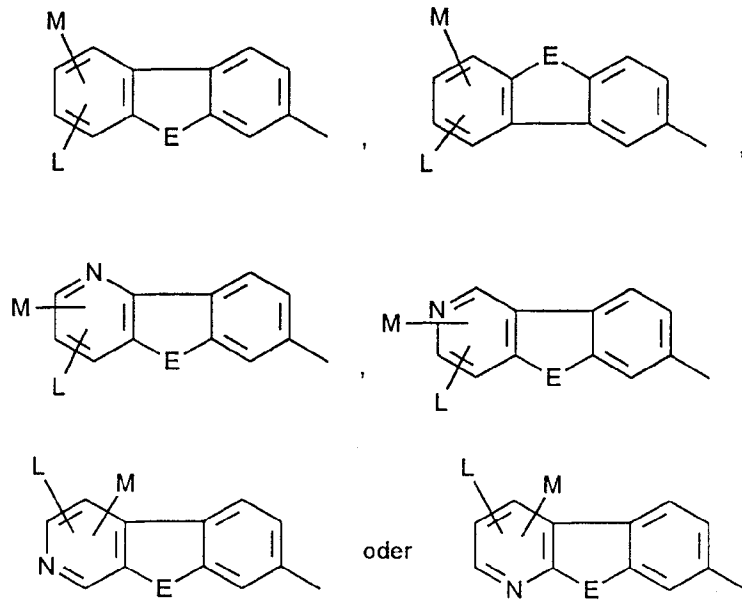
R<sup>8</sup> Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeutet,

R<sup>9</sup> und R<sup>10</sup> gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

R<sup>11</sup> Methyl oder Phenyl bedeutet,

25 R<sup>7</sup> Trifluormethyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeutet, das durch Fluor, Chlor, Brom oder Trifluormethyl substituiert ist,

A für einen Rest der Formel



steht,

worin

- 5 E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet,

worin

- 10 R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> und R<sup>17</sup> gleich oder verschieden sind und Wasserstoff, oder geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 3 Kohlenstoffatomen bedeuten,

L und M gleich oder verschieden sind und Wasserstoff,

- 15 Carboxyl, Cyano, Fluor, Chlor, Brom, Nitro, Formyl, Pyridyl, geradkettiges oder verzweigtes Alkyl, Acyl, Alkenyl oder Alkoxy-carbonyl mit jeweils bis zu 6 Kohlenstoffatomen oder einen Rest der Formel -NR<sup>18</sup>R<sup>19</sup> bedeuten,

worin

$R^{18}$  und  $R^{19}$  gleich oder verschieden sind und die oben angegebene Bedeutung von  $R^{16}$  und  $R^{17}$  haben und mit dieser gleich oder verschieden sind,

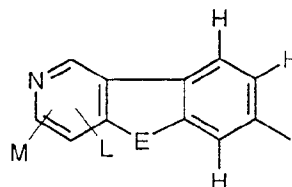
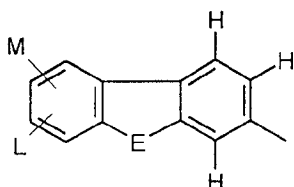
5 und deren Salze.

Ganz besonders bevorzugt sind erfindungsgemäße Verbindungen der allgemeinen Formel (I), in welcher

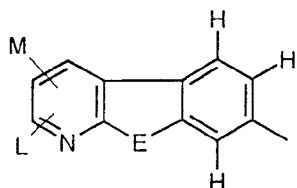
$R^1$  für einen Rest der Formel  $NH-CO-R^8$  steht, worin

10  $R^8$  geradkettiges oder verzweigtes Alkyl, Fluor- oder Chlor-substituiertes Alkyl, oder Alkoxy mit jeweils bis zu 4 Kohlenstoffatomen oder Cyclopropyl bedeutet;

A für einen Rest der Formel



oder



steht,

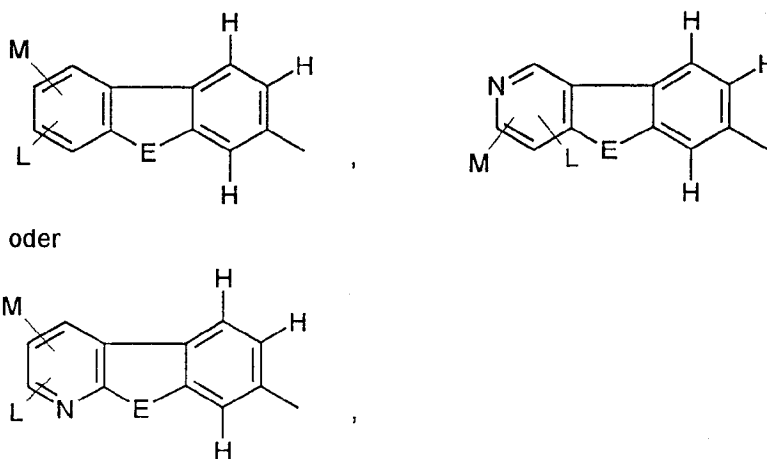
worin

15 E ein Sauerstoffatom oder die  $-CH_2-$ -Gruppe bedeutet,

L und M gleich oder verschieden sind und Wasserstoff, Pyridyl, Brom, Cyano, geradkettiges oder verzweigtes Alkenyl mit bis zu 5 Kohlenstoffatomen, Acetyl oder einen Rest der Formel  $-N(CH_3)_2$  bedeuten,

und deren Salze.

In den erfindungsgemäßen Verbindungen der allgemeinen Formel (I) steht der Substituent A besonders bevorzugt für einen Rest der Formel



5 worin

E ein Sauerstoffatom oder die  $-CH_2-$ -Gruppe bedeutet,

L und M gleich oder verschieden sind und Wasserstoff, Pyridyl, Brom, Cyano, geradkettiges oder verzweigtes Alkenyl mit bis zu 5 Kohlenstoffatomen, Acetyl oder einen Rest der Formel  $-N(CH_3)_2$  bedeuten.

10

In den erfindungsgemäßen Verbindungen der allgemeinen Formel (I) steht der Substituent  $R^1$  ganz besonders bevorzugt für einen Rest der Formel  $NH-CO-R^8$ ,  
worin

$R^8$  geradkettigen oder verzweigten Alkyl, Fluor- oder Chlor-substituiertes Alkyl oder Alkoxy mit jeweils bis zu 4 Kohlenstoffatomen oder Cyclopropyl bedeutet.

15

Außerdem wurden Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) gefunden, dadurch gekennzeichnet, daß man

[A] im Fall  $R^1 = OH$ ,



Verbindungen der allgemeinen Formel (II)



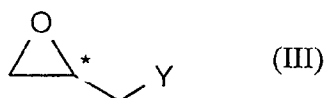
in welcher

A die oben angegebene Bedeutung hat

5 und

X für eine typische Carboxylschutzgruppe, vorzugsweise für Benzyl steht,

mit Epoxiden der allgemeinen Formel (III)



in welcher

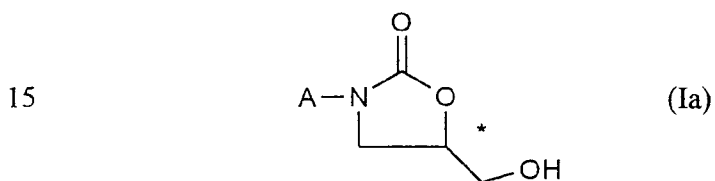
10 Y für C<sub>1</sub>-C<sub>6</sub>-Alkoxy-carbonyl steht,

in inerten Lösemitteln und in Anwesenheit einer Base umgesetzt,

oder

[B] im Fall R<sup>1</sup> ≠ OH

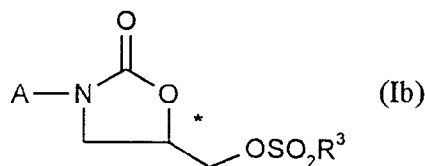
Verbindungen der allgemeinen Formel (Ia)



in welcher

A die oben angegebene Bedeutung hat,

durch Umsetzung mit (C<sub>1</sub>-C<sub>4</sub>)-Alkyl- oder Phenylsulfonsäurechloriden in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)



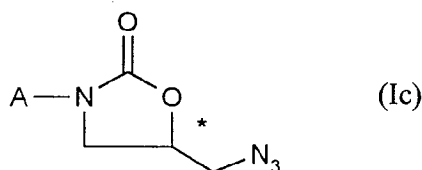
5 in welcher

A und R<sup>3</sup> die oben angegebene Bedeutung haben,

überführt,

anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (Ic)

10



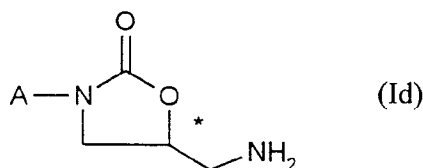
in welcher

A die oben angegebene Bedeutung hat,

herstellt,

15

diese in einem weiteren Schritt durch Umsetzung mit (C<sub>1</sub>-C<sub>4</sub>-Alkoxy)<sub>3</sub>-P oder PPh<sub>3</sub>, vorzugsweise (CH<sub>3</sub>O)<sub>3</sub>P in inerten Lösemitteln und mit Säuren in die Amine der allgemeinen Formel (Id)

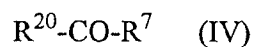


in welcher

A die oben angegebene Bedeutung hat,

überführt,

5 und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (IV)



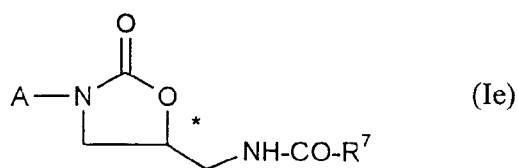
in welcher

$R^7$  die oben angegebene Bedeutung hat

und

10  $R^{20}$  für Halogen, vorzugsweise für Chlor oder für den Rest  $-OCOR^6$  steht,

in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



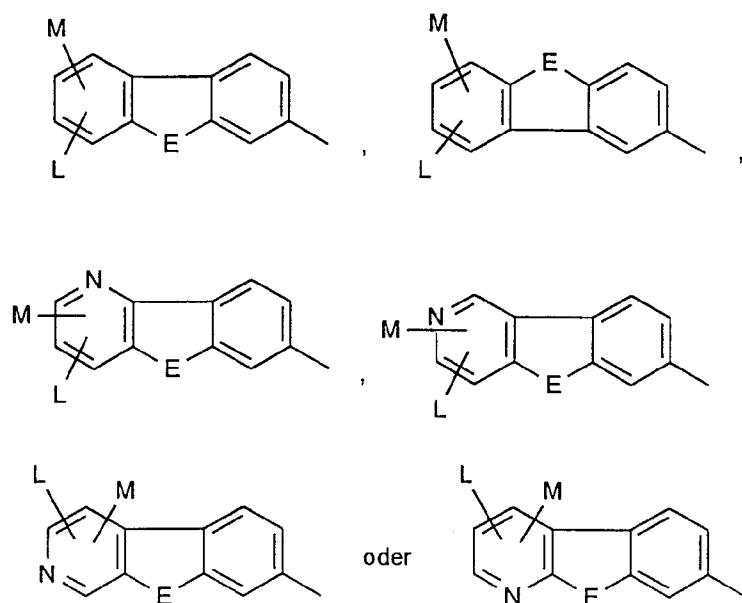
in welcher

A und  $R^7$  die oben angegebene Bedeutung haben,

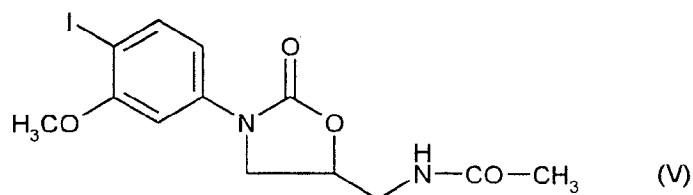
15 herstellt,

oder

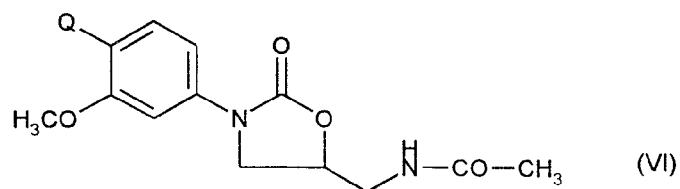
[C] im Fall, daß A für einen der oben aufgeführten Reste



zunächst die Verbindungen der Formel (V)



5 durch Umsetzung mit 2-Fluor- oder Chloro-pyridyltrimethylzinn-Verbindungen in Anwesenheit des Systems Bis(triphenylphosphin)palladium(II)chlorid / Cu(I)iodid in die Verbindungen der allgemeinen Formel (VI)



in welcher

Q für 2-Fluor- oder 2-Chlor-substituiertes Pyridyl steht,

10 überführt,

anschließend die Methoxygruppe in die freie Hydroxyfunktion überführt und in einem letzten Schritt eine Cyclisierung durchführt,

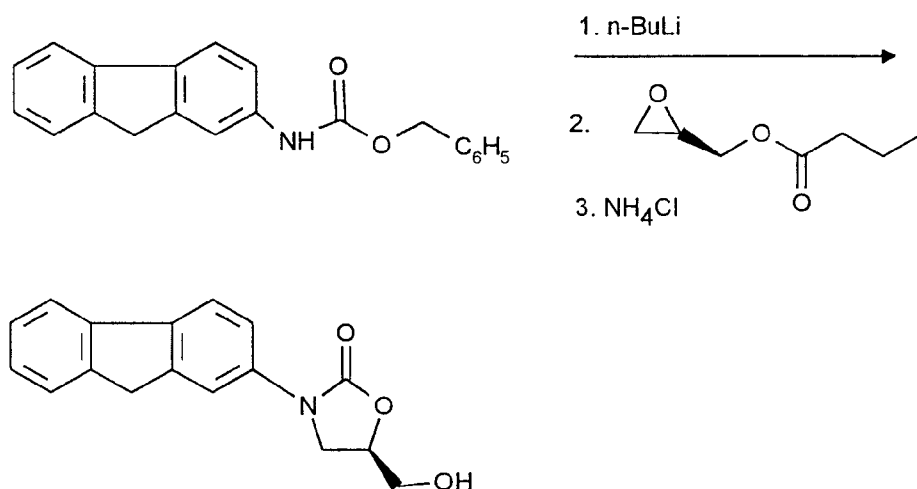
5 und im Fall  $E = SO_2$  oder  $SO$ , ausgehend von den entsprechenden amingschützten Verbindungen der allgemeinen Formel (I) mit  $E = S$ , eine Oxidation nach üblichen Methoden durchführt,

und im Fall  $L$  und/oder  $M = \text{Pyridyl}$  ebenfalls ausgehend von den entsprechenden geschützten, bromierten Aminen der allgemeinen Formel (I), eine Umsetzung mit Dialkyl-pyridylboranen durchführt,

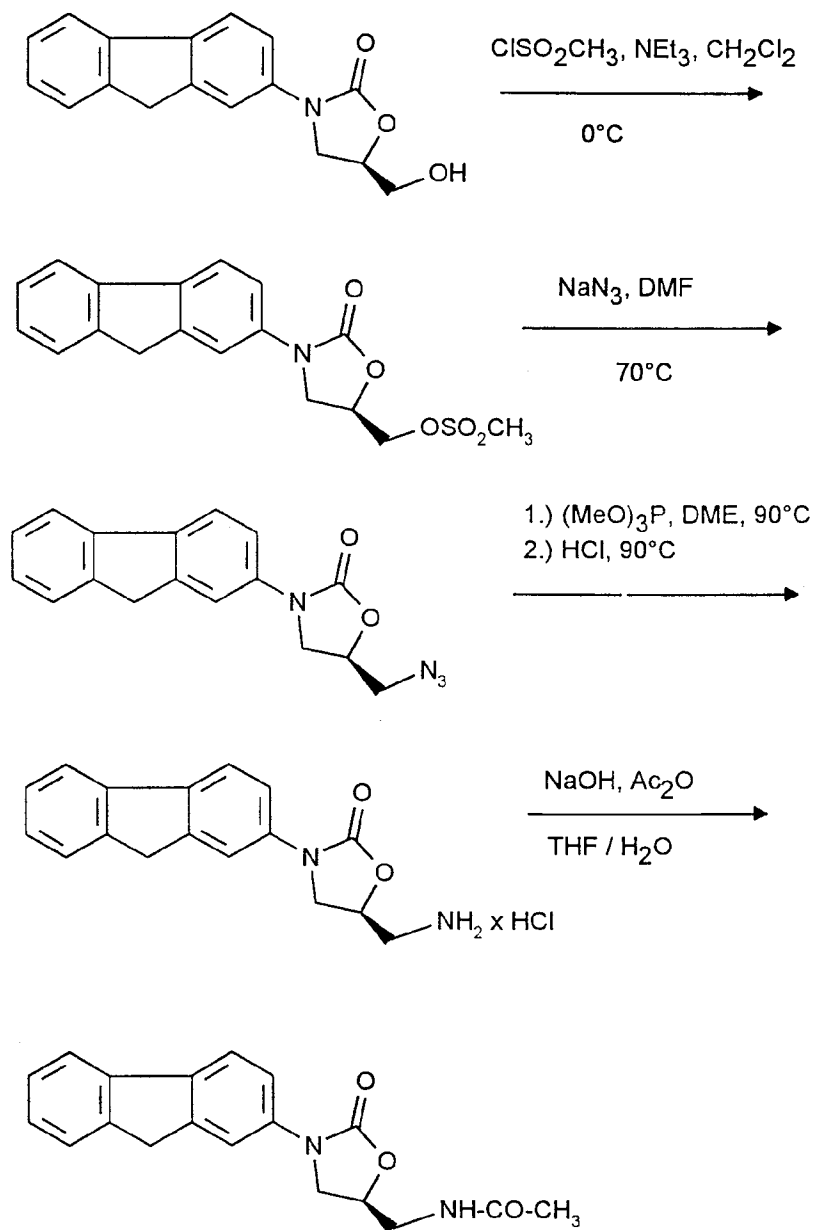
10 und gegebenenfalls die einzelnen Substituenten nach üblichen Methoden derivatisiert und/oder einführt.

Die erfindungsgemäßen Verfahren können durch folgende Formelschemata beispielhaft erläutert werden:

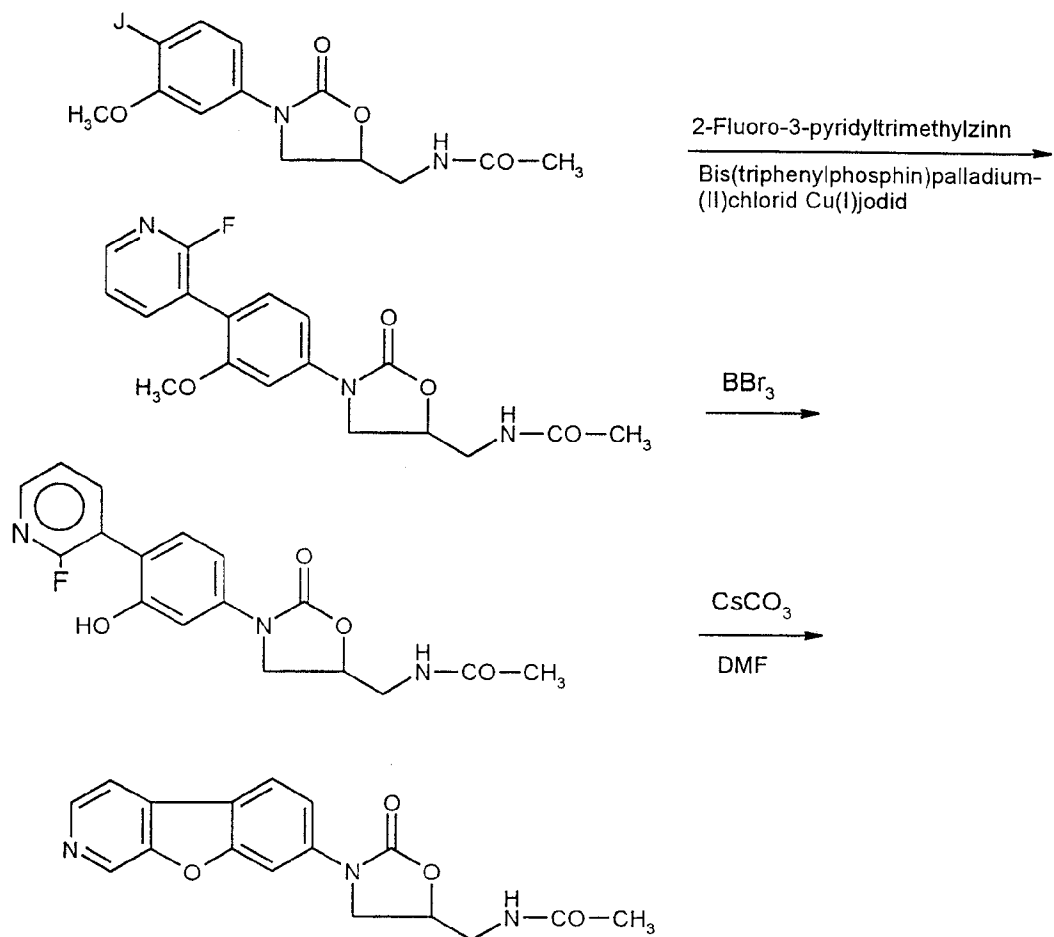
[A]



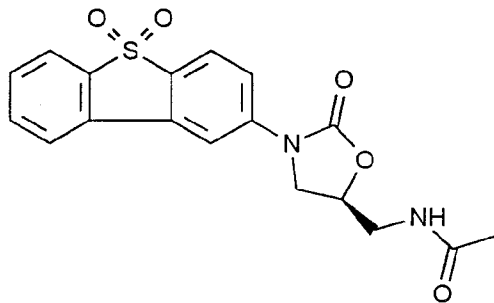
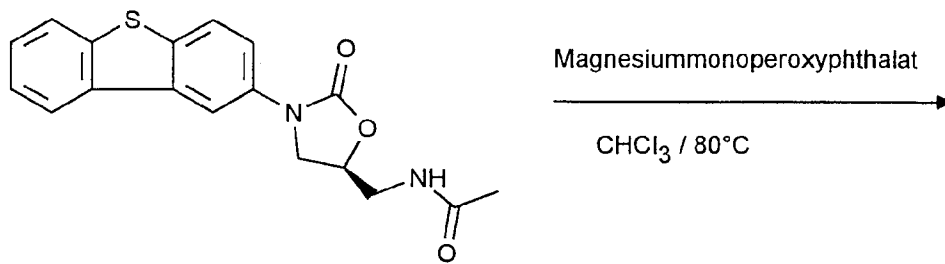
[B]



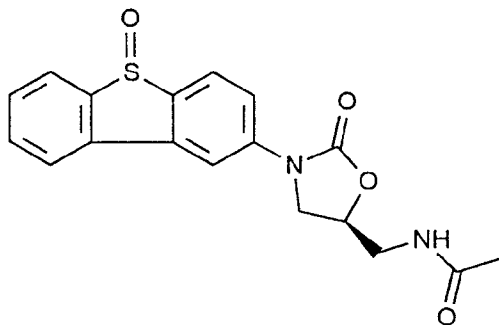
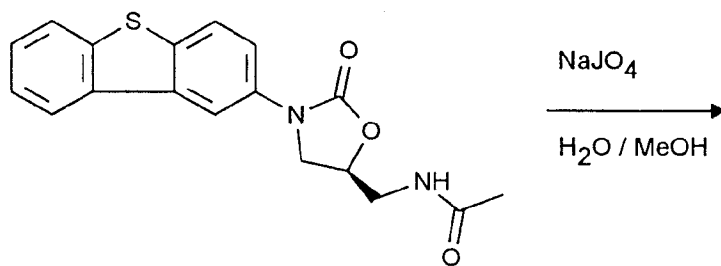
[C]



## Derivatisierungen

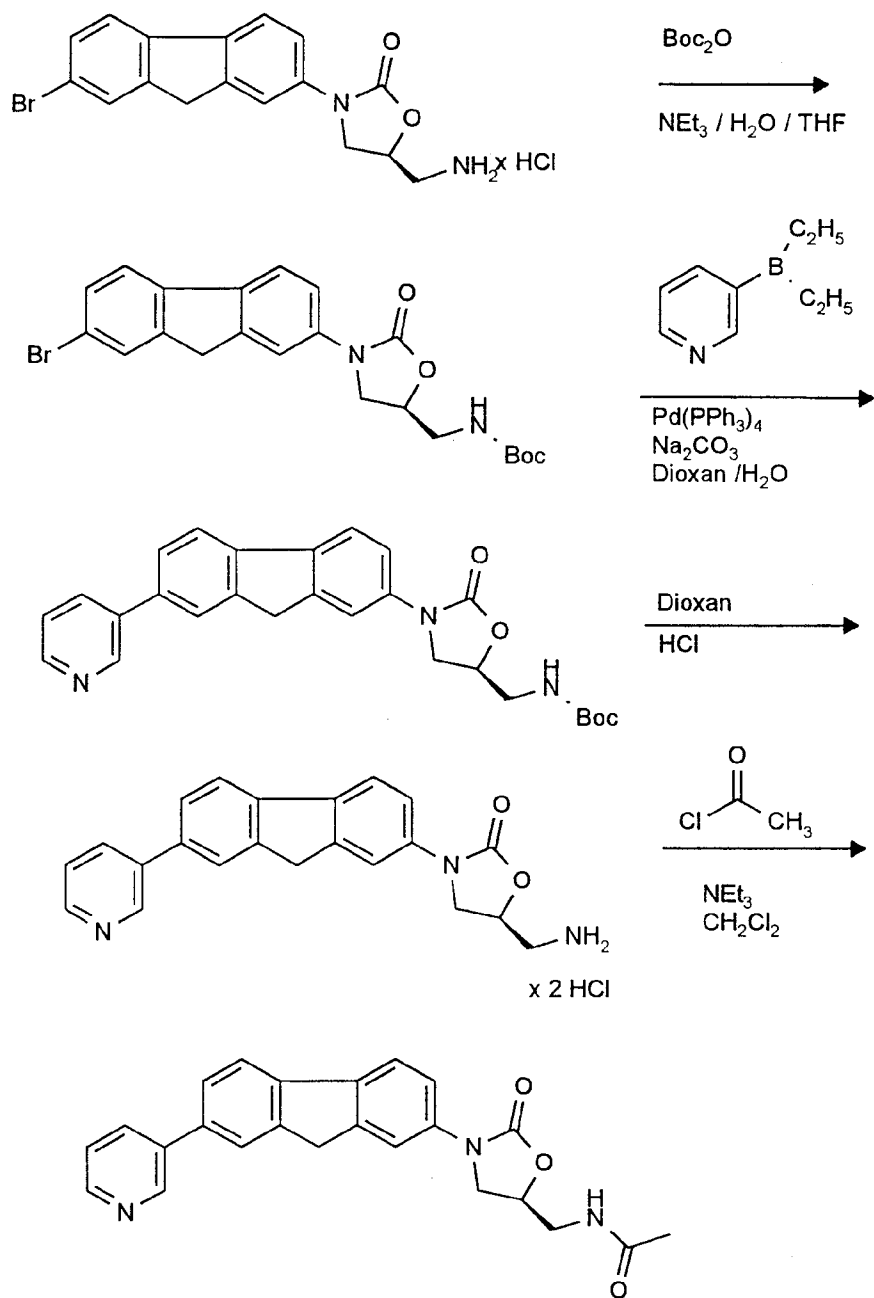


## Derivatisierungen

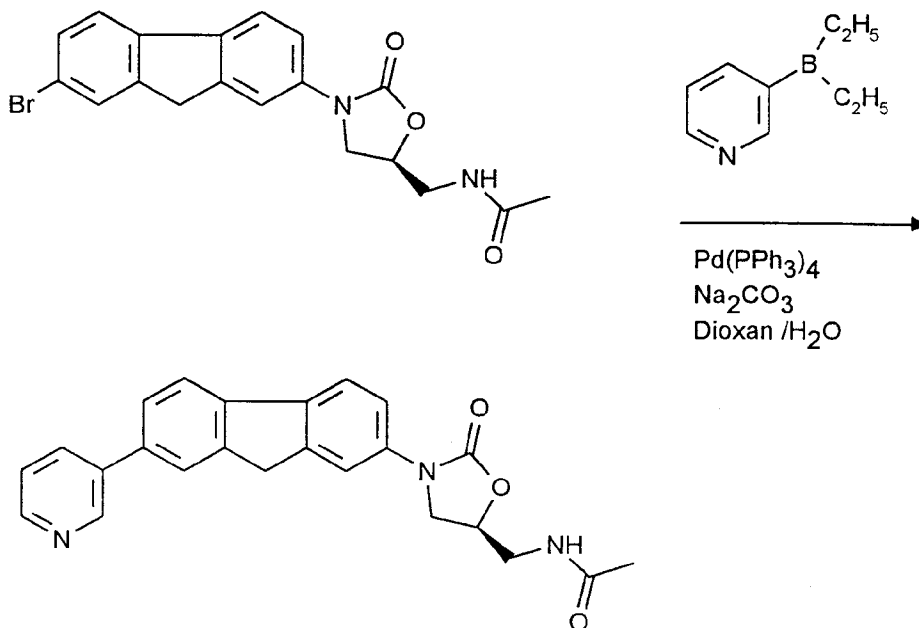




## Derivatisierungen



## Derivatisierungen



Als Lösemittel für das Verfahren [A] eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören 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 Kohlenwasserstoffe wie Hexan, Benzol, Dichlorbenzol, Xylol oder Toluol. Ebenso können Gemische der genannten Lösemittel verwendet werden. Bevorzugt sind Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether oder tert. Butylmethylether.

Das Verfahren [A] erfolgt mit Lithiumalkylverbindungen oder Lithium-N-silylamiden, wie beispielsweise n-Butyllithium, Lithiumdiisopropylamid oder Lithium-bis(trimethylsilyl)amid, vorzugsweise in Tetrahydrofuran in einem Temperaturbereich von -100°C bis +20°C, vorzugsweise von -75°C bis -40°C.

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 (II) eingesetzt.

Als Lösemittel für das Verfahren [B] eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören 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 Hexamethylphosphorsäuretriamid, 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. Bevorzugt sind Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether und tert. Butylmethylether.

Als Basen eignen sich die üblichen anorganischen oder organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat, oder Alkali-alkoholate wie beispielsweise Natrium- oder Kaliummethanolat, oder Natrium- oder Kaliummethanolat, 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 (Ia) 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 Reduktion der Azide erfolgt mit  $(\text{CH}_3\text{O})_3\text{P}$  und Salzsäure.

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 erfolgt im allgemeinen in einem Temperaturbereich von  $-50^{\circ}\text{C}$  bis zum jeweiligen Siedepunkt des Lösemittels, bevorzugt von  $-20^{\circ}\text{C}$  bis  $+90^{\circ}\text{C}$ .

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 vorzugsweise Boc mit Salzsäure in Dioxan, Fmoc mit Piperidin und Z mit HBr/HOAc oder durch Hydrogenolyse.

Die Oxidation zu den Verbindungen der allgemeinen Formel (I) mit  $\text{E} = \text{SO}_2$  verläuft im allgemeinen mit Oxidationsmitteln, wie beispielsweise meta-Chlorperbenzoesäure oder Magnesiummonoperoxyphthalat, vorzugsweise Magnesiumperoxyphthalat, in einem der oben aufgeführten Lösemittel, vorzugsweise

Chloroform in einem Temperaturbereich von 60°C bis 90°C, vorzugsweise bei 80°C und Normaldruck.

Die Oxidation zu den Verbindungen der allgemeinen Formel (I) mit E = SO verläuft im allgemeinen mit Oxidationsmitteln, wie beispielsweise meta-  
5 Chlorperbenzoesäure oder Natriumperjodat, vorzugsweise Natriumperjodat, in dem Lösemittelgemisch Wasser / Methanol, in einem Temperaturbereich von 0°C bis 50°C, vorzugsweise bei 20°C und Normaldruck.

Die Kupplungsreaktionen mit den Boronsäure- und Zinnarylverbindungen erfolgen ebenfalls in einem der oben aufgeführten Ether oder Kohlenwasserstoffe,  
10 vorzugsweise Tetrahydrofuran oder Toluol und in Anwesenheit eines Palladiumkomplexes.

Als Palladiumkomplexe eignen sich beispielsweise  $\text{Pd}[\text{P}(\text{C}_6\text{H}_5)_3]_4$ ,  $[(\text{C}_6\text{H}_5)_3\text{P}]_2\text{PdCl}$  oder  $(\text{C}_6\text{H}_5\text{CN})_2\text{PdCl}_2$ . Bevorzugt ist  $[(\text{C}_6\text{H}_5)_3\text{P}]_4\text{Pd}$ .

Die Umsetzung erfolgt in einem Temperaturbereich von Raumtemperatur bis  
15 150°C, vorzugsweise bei der Siedetemperatur des jeweiligen Lösemittels.

Die in Verfahrensvariante [C] verwendete Ankupplung von Trialkylzinn-Verbindungen an Verbindungen der Formel (V) erfolgt bevorzugt in Anwesenheit von Bis(triphenylphosphin)palladium(II) chlorid sowie von Cu(I)iodid oder Cu(I)oxid; als Lösungsmittel kann beispielsweise DMF verwendet werden. Die Umsetzung erfolgt in einem Temperaturbereich von Raumtemperatur bis zur Siedetemperatur  
20 des Lösungsmittels, bevorzugt bei 20°C bis 80°C, beispielsweise bei etwa 40°C.

Die Einführung des Pyridylrestes (Substituenten L/M) erfolgt im allgemeinen mit substituierten Dialkylpyridylboranen in Anwesenheit eines der oben aufgeführten Palladiumkomplexe, vorzugsweise  $\text{Pd}[\text{P}(\text{C}_6\text{H}_5)_3]_4$ , in einem Ether/Wassergemisch,  
25 vorzugsweise Dioxan/Wasser, in einem Temperaturbereich von 20°C bis 150°C, vorzugsweise bei 80°C und Normaldruck.

Die oben aufgeführten anderen Derivatisierungsreaktionen erfolgen im allgemeinen nach den in Compendium of Organic Synthetic Methods, T.T. Harrison und S. Harrison, Wiley Interscience, publizierten Methoden.

Bevorzugt werden Redoxreaktionen, reduktive Aminierung, Umesterung und die Halogenisierung von Methylgruppen mit N-Bromsuccinimid (NBS) oder N-Chlorsuccinimid (NCS) aufgeführt, die im folgenden beispielhaft erläutert werden.

5 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  
10 Lösemittel zu verwenden. Bevorzugt sind Dichlormethan, Dimethylsulfoxid und Dimethylformamid.

Die Alkylierung wird in den oben aufgeführten Lösemitteln bei Temperaturen von  
15 0°C bis +150°C, vorzugsweise bei Raumtemperaturen bis +100°C, bei Normaldruck durchgeführt.

Die Amidierung und die Sulfoamidierung erfolgen im allgemeinen in inerten Lösemitteln in Anwesenheit einer Base und eines Dehydratisierungsmittels.

20 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, Kohlenwasserstoffe wie Benzol, Xylol, Toluol, Hexan, Cyclohexan, oder Erdölfraktionen, Nitromethan, Dimethylformamid, Acetonitril oder Tetrahydrofuran. Ebenso ist es  
25 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  
30 Natriumcarbonat, Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natriummethanolat oder -ethanolat, Kaliummethanolat oder -ethanolat oder Kalium-

tert.-butylat, 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.

- 5 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  
10 allgemeinen in einer Menge von 1 bis 3 Mol, bevorzugt von 1 bis 1,5 Mol, bezogen auf 1 Mol der jeweiligen Carbonsäure, eingesetzt.

Als Dehydratisierungsreagenzien eignen sich Carbodiimide wie beispielsweise Diisopropylcarbodiimid, Dicyclohexylcarbodiimid oder N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimid-Hydrochlorid oder Carbonylverbindungen wie Carbonyldiimidazol oder 1,2-Oxazoliumverbindungen wie 2-Ethyl-5-phenyl-1,2-oxazolium-3-sulfonat oder Propanphosphorsäureanhydrid oder Isobutylchloroformat oder Benzotriazolyl-oxo-tris-(dimethylamino)phosphonium-hexafluorophosphat oder Phosphorsäurediphenylesteramid oder Methansulfonsäurechlorid, gegebenenfalls in Anwesenheit von Basen wie Triethylamin oder N-Ethylmorpholin oder N-Methylpiperidin oder 4-Dimethylaminopyridin.

20 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 wird Natriumhydroxid oder Kaliumhydroxid eingesetzt.

25 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.  
30 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.

5 Im allgemeinen wird die Verseifung bei Normaldruck durchgeführt. Es ist aber auch möglich, bei Unterdruck oder bei Überdruck zu arbeiten (z.B. von 0,5 bis 5 bar).

Bei der Durchführung der Verseifung wird die Base im allgemeinen in einer Menge von 1 bis 3 Mol, bevorzugt von 1 bis 1,5 Mol bezogen auf 1 Mol des Esters eingesetzt. Besonders bevorzugt verwendet man molare Mengen der Reaktanden.

10 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 (III) und (IV) sind an sich bekannt oder nach üblichen Methoden herstellbar.

15 Die Verbindungen der allgemeinen Formeln (Ia) - (Ie) sind neu und können wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (II) sind teilweise bekannt oder neu und können dann beispielsweise hergestellt werden, indem man

Verbindungen der allgemeinen Formel (VII)

20  $A-NH_2$  (VII)

in welcher

A die oben angegebene Bedeutung hat,

mit Chlorameisensäureethylester in Anwesenheit einer Base, vorzugsweise Natriumhydrogencarbonat im System Wasser / Tetrahydrofuran in einem  
25 Temperaturbereich von -10°C bis +200°C, vorzugsweise bei Raumtemperatur und Normaldruck umgesetzt.



Die Verbindungen der allgemeinen Formel (VII) sind an sich bekannt oder nach üblichen Methoden herstellbar.

Die Herstellung der Verbindungen der allgemeinen Formel (V) erfolgt im allgemeinen in einem Temperaturbereich von 0°C bis +60°C, vorzugsweise bei 40°C und Normaldruck.

Die Freisetzung der Hydroxyfunktion erfolgt in Dichlorethan in Anwesenheit von  $\text{BBr}_3$  bei Raumtemperatur und Normaldruck.

Die Cyclisierung erfolgt im allgemeinen in einem der oben aufgeführten Lösemittel, vorzugsweise Dimethylformamid (DMF), in Anwesenheit von Caesiumcarbonat bei Raumtemperatur und Normaldruck.

Die Verbindungen der allgemeinen Formeln (V) und (VI) sind an sich bekannt oder nach üblichen Methoden herstellbar.

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 Konzentration des Wirkstoffes enthielten. Die Agarplatten wurden mit einem Multipoint-Inokulator (Denley) beimpft. Zum Beimpfen wurden Übernachtskulturen 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 ( $\mu\text{g/ml}$ ) gibt die niedrigste Wirkstoffkonzentration an, bei der mit bloßem Auge kein Wachstum zu erkennen war.

MHK-Werte ( $\mu\text{g/ml}$ ):

Bsp.-Nr.	S.aureus 133	S.aureus 48N	S. aureus 25701	S.aureus 9TV	E. coli Neumann	Klebsiella pneumoniae	Pseudomonas aeruginosa W
62	0,5	0,5	0,5	0,25	>64	>64	>64
63	1	1	1	0,25	>64	>64	>64
64	1	1	1	0,5	>64	>64	>64
66	1	1	1	0,5	>64	>64	>64
67	1	1	1	0,5	>64	>64	>64
68	0,5	0,5	0,5	<0,25	>64	>64	>64
73	0,5	0,5	0,5	<0,25	>64	>64	>64
74	0,25	1	0,5	0,25	>64	>64	>64
75	1	1	0,5	0,25	>64	>64	>64
77	0,5	0,5	0,25	0,5	>64	>64	>64
78	1	1	0,25	0,5	>64	>64	>64
83	1	1	1	0,5	>64	>64	>64
84	1	1	1	1	>64	>64	>64

Bsp.-Nr.	S.aureus 133	S.aureus 48N	S. aureus 25701	S.aureus 9TV	E. coli Neumann	Klebsiella pneumoniae	Pseudomonas aeruginosa W
87	1	1	1	0,5	>64	>64	>64
88	0,25	0,5	0,5	0,25	>64	>64	>64
89	0,5	0,5	0,5	0,5	>64	>64	>64
104	1	1	1	1	>64	>64	>64
121	1	1	1	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 0,1Vol.-% 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 ( $\mu\text{g/ml}$ )****Keim: Mycobacterium smegmatis**

Bsp.-Nr.	DSM 43061	DSM 43465
63	8	4
68	32	16
73	32	16
77	8	4
78	16	16
83	2	1
87	2	2
88	1	0,25
89	1	0,5
90	4	4
99	8	>64
100	1	0,5
101	8	16
103	4	4
104	2	2
106	4	4
121	4	2
125	8	8

Die erfindungsgemäßen Verbindungen der allgemeinen Formel (I) weisen bei geringer Toxizität ein breites antibakterielles Spektrum, speziell gegen gram-positive Bakterien sowie Mycobacterien, Haemophilus influenzae und anaerobe Keime. Diese Eigenschaften ermöglichen ihre Verwendung als chemotherapeutische Wirkstoffe in der Human- und Tiermedizin.

5

Besonders wirksam sind die erfindungsgemäßen Verbindungen gegen Bakterien und bakterienähnliche 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.

10

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 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:

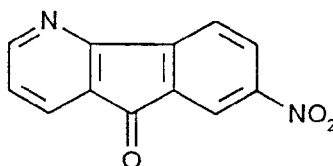
- I     Dichlormethan / Methanol  
II    Dichlormethan  
5    III   Dichlormethan / Petrolether

Abkürzungen:

	Boc	tert. Butyloxycarbonyl
	DMF	Dimethylformamid
	$\text{Pd}(\text{P}(\text{C}_6\text{H}_5)_3)_4$	Tetrakis(triphenylphosphin)palladium
10	BuLi	Butyllithium
	LiHMDS	Lithiumhexamethyldisilazan
	Ph	Phenyl
	Me	Methyl
	THF	Tetrahydrofuran

Ausgangsverbindungen**Beispiel I**

7-Nitro-4-azafluorenon



- 5 18 g (0,1 mol) 4-Azafluorenon werden in 44 ml Eisessig, 44 ml konzentrierter Schwefelsäure und 48 ml rauchender Salpetersäure gelöst und drei Stunden auf 100°C erwärmt. Der abgekühlte Ansatz wird auf Eiswasser gegeben, die entstandenen Kristalle abgesaugt, in Natriumcarbonat-Lösung verrührt und gründlich mit Wasser und Eisessig gewaschen.
- 10 Ausbeute: 20 g (88% d.Th.)  
Schmp.: 181-184°C  
 $R_f = 0,45$  (I, 100:1)

Analog zum Beispiel I werden die in Tabelle I aufgeführten Verbindungen hergestellt:

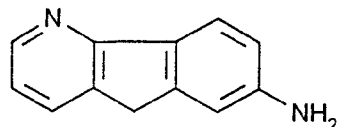
15 **Tabelle I:**

Bsp.-Nr.	Struktur	Ausbeute (% d.Th.)	Fp. (°C)	$R_f$
II		86	203-205	0,35 (I, 100:1)



**Beispiel III**

## 7-Amino-4-azafluoren



5,74 g (0,025 mol) 7-Nitro-4-azafluoren werden mit 9 ml Hydrazinhydrat in 50 ml Diethylenglykol zunächst 15 Minuten auf 100°C und anschließend eine Stunde auf 195°C erwärmt. Das auf ca. 80°C abgekühlte Gemisch wird auf Eiswasser gegeben, die Kristalle werden isoliert, in Essigester aufgenommen, die organische Phase über Natriumsulfat getrocknet und einrotiert. Das Rohprodukt wird an Kieselgel (Laufmittel Dichlormethan : Methanol 100:5) gereinigt.

10 Ausbeute: 2 g (37% d.Th.)

$R_f = 0,32$  (I, 100:5)

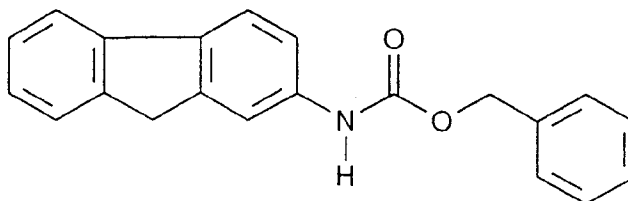
Analog zum Beispiel III werden die in Tabelle II aufgeführten Verbindungen hergestellt:

**Tabelle II:**

Bsp.-Nr.	Struktur	Ausbeute (% d.Th.)	Smp. (°C)	$R_f$
IV		70%	198-200	0,53 (I, 9:1)

**Beispiel V**

## 2-Benzyloxycarbonylaminofluoren



1,99 g (0,011 mol) 2-Aminofluoren werden in 12 ml Wasser, 24 ml gesättigter Natriumhydrogencarbonatlösung und 24 ml THF bei 0°C vorgelegt. Anschließend werden 1,76 ml (0,012 mol) Chlorameisensäureethylester zugetropft und eine Stunde bei Raumtemperatur nachgerührt. Der Ansatz wird mit Essigester versetzt, die organische Phase abgetrennt, mit Wasser gewaschen, über Natriumsulfat getrocknet und einrotiert.

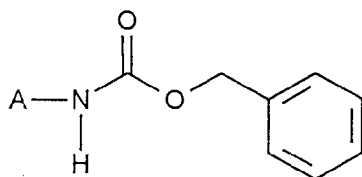
Ausbeute: 3,1 g (91% d.Th.)

Schmp.: 142-144°C

R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>): 0,63

10 Analog zum Beispiel V werden die in der Tabelle III aufgeführten Verbindungen hergestellt:

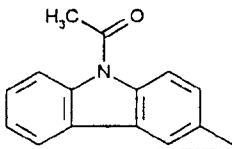
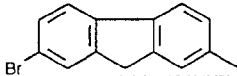
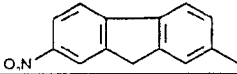
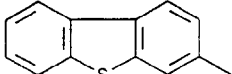
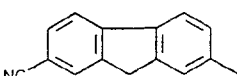
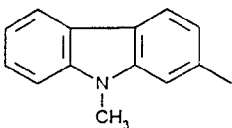
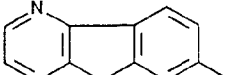
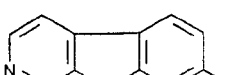
Tabelle III:



15

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
VI		70	128-130	0,5 (II)
VII		96	155-158	0,77 (I, 100:2)
VIII		97	120-122	0,8 (II)
IX		73	151-153	0,45 (II)
X		95	165-167	0,85 (I, 100:5)
XI		97	146-148	0,71 (II)

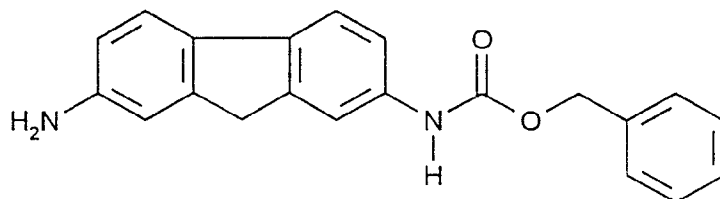
20

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
XII		95	83-85	0,56 (I, 100:1)
XIII		99	163-165	0,33 (II)
XIV		92	204-207	0,91 (III, 2:1)
XV		64	135-137	0,63 (II)
XVI		80	183-185	0,40 (II)
XVII		51	147-149	0,45 (II)
XVIII		84	168-170	0,29 (I, 100:5)
XIX		36	-	0,28 (I, 100:5)

5

**Beispiel XX**

10 2-Amino-7-benzyloxycarbonylamino-fluoren



15

24,86 g (0,069 mol) der in Beispiel XIV erhaltenen Verbindung werden in 460 ml Ethanol, 120 ml Wasser und 4,8 g Calciumchlorid zum Rückfluß erhitzt. Anschließend werden 142,6 g (2,07 mol) Zink-Staub portionsweise zugegeben und eine Stunde Rückfluß gekocht. Es wird heiß filtriert und eingeeignet. Das

Rohprodukt wird in Methanol / Dichlormethan 1:3 verrührt. Der erhaltene Feststoff wird isoliert und getrocknet. Die Mutterlauge wird einrotiert und der Rückstand an Kieselgel (Laufmittel: CH<sub>2</sub>Cl<sub>2</sub> / MeOH 100:5) gereinigt.

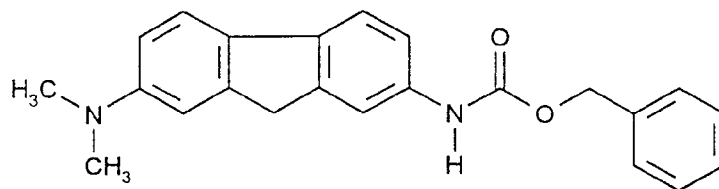
Ausbeute: 14 g (61% d.Th.)

5 Schmp.: 155-157°C

R<sub>f</sub> (I, 100:5): 0,64

### Beispiel XXI

2-Benzoyloxycarbonylamino-7-dimethylamino-9-fluoren



10 7 g (0,0224 Mol) der in Beispiel XX erhaltenen Verbindung werden mit 5,6 ml (0,07 mol) einer 30% Formaldehydlösung in 70 ml Methanol vorgelegt. Zu dieser Suspension wird eine Lösung aus 1,47 g (0,0224 mol) Natriumcyanoborhydrid und 1,54 g (0,0112 mol) Zinkchlorid in 70 ml Methanol gegeben. Es wird zwei Stunden bei Raumtemperatur nachgerührt, mit 140 ml 0,1 N Natronlauge und

15 Essigester versetzt, die organische Phase abgetrennt, über Natriumsulfat getrocknet und einrotiert. Das erhaltene Rohprodukt wird an Kieselgel (Laufmittel: Dichlormethan) gereinigt.

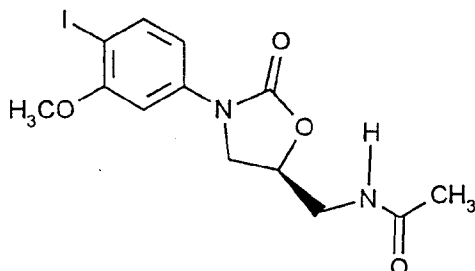
Ausbeute: 4,4 g (55% d.Th.)

Schmp.: 170-173°C

20 R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>): 0,17

**Beispiel XXII**

(5S)-3-(3-Methoxy-4-iodophenyl)-5-acetaminomethyl-2-oxazolidinon



5 Zu einer Suspension von (5S)-(3-Methoxyphenyl)-5-acetylaminomethyl-2-oxazolidinon (J. Med. Chem. 1992, 35; 264 mg, 1,0 mmol), Silberacetat (250 mg, 1,5 mmol), Dichlormethan (30 ml) und Acetonitril (20 ml) wird eine Lösung aus Iod (254 mg, 1,0 mmol) in Dichlormethan (25 ml) gegeben. Nach 16 h wird mit Wasser und Dichlormethan versetzt, die wäßrige Phase mit Dichlormethan extrahiert, die vereinigten organischen Phasen mit ges. NaCl-Lösung gewaschen, über MgSO<sub>4</sub> getrocknet und die Lösemittel in Vakuum abgezogen.

10 Ausbeute: 370 mg (95% d.Th.)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 7,70 (d, 1H); 7,42 (d, 1H); 6,60 (dd, 1H); 6,25 (bt, 1H); 4,78 (m, 1H); 4,05 (t, 1H); 3,89 (s, 3H); 3,50 - 3,85 (m, 3H); 2,00 (s, 3H).

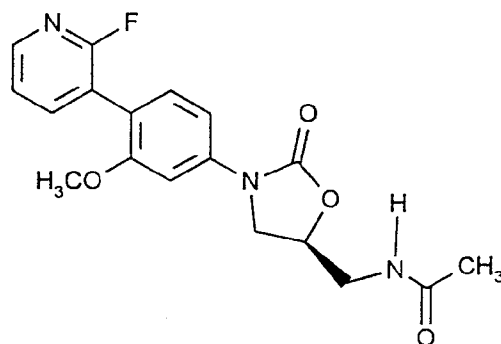
15 Analog der Vorschrift des Beispiel XXII werden die in Tabelle IV aufgeführten Verbindungen hergestellt:

**Tabelle IV:**

Bsp.-Nr.	Struktur	Ausbeute (% d.Th.)	R <sub>f</sub>
XXIII		90	0,33

**Beispiel XXIV**

(5S)-3-(4-(2-Fluoro-3-pyridyl)-3-methoxyphenyl)-5-acetaminomethyl-2-oxazolidinon



5 Eine Mischung der Verbindung aus Beispiel XXII (780 mg; 2,0 mmol) gelöst in 20 ml DMF, (2-Fluoro-3-pyridyl)trimethylzinn (Tetrahedron 1994, 50, 2454; 926 mg; 2,4 mmol) und Bis(triphenylphosphin)palladium(II)chlorid (83,6 mg; 0,12 mmol) wird mit Kupfer(I)iodid (24,2 mg, 0,18 mmol) versetzt und 17 h bei 40°C gerührt. Zur Aufarbeitung wird über Celite filtriert, und das Rohprodukt durch Chromatographie gereinigt.

Ausbeute: 450 mg (63%)

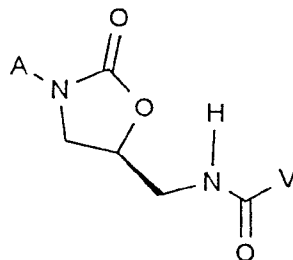
$R_f$  (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 10:1) = 0,34

MS (ESI): m/z = 360 (M+H<sup>+</sup>)

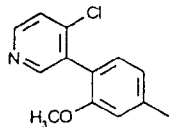
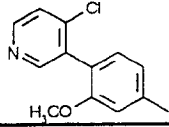
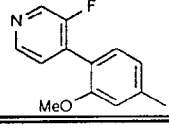
15 <sup>1</sup>H-NMR (D<sub>6</sub>-DMSO): 8,20 (m, 2H); 7,95 (t, 1H); 7,45 (m, 2H); 7,30 (d, 1H); 7,15 (dd, 1H); 4,70 (m, 1H); 4,25 (t, 1H); 3,85 (dd, 1H); 3,80 (s, 3H); 3,45 (t, 2H); 1,95 (s, 3H).

In Analogie zur Vorschrift des Beispiels XXIV wurden die in der Tabelle V aufgeführten Verbindungen dargestellt:

**Tabelle V:**

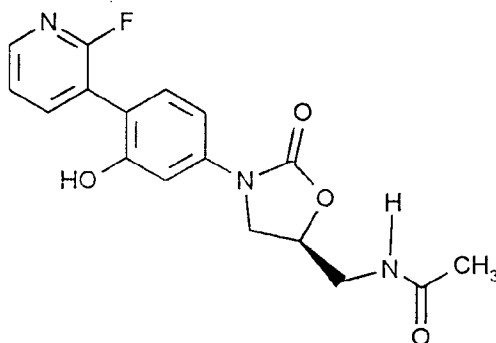


20

Bsp.-Nr.	A	V	Ausbeute (% d.Th.)	R <sub>f</sub> (I)
XXV		CH <sub>3</sub>	30	0,28 (10:1)
XXVI		OCH <sub>3</sub>	44	0,31 (100:5)
XXVII		CH <sub>3</sub>	33	0,14 (10:1)

5 **Beispiel XXVIII**

(5S)-3-(4-(2-Fluoro-3-pyridyl)-3-hydroxyphenyl)-5-acetaminomethyl-2-oxazolidinon



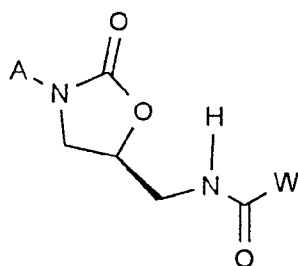
10 Eine Lösung der Verbindung aus Beispiel XXIV (285 mg; 0,8 mmol) in Dichlormethan (10 ml) wird bei -25°C mit BBr<sub>3</sub> (1 M in Dichlormethan, 5,55 ml, 5,55 mmol) versetzt und anschließend weitere 14 h bei Raumtemperatur gerührt. Das Reaktionsgemisch wird auf Puffer-Lösung (pH = 7) gegeben, mit NaCl gesättigt und mit Essigester extrahiert (3 x). Die organische Phase wird über Natriumsulfat getrocknet und die Lösemittel im Vakuum abgezogen.

Ausbeute: 220 mg (79% d.Th.)

15 <sup>1</sup>H-NMR (D<sub>6</sub>-DMSO): δ = 9,90 (s, 1H); 8,25 (t, 1H); 8,15 (d, 1H); 7,90 (t, 1H); 7,85 (m, 1H); 7,20 (d, 1H); 6,95 (d, 1H); 4,70 (m, 1H); 4,10 (t, 1H); 3,70 (m, 1H); 3,35 (m, 2H).

In Analogie zur Vorschrift des Beispiels XXVIII werden die in der Tabelle VI aufgeführten Verbindungen hergestellt:

Tabelle VI:



5

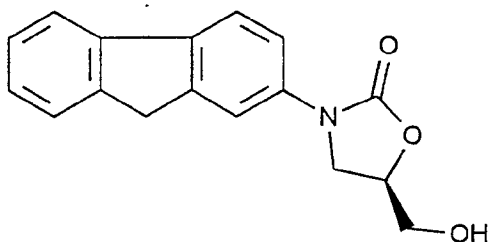
Bsp.-Nr.	A	W	Ausbeute (% d.Th.)	R <sub>f</sub> (I)
XXIX		CH <sub>3</sub>	91	0,17 (10:1)
XXX		OCH <sub>3</sub>	46	0,19 (100:5)
XXXI		CH <sub>3</sub>	81	0,33 (10:1)



## Herstellungsbeispiele

### Beispiel 1

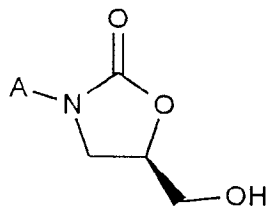
(5R)-3-(2-Fluorenyl)-5-hydroxymethyl-oxazolidin-2-on



- 5 3,15 g (0,01 mol) der im Beispiel V erhaltenen Verbindung werden in 40 ml THF p.a. bei  $-78^{\circ}\text{C}$  unter Argon vorgelegt. Es werden 4 ml (0,01 mol) 2,5 molare Butyllithiumlösung in Hexan und anschließend 1,4 ml (0,01 mol) (R)-Buttersäure-2,3-epoxypropylester zugetropft. Man läßt auf Raumtemperatur kommen und rührt fünf Stunden nach. Der Ansatz wird mit gesättigter Ammoniumchloridlösung und
- 10 Essigester gequench, zusätzlich mit Dichlormethan / Methanol versetzt und die organische Phase wird abgetrennt. Der nach dem Trocknen und Einrotieren erhaltene Rückstand wird in Methanol verrührt und die erhaltenen Kristalle getrocknet.  
Ausbeute: 2 g (71% d.Th.)  
Schmp.:  $230-234^{\circ}\text{C}$
- 15  $R_f$  (I, 9:1) : 0,5

Analog zum Beispiel 1 konnten die in Tabelle 1 aufgeführten Verbindungen aus den entsprechenden Benzyloxycarbonylaminoverbindungen erhalten werden.

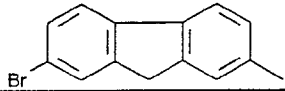
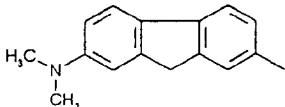
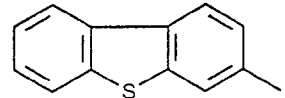
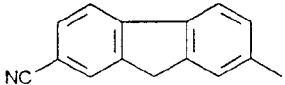
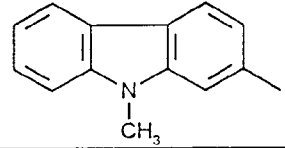
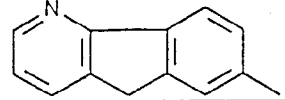
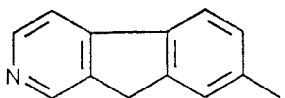
Tabelle 1:



5

Bsp.-Nr.	A	Base	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
2		BuLi	78	170-172	0,28 (I, 100:5)
3		BuLi	60	195-197	0,24 (I, 100:5)
4		BuLi	68	180-182	0,29 (I, 100:5)
5		BuLi	Rohprodukt	231-233	0,32 (I, 100:5)
6		LiHMDS	61	225-227	0,31 (I, 100:5)
7		LiHMDS	83	228-230	0,26 (I, 100:5)
8		BuLi	88	178-180	0,33 (I, 100:5)
9		LiHMDS	53	218-221	0,19 (I, 100:5)

10

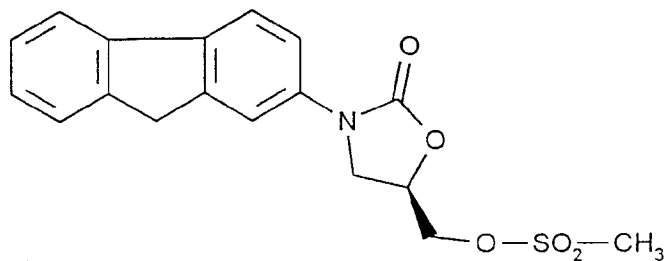
Bsp.- Nr.	A	Base	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
10		LiHMDS	67	198-200	0,33 (1, 100:5)
11		LiHMDS	46	235-238	0,38 (1, 100:5)
12		BuLi	86	257-259	0,32 (1, 100:5)
13		LiHMDS	78	-	0,27 (1, 100:5)
14		BuLi	95	-	0,29, (1, 100:5)
15		LiHMDS	64	208-210	0,24 (1, 100:5)
16		LiHMDS	35	175-177	0,15 (1, 100:5)

5

**Beispiel 17**

(5R)-3-(2-Fluorenyl)-5-(methansulfonyloxymethyl)-oxazolidin-2-on

10



9,8 g (0,035 mol) der in Beispiel 1 erhaltenen Verbindung werden mit 9,6 ml (0,069 mol) Triethylamin in 200 ml Dichlormethan vorgelegt. Bei 0°C werden 5

5 ml (0,065 mol) Methansulfonylchlorid zugetropft und 20 Minuten bei 0°C und fünf Stunden bei Raumtemperatur nachgerührt. Das Reaktionsgemisch wird eingengt, der Rückstand zweimal in Dichlormethan / Methanol aufgekocht, die vereinigten Filtrate mit Wasser gewaschen, über Natriumsulfat getrocknet und

einrotiert. Das erhaltene Rohprodukt wird an Kieselgel (Laufmittel: Dichlormethan / Methanol 100:2) gereinigt.

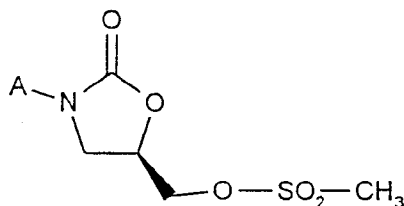
Ausbeute: 8,3 g (66% d.Th.)

Schmp.: 183-186°C

R<sub>f</sub> (I, 100:2): 0,35

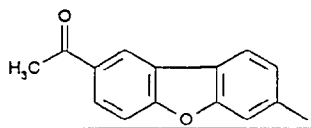
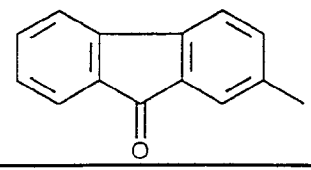
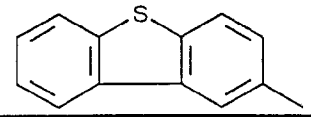
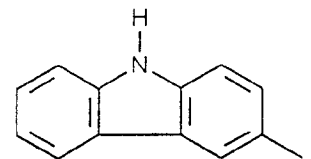
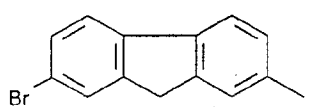
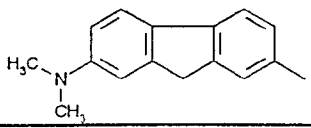
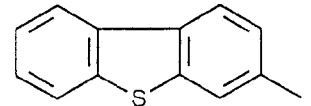
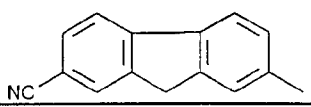
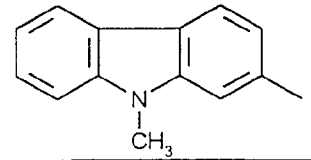
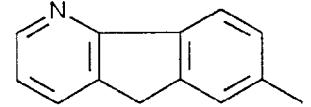
10 Analog zum Beispiel 17 werden die in Tabelle 2 aufgeführten Verbindungen erhalten:

Tabelle 2:



15

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
18		88	-	0,33 (I, 100:2)
19		70	195-199	0,65 (I, 100:5)
20		quant.	170-172	0,59 (I, 100:5)
21		Rohprodukt	-	0,48 (I, 100:2)

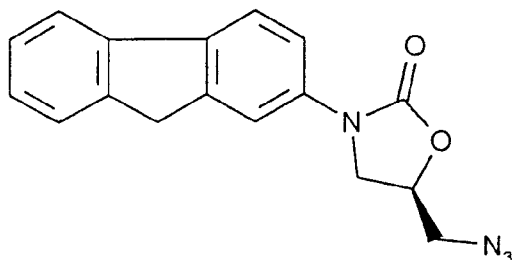
Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
22		86	207-210	0,70 (I, 100:5)
23		97	199-202	0,75 (I, 100:5)
24		93	175-177	0,74 (I, 100:5)
25		Rohprodukt	-	-
26		98	170-172	0,69 (I, 100:5)
27		58	235-238	0,64 (I, 100:5)
28		quant.	218-220	0,71 (I, 100:5)
29		71	191-194	0,61 (I, 100:2)
30		98	-	0,57 (I, 100:5)
31		93	195-197	0,57 (I, 100:5)

5

10

**Beispiel 32**

(5R)-3-(2-Fluorenyl)-5-azidomethyl)-oxazolidin-2-on



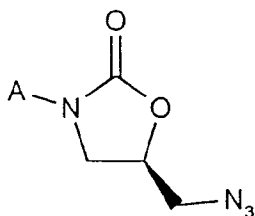
8,23 g (0,023 mol) der Verbindung aus Beispiel 17 werden mit 1,94 g (0,03 mol) Natriumazid in 27 ml DMF unter Argon zwei Stunden bei 70°C gerührt. Das abgekühlte Reaktionsgemisch wird auf Eiswasser gegeben, und der ausfallende Feststoff isoliert. Das erhaltene Rohprodukt wird mit Methanol verrieben und mit Ether gewaschen.

Ausbeute: 6,9 g (98% d.Th.)

Schmp.: 152-155°C

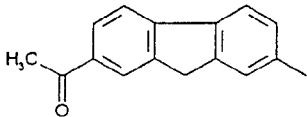
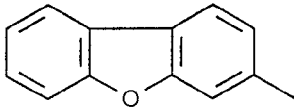
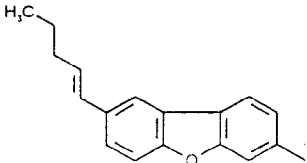
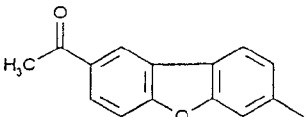
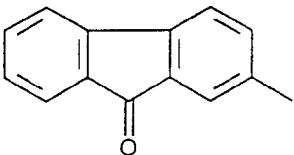
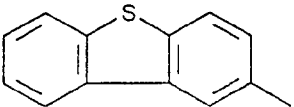
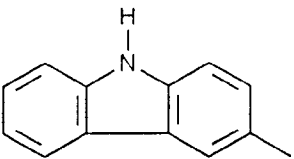
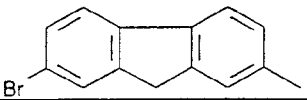
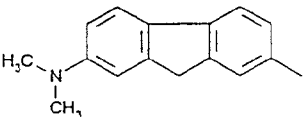
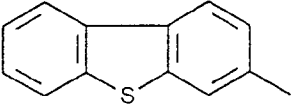
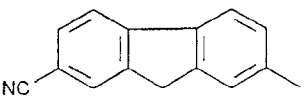
R<sub>f</sub> (I, 100:2): 0,75

Analog zu Beispiel 32 werden die in Tabelle 3 aufgeführten Verbindungen synthetisiert:

**Tabelle 3:**

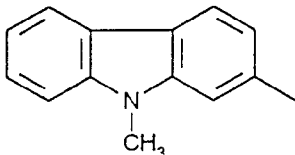
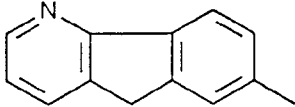
15

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
33		87	-	0,69 (I, 100:2)

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
34		98	168-170	0,60 (I, 100:5)
35		89	161-163	0,30 (II)
36		quant.	-	0,8 (I, 100:2)
37		96	168-170	0,81 (I, 100:5)
38		89	148-151	0,14 (II)
39		94	Öl	0,78 (I, 100:2)
40		55	208-210	0,59 (I, 100:2)
41		91	198-200	0,91 (I, 100:2)
42		77	190-193	0,7 (I, 100:2)
43		92	159-162	0,56 (I, 100:1)
44		96	198-200	0,67 (I, 100:2)

5

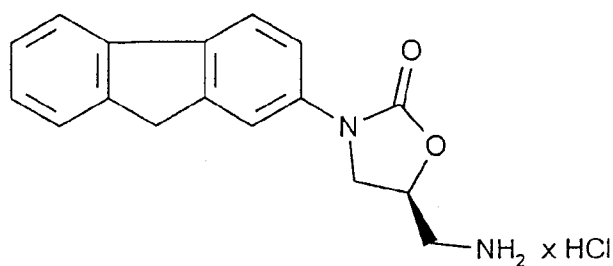
10

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
45		96	-	0,8 (I, 100:2)
46		100	158-160	0,64 (I, 100:5)

**Beispiel 47**

(5S)-3-(2-Fluorenyl)-5-(aminomethyl)-oxazolidin-2-on Hydrochlorid

5



10

5,48 g (0,0179 mol) der Verbindung aus Beispiel 32 werden in 30 ml Ethylenglykoldimethylether auf 50°C erwärmt. Bei dieser Temperatur werden langsam 2,5 ml (0,021 mol) Trimethylphosphit zugetropft. Anschließend wird 30 Minuten bei 100°C nachgerührt. Nach Zugabe von 3,58 ml 6 N Salzsäure wird nochmals eine Stunde bei 100°C nachgerührt und auf Raumtemperatur abgekühlt. Die ausgefallenen Kristalle werden isoliert, mit Methanol / Ether versetzt, isoliert und nochmals mit Methanol verrieben.

Ausbeute: 3,5 g (48% d.Th.)

Schmp.: 293-296°C (unter Zersetzung)

15

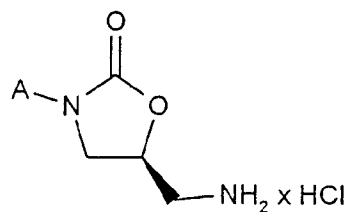
R<sub>f</sub> (I, 9:1): 0,29

Die säulenchromatographische Reinigung der Mutterlauge liefert nochmals 800 mg des freien Amins (12%), Schmp.: 173-175°C.

Analog zum Beispiel 47 werden die Verbindungen der Tabelle 4 hergestellt:



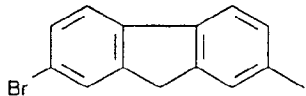
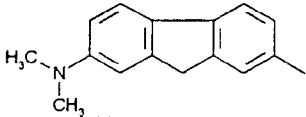
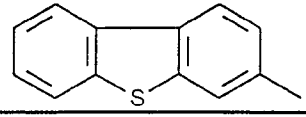
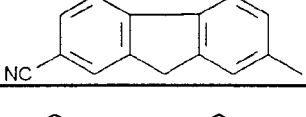
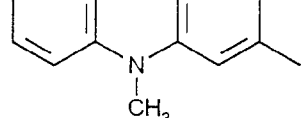
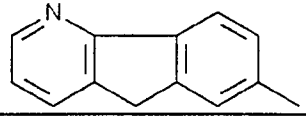
Tabelle 4:



Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
48		91	-	0,32 (I, 9:1)
49		60	>280	0,38 (I, 9:1)
50		55	>270	0,38 (I, 2:1)
51		50	255-258	0,16 (I, 100:5)
52		97	>260	0,43 (I, 2:1)
53		66	240-244	0,21 (I, 9:1)
54		68	249-252	0,45 (I, 2:1)
55		quant.	215-218	0,32 (I, 2:1)

5

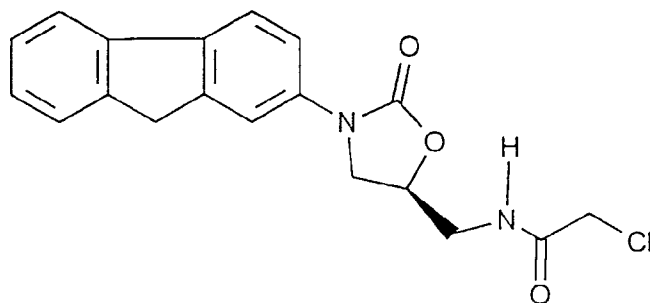
10

Bsp.-Nr.	A	Ausbeute (% d.Th.)	Schmp. (°C)	R <sub>f</sub> *
56		76	>260	0,34 (I, 2:1)
57		88	245	0,54 (I, 2:1)
58		80	>260	0,35 (I, 9:1)
59		68	>260	0,20 (I, 9:1)
60		67	>260	0,54 (I, 2:1)
61		94	231-234 (Z)	0,27 (I, 2:1)

5

**Beispiel 62**

(5S)-3-(2-Fluorenyl)-5-(chlor-acetylaminoethyl)-oxazolidin-2-on



10 316 mg (1 mmol) der Verbindung aus Beispiel 54 werden mit 0,3 ml (2,2 mmol) Triethylamin in 15 ml Dichlormethan vorgelegt und 0,08 ml (1 mmol) Chloracetylchlorid zugetropft. Es wird drei Stunden bei Raumtemperatur nachgerührt, mit Wasser und Dichlormethan versetzt, die organische Phase abgetrennt und ein-

rotiert. Das Rohprodukt wird an Kieselgel (Laufmittel: Dichlormethan / Methanol 100:5) gereinigt. Das erhaltene Produkt wird in Dichlormethan / Ether verrieben.

Ausbeute: 216 mg (60% d.Th.)

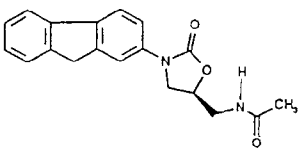
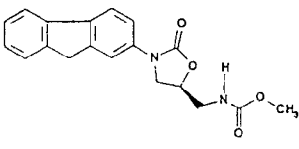
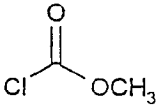
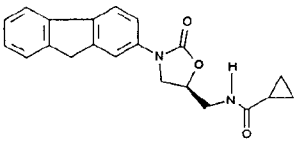
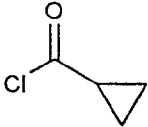
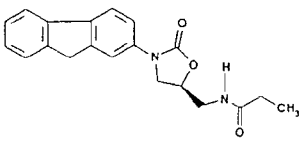
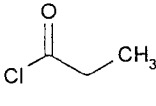
Schmp.: 208-210°C

5  $R_f$  (I, 100:5): 0,43

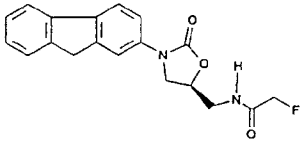
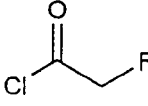
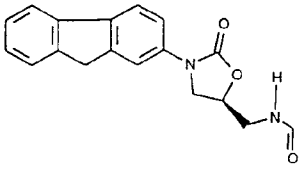
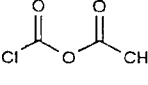
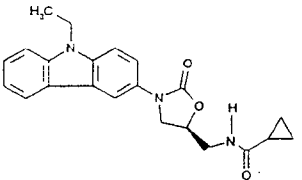
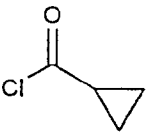
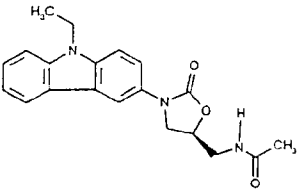
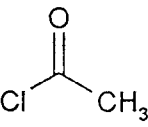
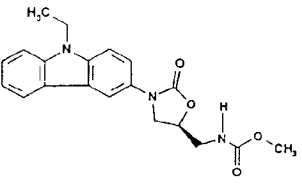
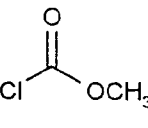
Analog zum Beispiel 62 werden bei der Umsetzung der Amine (Beispiele 27-39) mit den angegebenen Acetylierungsmitteln die in Tabelle 5 aufgeführten Verbindungen erhalten:

Tabelle 5:

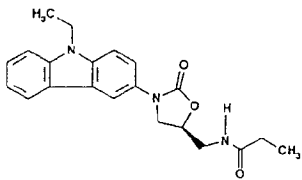
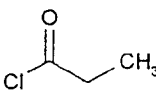
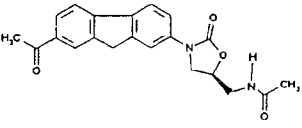
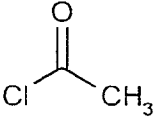
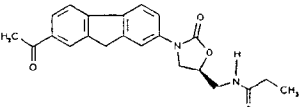
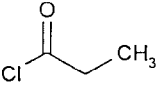
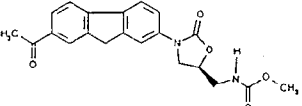
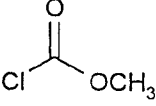
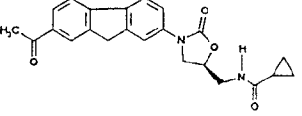
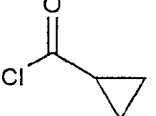
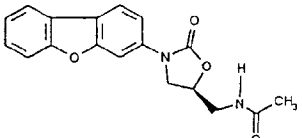
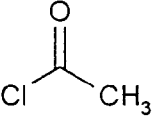
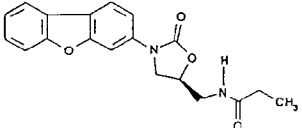
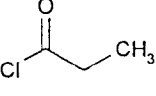
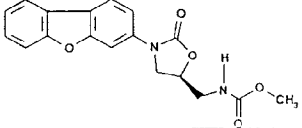
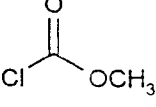
10

Bsp.-Nr.	Struktur	Acetylierungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	$R_f$
63		Ac <sub>2</sub> O	62	208-210	0,44 (I, 100:5)
64			26	190-192	0,16 (I, 100:2)
65			62	235-237	0,28 (I, 100:5)
66			64	220-222	0,16 (I, 100:5)

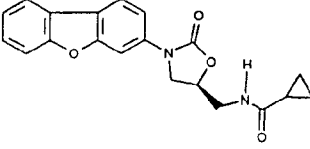
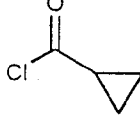
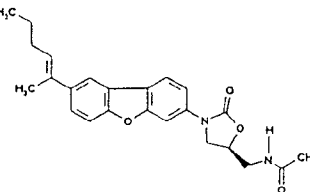
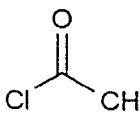
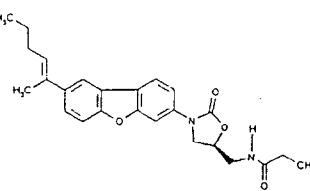
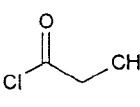
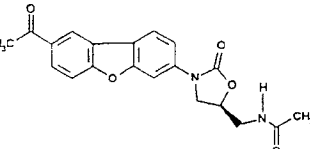
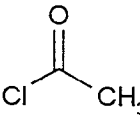
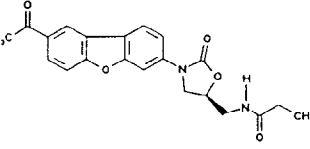
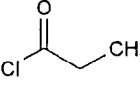
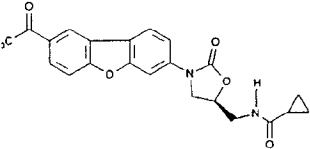
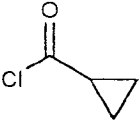
15

Bsp.- Nr.	Struktur	Acetylie- rungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
67			67	218-220	0,45 (I, 100:5)
68			60	180-182	0,33 (I, 100:5)
69			54	108-110	0,20 (I, 100:2)
70			68	118-120	0,05 (I, 100:5)
71			56	150-152	0,22 (I, 100:2)

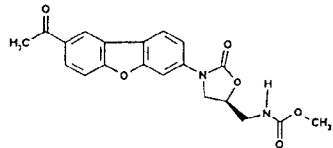
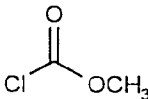
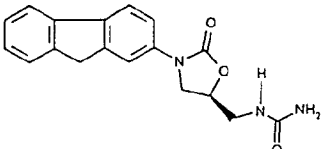
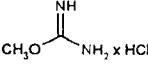
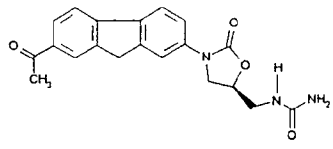
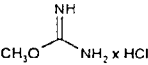
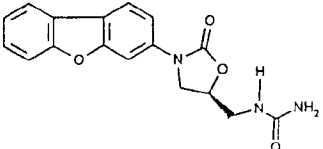
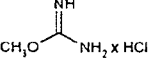
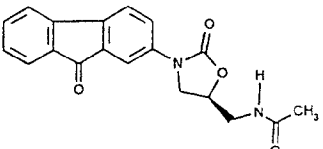
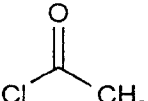
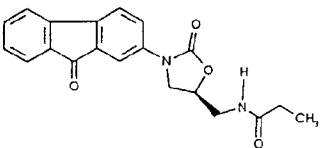
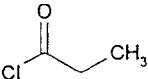
5

Bsp.- Nr.	Struktur	Acetylie- rungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
72			59	228-230	0,09 (I, 100:2)
73			61	243-245	0,33 (I, 100:5)
74			68	245-247	0,27 (I, 100:2)
75			41	217-219	0,34 (I, 100:5)
76			74	257-259	0,33 (I, 100:5)
77			80	216-218	0,27 (I, 100:5)
78			77	220-222	0,17 (I, 100:5)
79			47	200-202	0,51 (I, 100:5)

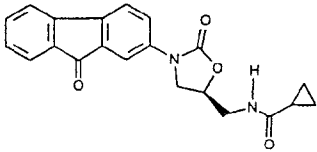
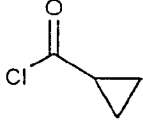
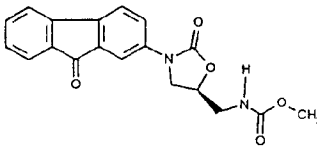
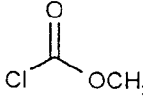
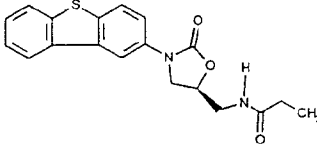
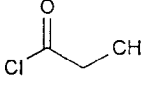
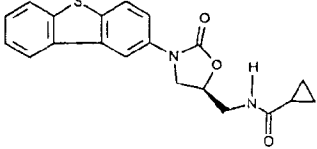
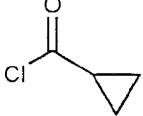
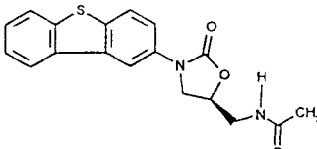
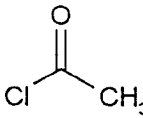
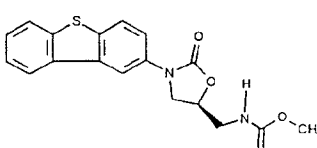
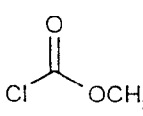
5

Bsp.- Nr.	Struktur	Acetylie- rungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
80			79	228- 230	0,16 (I, 100:2)
81			43	183- 185	0,24 (I, 100:5)
82			40	184- 186	0,41 (I, 100:5)
83			26	245- 247	0,24 (I, 100:5)
84			36	253- 255	0,24 (I, 100:5)
85			28	260- 262	0,16 (I, 100:5)

5

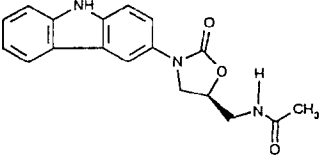
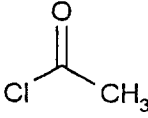
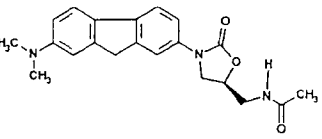
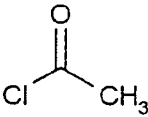
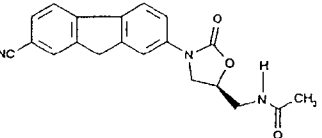
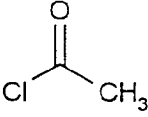
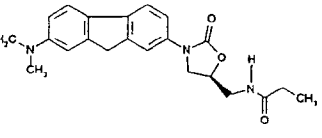
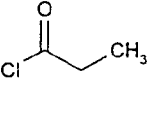
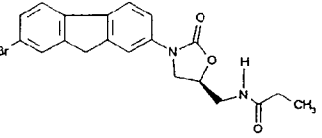
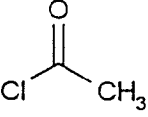
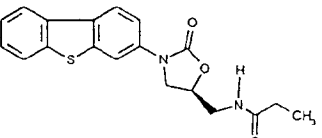
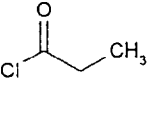
Bsp.- Nr.	Struktur	Acetylie- rungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
86			27	208- 210	0,56 (I, 100:5)
87			43	>250° C	0,53 (I, 10:1)
88			16	-	0,56 (I, 10:1)
89			51	>250	0,55 (I, 10:1)
90			51	248- 250	0,31 (I, 100:5)
91			63	203- 205	0,37 (I, 100:5)

5

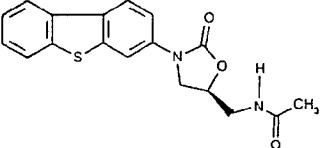
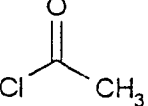
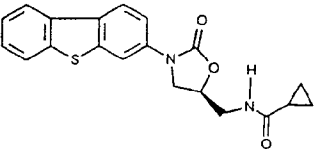
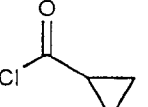
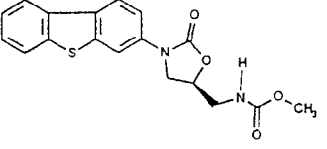
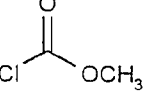
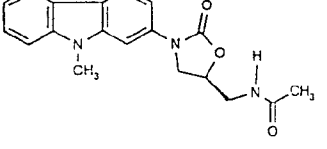
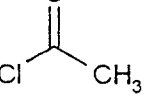
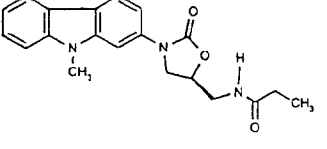
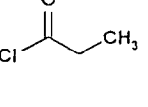
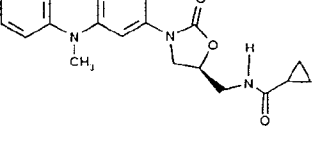
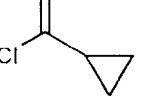
Bsp.- Nr.	Struktur	Acetylie- rungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
92			46	233- 235	0,20 (I, 100:2)
93			12	145- 147	0,48 (I, 100:5)
94			60	175- 177	0,16 (I, 100:2)
95			64	198- 200	0,45 (I, 100:5)
96			28	181- 183	0,48 (I, 100:5)
97			18	130- 132	0,61 (I, 100:5)

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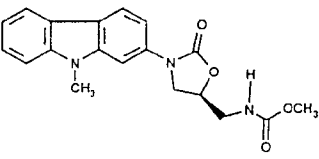
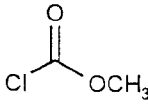
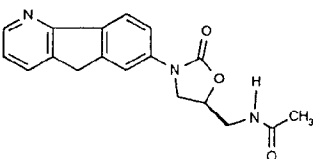
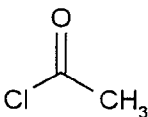
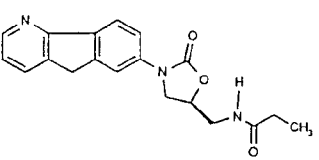
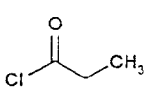
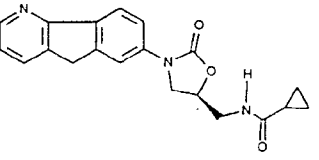
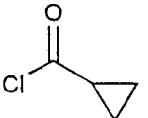
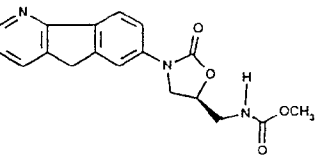
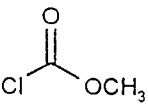


Bsp.-Nr.	Struktur	Acetylierungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
98			30	178-181	0,24 (I, 100:5)
99			46	228-230	0,16 (I, 100:5)
100			57	180-182	0,32 (I, 100:5)
101			26	218-220	0,16 (I, 100:5)
102			77	238-240	0,22 (I, 100:5)
103			71	228-230	0,28 (I, 100:5)

5

Bsp.- Nr.	Struktur	Acetylie- rungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
104			74	225- 227	0,4 (I, 100:5)
105			70	235- 237	0,45 (I, 100:5)
106			36	203- 205	0,62 (I, 100:5)
107			82	237- 239	0,2 (I, 100:2)
108			88	197- 199	0,11 (I, 100:2)
109			87	215- 217	0,15 (I, 100:2)

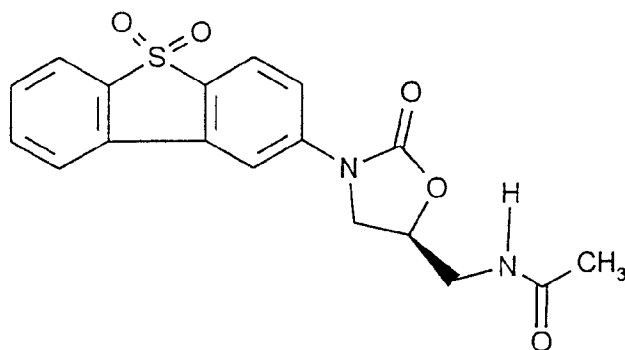
5

Bsp.-Nr.	Struktur	Acetylierungsmittel	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
110			56	175-177	0,17 (I, 100:2)
111			53	177-179	0,26 (I, 100:5)
112			68	198-200	0,27 (I, 100:5)
113			63	208-210	0,24 (I, 100:5)
114			31	207-209	I, 100:5)

5

**Beispiel 115**

(5S)-3-(5,5-Dioxo-2-dibenzothiophenyl)-5-(acetylaminomethyl)-oxazolidin-2-on



102 mg (0,3 mmol) der Verbindung aus Beispiel 96 werden mit 202 mg (0,45  
5 mmol) Monoperoxyphthalsäure Magnesiumsalz in 20 ml Chloroform 15 Stunden  
bei Raumtemperatur gerührt. Anschließend wird drei Stunden bei Rückfluß  
gekocht. Die abgekühlte Lösung wird mit gesättigter Natriumhydrogensulfid-  
Lösung gewaschen, über Natriumsulfat getrocknet und einrotiert. Das Rohprodukt  
wird an Kieselgel (Laufmittel: Dichlormethan / Methanol 100:5) gereinigt. Die  
10 erhaltenen Kristalle werden nochmals mit Ether verrührt.

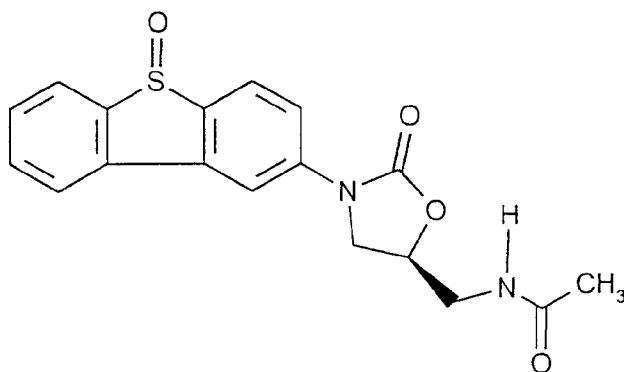
Ausbeute: 50 mg (45% d.Th.)

Schmp.: 203-206°C

R<sub>f</sub> (I, 100:5): 0,26

**Beispiel 116**

15 (5S)-3-(5-Oxo-2-dibenzothiophenyl)-5-(acetylaminomethyl)-oxazolidin-2-on



Zu 67,2 mg (0,314 mmol) Natrium-meta-periodat in 0,7 ml Wasser werden bei 0°C 102 mg (0,3 mmol) der Verbindung aus Beispiel 96 gegeben. Es wird 1 ml Methanol zugesetzt und drei Stunden bei 0°C gerührt. Nach Zugabe von 1 ml Chloroform und 1 ml Methanol wird vier Tage bei Raumtemperatur gerührt. Es werden nochmals 67 mg Natriumperiodat in 2 ml Wasser zugegeben und nochmals zwei Tage bei Raumtemperatur gerührt. Das Reaktionsgemisch wird eingengt und der Rückstand an Kieselgel (Laufmittel: Dichlormethan / Methanol 100:5) chromatographiert. Das Produkt wird abschließend mit Ether verrieben.

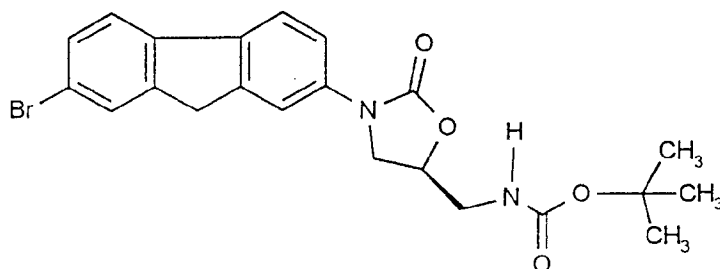
Ausbeute: 32 mg (29% d.Th.)

Schmp.: 130-132°C

R<sub>f</sub> (I, 100:5) 0,2

### Beispiel 117

(5S)-3-(7-Brom-2-fluorenyl)-5-(tert.butoxycarbonyl-aminomethyl)-oxazolidin-2-on



5,6 g (0,0142 mol) der Verbindung aus Beispiel 56 werden mit 2,13 ml (0,016 mol) Triethylamin in 140 ml Wasser vorgelegt und anschließend 3,4 g (0,016 mol) Pyrokohlensäuredi-tert.-butylester in 70 ml THF zugegeben. Es wird drei Stunden bei Raumtemperatur gerührt, mit Wasser und Essigester versetzt, die organische Phase abgetrennt, über Natriumsulfat getrocknet und einrotiert. Das Rohprodukt wird mit Ether verrieben.

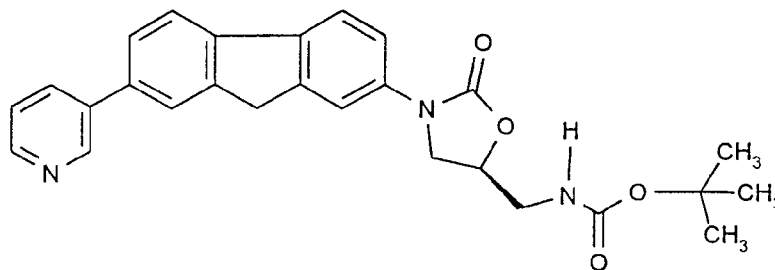
Ausbeute: 6,4 g (98% d.Th.)

Schmp.: 158-160°C

R<sub>f</sub> (I, 100:2): 0,45

**Beispiel 118**

(5S)-3-[7-(3-Pyridyl)-2-fluorenyl]-5-(tert.butoxycarbonylaminomethyl)-oxazolidin-2-on



5 3,3 g (7,2 mmol) der in Beispiel 117 erhaltenen Verbindung werden mit 1,8 g  
 (12,24 mmol) Diethyl-(3-pyridyl)boran und 247 mg (0,2 mmol) (Tetrakis-  
 triphenylphosphin)palladium in 40 ml Dioxan eine Stunde bei Rückfluß gekocht.  
 Nach Zugabe von 5 ml 2 M Natriumcarbonatlösung wird weitere 15 Stunden  
 10 gekocht. Der abgekühlte Ansatz wird einrotiert, der Rückstand in Dichlormethan  
 mit wenig Methanol aufgenommen, über Natriumsulfat getrocknet und einrotiert.  
 Der Rückstand wird an Kieselgel (Laufmittel: Dichlormethan / Methanol 100:5)  
 chromatographiert.

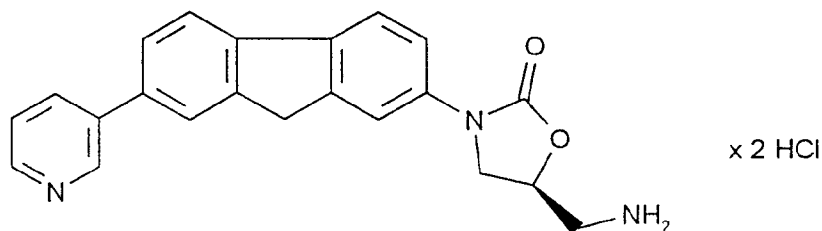
Ausbeute: 2,3 g (69% d.Th.)

Schmp.: 213-215°C

15  $R_f$  (I, 100:5): 0,19

**Beispiel 119**

(5S)-3-[7-(3-Pyridyl)-2-fluorenyl]-5-(aminomethyl)-oxazolidin-2-on Dihydrochlorid



20 2,3 g (5 mmol) der Verbindung aus Beispiel 118 werden in 40 ml Dioxan und  
 7,5 ml halbkonzentrierter Salzsäure 15 Stunden bei Raumtemperatur gerührt. Das

Lösemittel wird abdekantiert, der Rückstand mit Methanol / Ether verrieben, und die Kristalle werden isoliert.

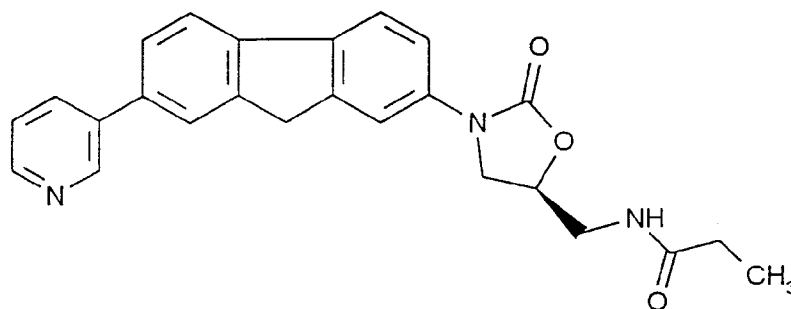
Ausbeute: 1,8 g

Schmp.: >260°C

5  $R_f$  (I, 2:1): 0,4

### Beispiel 120

(5S)-3-[7-(3-Pyridyl)-2-fluorenyl]-5-(propionyl-aminomethyl)-oxazolidin-2-on



300 mg (0,7 mmol) der in Beispiel 119 erhaltenen Verbindung werden mit 0,34 ml  
 10 (2,5 mmol) Triethylamin in 15 ml Dichlormethan vorgelegt. Bei ca. 5°C werden  
 0,06 ml (0,7 mmol) Propionylchlorid zugegeben und eine Stunde bei  
 Raumtemperatur nachgerührt. Der Ansatz wird direkt an Kieselgel (Laufmittel:  
 Dichlormethan / Methanol 100:5) chromatographiert.

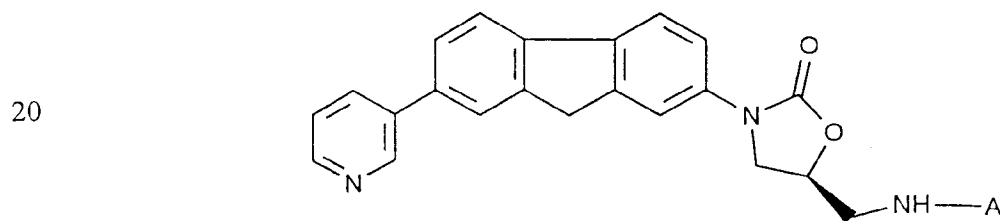
Ausbeute: 186 mg (64% d.Th.)

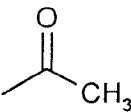
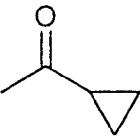
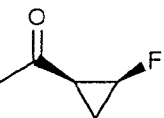
15 Schmp.: 240-242°C

$R_f$  (I, 100:5): 0,27

Analog zur Umsetzung des Beispiel 120 werden die in Tabelle 6 aufgeführten  
 Verbindungen synthetisiert:

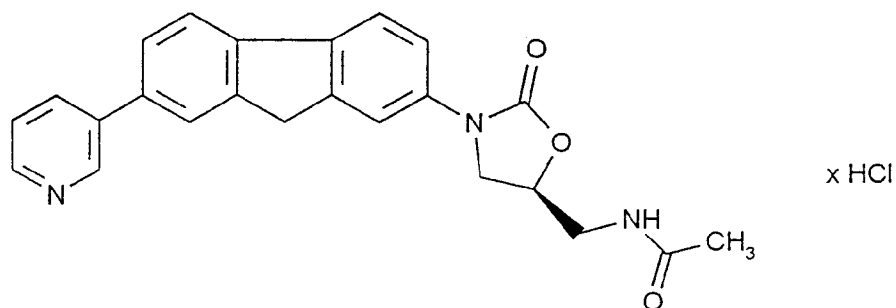
Tabelle 6:



Bsp.-Nr.:	A	Ausbeute (% d.Th.)	Fp. (°C)	R <sub>f</sub>
121		51	248-250	0,19 (I, 100:5)
122		38	253-255	0,20 (I, 100:5)
123		20	254-256	0,22 (I, 100:5)

5 **Beispiel 124**

(5S)-3-[7-(3-Pyridyl)-2-fluorenyl]-5-(acetylaminomethyl)-oxazolidin-2-on  
Hydrochlorid



10 147 mg (0,33 mmol) der Verbindung aus Beispiel 121 werden in 4 ml  
Dichlormethan und 4 ml Dioxan gelöst und mit 1 ml 4 M Salzsäurelösung in  
Dioxan versetzt. Nach 15 Stunden wird einrotiert, der Rückstand mit Methanol  
verrieben und mit Ether kristallisiert.

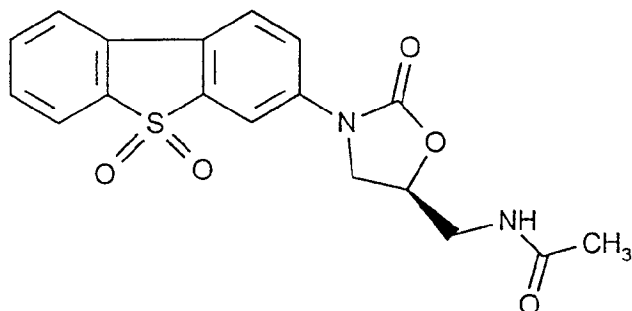
Ausbeute: 131 mg (89% d.Th.)

Schmp.: 218-220°C



**Beispiel 125**

(5S)-3-(S,S-Dioxo-3-dibenzothiophenyl)-5-(acetylamino-methyl)-oxazolidin-2-on



5 Analog zum Beispiel 121 wird bei der Umsetzung der Verbindung aus Beispiel 107 die Titelverbindung erhalten.

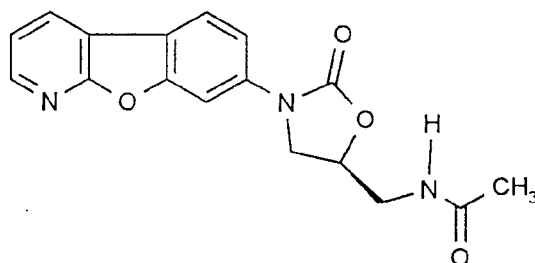
Ausbeute: 82%

Schmp.: 238-240°C

R<sub>f</sub> (I, 100:5): 0,26

**Beispiel 126**

10 (5S)-3-(Benzo[4,5]furo[2,3-b]pyridin-7-yl)-5-acetylamino-methyl-2-oxazolidinon



15 Eine Mischung der Verbindung aus Beispiel XXVII (205 mg, 0,6 mmol) und Cs<sub>2</sub>CO<sub>3</sub> (580 mg, 1,8 mmol) in DMF (10 ml) wird 3 h bei 40°C gerührt. Anschließend wird das DMF im Vakuum abgezogen, der Rückstand mit Wasser versetzt, der Niederschlag abgesaugt, mit Dichlormethan gerührt und abfiltriert.

Ausbeute: 74 mg (40% d.Th.)

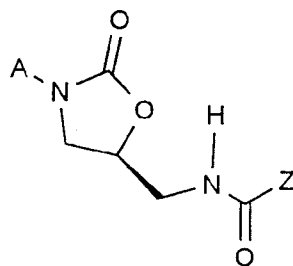
R<sub>f</sub> (Dichlormethan / Methanol = 10:1) = 0,30

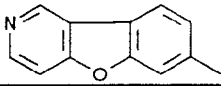
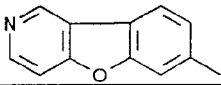
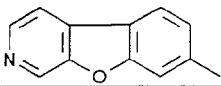
MS (CI): 326 (M+H<sup>+</sup>)

$^1\text{H-NMR}$  ( $\text{D}_6\text{-DMSO}$ ):  $\delta = 8,55$  (dd, 1H); 8,40 (dd, 1h); 8,30 (bt, 1H); 8,20 (d, 1H); 7,65 (dd, 1h); 7,45 (dd, 1H); 4,75 (m, 1H); 4,30 (t, 1H); 3,85 (dd, 1H); 3,45 (t, 1H); 1,98 (s, 3H).

In Analogie zur Vorschrift des Beispiels 126 werden die in der Tabelle 7 aufgeführten Verbindungen dargestellt:

Tabelle 7:

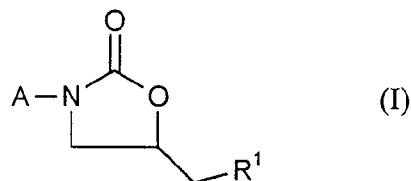


Bsp.-Nr.	A	Z	Ausbeute (% d.Th.)	MS (CI)	R <sub>f</sub> (I)
127		CH <sub>3</sub>	16	343 (M+NH <sub>4</sub> <sup>+</sup> )	0,22 (10:1)
128		OCH <sub>3</sub>	26	-	0,24 (100:5)
129		CH <sub>3</sub>	22	326 (M+H <sup>+</sup> )	0,5 (10:1)

10

Patentansprüche

1. Verbindungen der allgemeinen Formel (I)



in welcher

5             $R^1$     für Azido, Hydroxy oder für eine Gruppe der Formel  $-OR^2$ ,  
 $O-SO_2R^3$ ,  $-(CO)_aNR^4R^5$ ,  $D-R^6$  oder  $-CO-R^7$  steht,

worin

$R^2$     geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet,

10            $R^3$     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,

a        eine Zahl 0 oder 1 bedeutet,

15            $R^4$  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,

20           oder

R<sup>4</sup> oder R<sup>5</sup> eine Gruppe der Formel -CO-R<sup>8</sup>, P(O)(OR<sup>9</sup>)(OR<sup>10</sup>) oder -SO<sub>2</sub>-R<sup>11</sup> bedeutet,

worin

5 R<sup>8</sup> Cycloalkyl mit 3 bis 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Halogen substituiert ist, oder  
Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl oder Wasserstoff bedeutet,

10 oder

geradkettiges oder verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert ist,

15 oder

geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeutet,

oder

eine Gruppe der Formel -NR<sup>12</sup>R<sup>13</sup> bedeutet,

20 worin

R<sup>12</sup> und R<sup>13</sup> gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,

25 oder

5

R<sup>8</sup> einen 5- bis 6-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeutet,

R<sup>9</sup> und R<sup>10</sup> gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,

R<sup>11</sup> geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet,

D die Gruppe  $\text{—}\overset{\text{O}}{\parallel}\text{C—O—}$  oder  $\text{—}\overset{\text{O}}{\parallel}\text{S—}$  bedeutet,

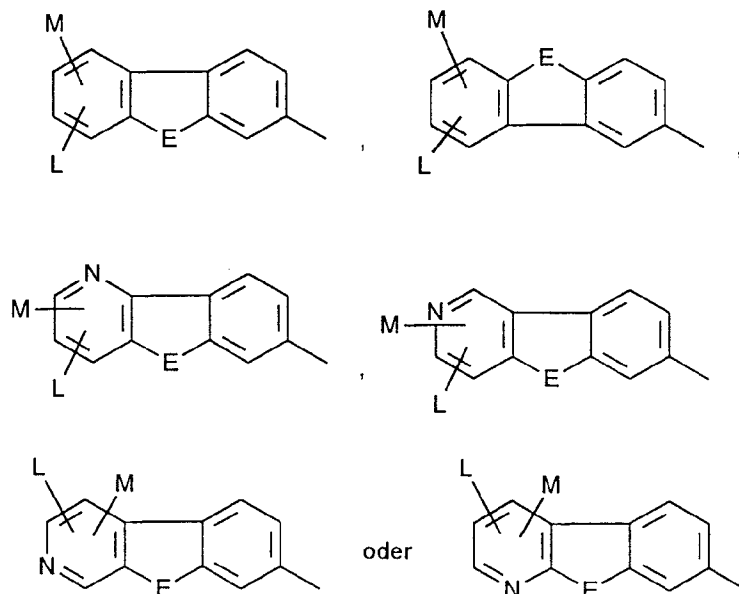
10

R<sup>6</sup> Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen bedeutet,

R<sup>7</sup> Trifluormethyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet, das durch Halogen oder Trifluormethyl substituiert ist,

15

A für einen Rest der Formel



steht,

worin

5 E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet,

worin

10 R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> und R<sup>17</sup> gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeuten,

15 L und M gleich oder verschieden sind und Wasserstoff, Hydroxy, Carboxyl, Cyano, Halogen, Nitro, Formyl, Pyridyl, geradkettiges oder verzweigtes Alkyl, Acyl, Alkenyl, Alkoxy oder Alkoxycarbonyl mit jeweils bis zu 8 Kohlenstoffatomen oder einen Rest der Formel -NR<sup>18</sup>R<sup>19</sup> bedeuten,

worin

20 R<sup>18</sup> und R<sup>19</sup> gleich oder verschieden sind und die oben angegebene Bedeutung von R<sup>16</sup> und R<sup>17</sup> haben und mit dieser gleich oder verschieden sind,

und deren Stereoisomere und Salze.

2. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher

R<sup>1</sup> für Azido, Hydroxy oder für eine Gruppe der Formel -OR<sup>2</sup>, O-SO<sub>2</sub>R<sup>3</sup>, -(CO)<sub>a</sub>NR<sup>4</sup>R<sup>5</sup>, D-R<sup>6</sup> oder -CO-R<sup>7</sup> steht,

25

worin

R<sup>2</sup> geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,

R<sup>3</sup> geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Phenyl oder TolyI bedeutet,

5 a eine Zahl 0 oder 1 bedeutet,

R<sup>4</sup> und R<sup>5</sup> gleich oder verschieden sind und  
Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen oder tert.-Butoxycarbonyl bedeuten,

10

oder

R<sup>4</sup> oder R<sup>5</sup> eine Gruppe der Formel -CO-R<sup>8</sup>, P(O)(OR<sup>9</sup>)(OR<sup>10</sup>) oder -SO<sub>2</sub>-R<sup>11</sup> bedeutet,

worin

15 R<sup>8</sup> Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl bedeutet, die gegebenenfalls durch Fluor, Chlor oder Brom substituiert sind, oder  
Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl oder  
20 Wasserstoff bedeutet,

oder

geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder  
25 geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeutet, oder  
eine Gruppe der Formel -NR<sup>12</sup>R<sup>13</sup> bedeutet,

worin

5

$R^{12}$  und  $R^{13}$  gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,

oder

$R^8$  Isoxazolyl, Furyl, Thienyl, Pyrrol, Oxazolyl oder Imidazolyl bedeutet,

10

$R^9$  und  $R^{10}$  gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

$R^{11}$  geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet,

D die Gruppe  $\begin{array}{c} \text{O} \\ || \\ -\text{C}-\text{O}- \end{array}$  oder  $\begin{array}{c} \text{O} \\ || \\ -\text{S}- \\ || \\ \text{O} \end{array}$  bedeutet,

15

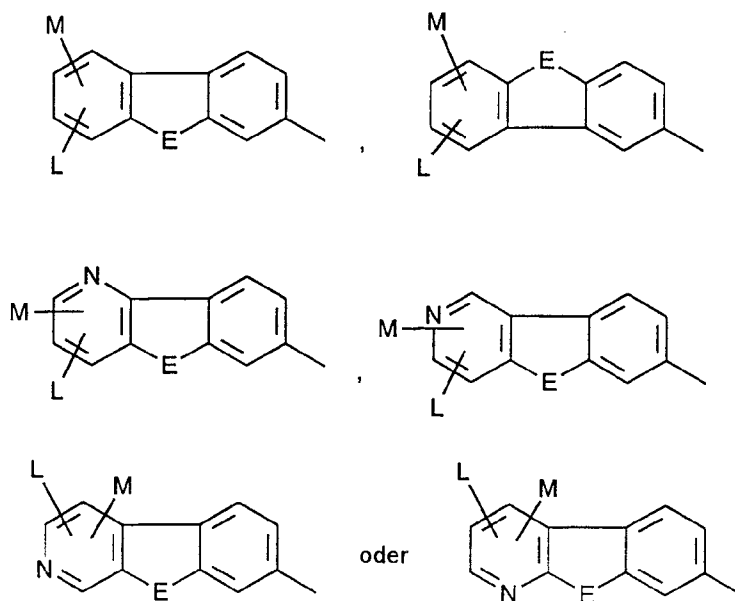
$R^6$  Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,

$R^7$  Trifluormethyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet, das durch Fluor, Chlor, Brom oder Trifluormethyl substituiert ist,

20

A für einen Rest der Formel





steht,

worin

5 E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet,

worin

10 R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> und R<sup>17</sup> gleich oder verschieden sind und Wasserstoff, oder geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeuten,

15 L und M gleich oder verschieden sind und Wasserstoff, Carboxyl, Cyano, Fluor, Chlor, Brom, Nitro, Formyl, Pyridyl, geradkettiges oder verzweigtes Alkyl, Acyl, Alkenyl oder Alkoxycarbonyl mit jeweils bis zu 7 Kohlenstoffatomen oder einen Rest der Formel -NR<sup>18</sup>R<sup>19</sup> bedeuten,

worin

$R^{18}$  und  $R^{19}$  gleich oder verschieden sind und die oben angegebene Bedeutung von  $R^{16}$  und  $R^{17}$  haben und mit dieser gleich oder verschieden sind,

5 und deren Stereoisomere und Salze.

3. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher

$R^1$  für Azido, Hydroxy oder für eine Gruppe der Formel  $-OR^2$ ,  $O-SO_2R^3$ ,  $-(CO)_aNR^4R^5$  oder  $-CO-R^7$  steht,

worin

10  $R^2$  geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet,

$R^3$  Methyl, Ethyl, Phenyl oder TolyI bedeutet,

a eine Zahl 0 oder 1 bedeutet,

15  $R^4$  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 oder tert.Butoxycarbonyl bedeuten,

oder

20  $R^4$  oder  $R^5$  eine Gruppe der Formel  $-CO-R^8$ ,  $P(O)(OR^9)(OR^{10})$  oder  $-SO_2R^{11}$  bedeutet,

worin

$R^8$  Cyclopropyl bedeutet, das gegebenenfalls durch Fluor substituiert ist, oder

Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl oder Wasserstoff bedeutet,

oder

5 geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder

10 geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 4 Kohlenstoffatomen bedeutet, oder  
eine Gruppe der Formel  $-NR^{12}R^{13}$  bedeutet,

worin

15  $R^{12}$  und  $R^{13}$  gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

oder

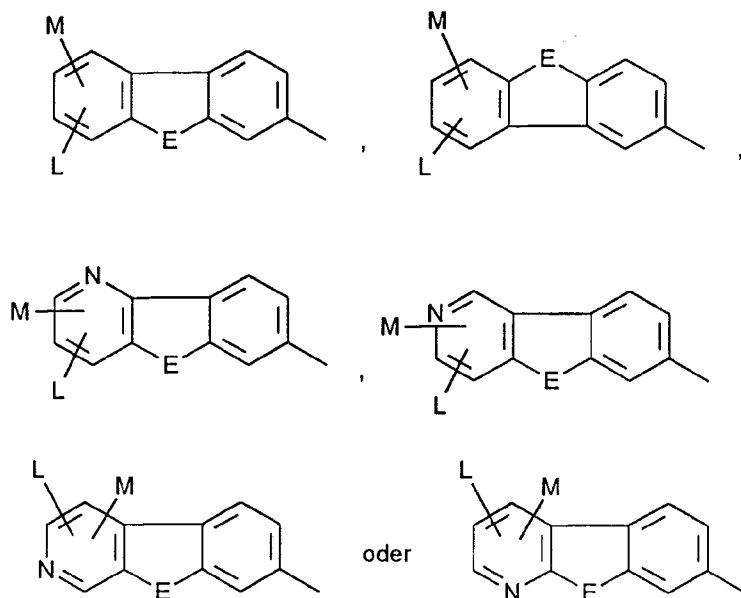
$R^8$  Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeutet,

20  $R^9$  und  $R^{10}$  gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

$R^{11}$  Methyl oder Phenyl bedeutet,

25  $R^7$  Trifluormethyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeutet, das durch Fluor, Chlor, Brom oder Trifluormethyl substituiert ist,

A für einen Rest der Formel



steht,

worin

5

E ein Sauerstoff- oder Schwefelatom bedeutet, oder die CO-, CH<sub>2</sub>-, SO- oder SO<sub>2</sub>-Gruppe bedeutet, oder eine Gruppe der Formel -NR<sup>14</sup>, C=NR<sup>15</sup> oder -C=N-NR<sup>16</sup>R<sup>17</sup> bedeutet,

worin

10

R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup> und R<sup>17</sup> gleich oder verschieden sind und Wasserstoff, oder geradkettiges oder verzweigtes Alkyl oder Acyl mit jeweils bis zu 3 Kohlenstoffatomen bedeuten,

L und M gleich oder verschieden sind und Wasserstoff,  
 Carboxyl, Cyano, Fluor, Chlor, Brom, Nitro, Formyl,  
 Pyridyl, geradkettiges oder verzweigtes Alkyl, Acyl, Alkenyl  
 oder Alkoxy-carbonyl mit jeweils bis zu 6 Kohlenstoffatomen  
 5 einen Rest der Formel  $-NR^{18}R^{19}$  bedeuten,

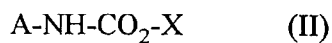
worin

$R^{18}$  und  $R^{19}$  gleich oder verschieden sind und die oben  
 angegebene Bedeutung von  $R^{16}$  und  $R^{17}$  haben und  
 10 mit dieser gleich oder verschieden sind,

und deren Stereoisomere und Salze.

4. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I)  
 gemäß Anspruch 1, dadurch gekennzeichnet, daß man

[A] im Fall  $R^1 = OH$ ,  
 15 Verbindungen der allgemeinen Formel (II)



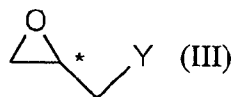
in welcher

A die oben angegebene Bedeutung hat

und

- 20 X für eine typische Carboxylschutzgruppe, vorzugsweise für Benzyl  
 steht,

mit Epoxiden der allgemeinen Formel (III)



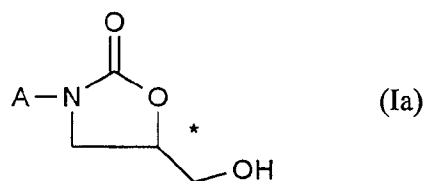
in welcher

Y für C<sub>1</sub>-C<sub>6</sub>-Alkoxy-carbonyl steht,

in inerten Lösemitteln und in Anwesenheit einer Base umgesetzt,

oder

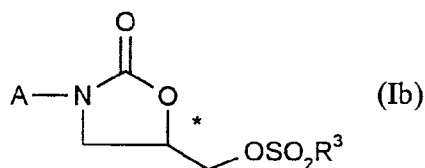
- 5 [B] im Fall R<sup>1</sup> ≠ OH  
Verbindungen der allgemeinen Formel (Ia)



in welcher

A die oben angegebene Bedeutung hat,

- 10 durch Umsetzung mit (C<sub>1</sub>-C<sub>4</sub>)-Alkyl- oder Phenylsulfonsäurechloriden in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)

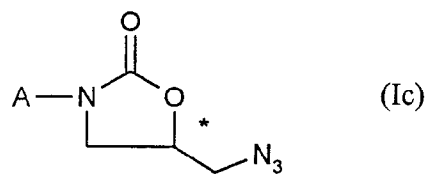


in welcher

- 15 A und R<sup>3</sup> die oben angegebene Bedeutung haben,

überführt,

anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (Ic)

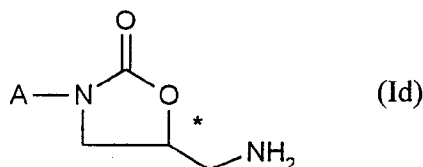


in welcher

A die oben angegebene Bedeutung hat,

herstellt,

- 5 diese in einem weiteren Schritt durch Umsetzung mit  $(C_1-C_4\text{-Alkyl-O})_3\text{-P}$  oder  $\text{PPh}_3$ , vorzugsweise  $(\text{CH}_3\text{O})_3\text{P}$  in inerten Lösemitteln und mit Säuren in die Amine der allgemeinen Formel (Id)

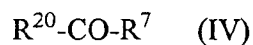


in welcher

- 10 A die oben angegebene Bedeutung hat,

überführt,

und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (IV)



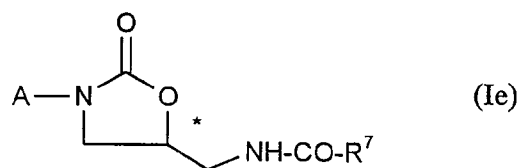
- 15 in welcher

$\text{R}^7$  die oben angegebene Bedeutung hat

und

$\text{R}^{20}$  für Halogen, vorzugsweise für Chlor oder für den Rest  $-\text{OCOR}^6$  steht,

in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



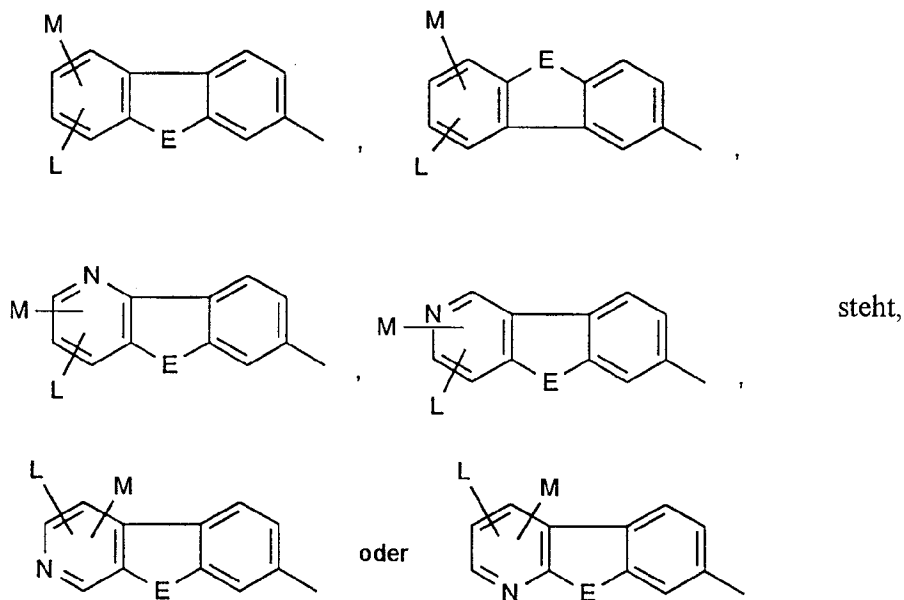
in welcher

A und R<sup>7</sup> die oben angegebene Bedeutung haben,

5 herstellt,

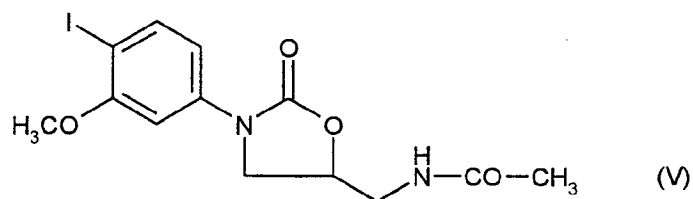
oder

[C] im Fall, daß A für einen der oben aufgeführten Reste



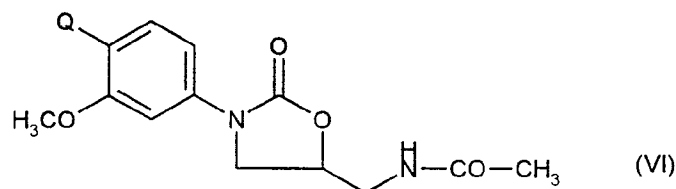
zunächst die Verbindungen der Formel (V)





durch Umsetzung mit 2-Fluoro- oder Chloro-pyridyltrimethylzinn-Verbindungen in Anwesenheit des Systems Bis(triphenylphosphin)palladium-(II)chlorid / Cu(I)iodid in die Verbindungen der allgemeinen Formel (VI)

5



in welcher

Q für 2-Fluor- oder 2-Chlor-substituiertes Pyridyl steht,

überführt,

10

anschließend die Methoxygruppe in die freie Hydroxyfunktion überführt und in einem letzten Schritt eine Cyclisierung durchführt,

und im Fall E = SO<sub>2</sub> oder SO ausgehend von den entsprechenden amingeschützten Verbindungen der allgemeinen Formel (I) mit E = S eine Oxidation nach üblichen Methoden durchführt,

15

und im Fall L und/oder M = Pyridyl ebenfalls ausgehend von den entsprechenden geschützten, bromierten Aminen der allgemeinen Formel (I) eine Umsetzung mit Dialkyl-pyridylboranen durchführt,

und gegebenenfalls die einzelnen Substituenten nach üblichen Methoden derivatisiert und/oder einführt.

20

5. Verwendung von Verbindungen gemäß Anspruch 1 zur Herstellung von Arzneimitteln.

6. Arzneimittel enthaltend Verbindungen gemäß Anspruch 1.

# INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/EP 98/04252

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07D263/24 C07D263/20 A61K31/42 C07D413/04 C07D413/10  
 C07D491/04 //(C07D491/04,307:00,221:00)

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 A61K

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	US 5 254 577 A (CARLSON RANDALL K ET AL) 19 October 1993 cited in the application see column 43, compounds 117, 118 see claims ---	1, 5, 6
Y	EP 0 425 209 A (TANABE SEIYAKU CO) 2 May 1991 see claims ---	1, 5, 6
Y	WO 97 17346 A (SYNTHELABO) 15 May 1997 see claims 1, 8, 10 ---	1, 5, 6
Y	EP 0 694 544 A (BAYER AG) 31 January 1996 cited in the application see claims ---	1, 5, 6
	-/--	

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

Date of the actual completion of the international search

14 October 1998

Date of mailing of the international search report

26/10/1998

Name and mailing address of the ISA

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 359 418 A (THE UPJOHN COMPANY) 21 March 1990 see page 14, line 22 - line 55; claims 1,4,7 ---	1,5,6
Y	WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 see page 8, line 26 - page 9, line 26; claims -----	1,5,6

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/04252

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Information on patent family members

Int. ional Application No

PCT/EP 98/04252

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			05-08-1997

# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 98/04252

## A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 6 C07D263/24 C07D263/20 A61K31/42 C07D413/04 C07D413/10  
C07D491/04 //(C07D491/04, 307:00, 221:00)

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

## B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 6 C07D A61K

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 <sup>1</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	US 5 254 577 A (CARLSON RANDALL K ET AL) 19. Oktober 1993 in der Anmeldung erwähnt siehe column 43, compounds 117, 118 siehe Ansprüche	1, 5, 6
Y	EP 0 425 209 A (TANABE SEIYAKU CO) 2. Mai 1991 siehe Ansprüche	1, 5, 6
Y	WO 97 17346 A (SYNTHELABO) 15. Mai 1997 siehe Ansprüche 1, 8, 10	1, 5, 6
Y	EP 0 694 544 A (BAYER AG) 31. Januar 1996 in der Anmeldung erwähnt siehe Ansprüche	1, 5, 6
	--- -/--	

Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

Siehe Anhang Patentfamilie

<sup>1</sup> Besondere Kategorien von angegebenen Veröffentlichungen

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

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"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

14. Oktober 1998

Absenddatum des internationalen Recherchenberichts

26/10/1998

Name und Postanschrift der Internationalen 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

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie <sup>o</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	EP 0 359 418 A (THE UPJOHN COMPANY) 21. März 1990 siehe Seite 14, Zeile 22 - Zeile 55; Ansprüche 1,4,7 ---	1,5,6
Y	WO 93 09103 A (THE UPJOHN COMPANY) 13. Mai 1993 siehe Seite 8, Zeile 26 - Seite 9, Zeile 26; Ansprüche -----	1,5,6



# INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP 98/04252

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
US 5254577 A	19-10-1993	US 4948801 A	14-08-1990
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		CA 1337526 A	07-11-1995
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EP 0425209 A	02-05-1991	AT 122344 T	15-05-1995
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PCT/EP 98/04252

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<p>(21) Internationales Aktenzeichen: PCT/EP98/06454</p> <p>(22) Internationales Anmeldedatum: 12. Oktober 1998 (12.10.98)</p> <p>(30) Prioritätsdaten: 197 47 261.3 25. Oktober 1997 (25.10.97) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): KETTELHOIT, Stefan [DE/DE]; Robert-Medenwald-Strasse 5, D-51375 Leverkusen (DE). KANIKANTI, Ranga-Rao [IN/DE]; Quettinger Strasse 24A, D-51381 Leverkusen (DE). BRENDDEL, Erich [DE/DE]; Im Wöll 10, D-42657 Solingen (DE). WEISEMANN, Claus [DE/DE]; Fontanestrasse 5, D-51429 Bergisch Gladbach (DE). CHANTRAINE, Ernst [DE/DE]; Morgengraben 1, D-51061 Köln (DE). EISELE, Michael [DE/DE]; An der Flora 2a, D-51469 Bergisch Gladbach (DE). BOSCHE, Patrick [DE/DE]; Schlinghofener Strasse 36, D-51519 Odenthal (DE).</p> <p>(74) Gemeinsamer Vertreter: BAYER AKTIENGESELLSCHAFT; D-51368 Leverkusen (DE).</p>	<p>(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, 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), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches 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, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Veröffentlicht</b> <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i></p>	
<p>(54) Title: OSMOTIC MEDICAMENT RELEASING SYSTEM</p>		
<p>(54) Bezeichnung: OSMOTISCHES ARZNEIMITTELFREISETZUNGSSYSTEM</p>		
<p>(57) Abstract</p>		
<p>The invention relates to an osmotic medicament releasing system which is to be administered orally, said system being comprised of a membrane and a dihydropyridine core, and to a method for the production of said releasing system. In addition, the invention relates to an osmotic medicament releasing system for use as medicaments for humans and animals and to the application of said osmotic medicament releasing system in order to produce a medicament to treat and/or prevent diseases in humans and animals.</p>		
<p>(57) Zusammenfassung</p>		
<p>Die vorliegende Erfindung betrifft ein oral zu verabreichendes osmotisches Arzneimittelfreisetzungssystem, das aus einer Hülle und einem dihydropyridinhaltigen Kern besteht, sowie ein Verfahren zu dessen Herstellung. Die Erfindung betrifft weiter ein osmotisches Arzneimittelfreisetzungssystem zur Anwendung als Arzneimittel bei Menschen oder Tieren sowie die Verwendung des osmotischen Arzneimittelfreisetzungssystems zur Herstellung eines Arzneimittels zur Behandlung und/oder Prävention von Erkrankungen bei Menschen und Tieren.</p>		

**LEDIGLICH ZUR INFORMATION**

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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### Osmotisches Arzneimittelfreisetzungssystem

Die vorliegende Erfindung betrifft ein oral zu verabreichendes osmotisches Arznei-  
mittelfreisetzungssystem, das aus einer Hülle und einem wirkstoffhaltigen Kern be-  
steht, sowie ein Verfahren zu dessen Herstellung. Die Erfindung betrifft weiter ein  
osmotisches Arzneimittelfreisetzungssystem zur Anwendung als Arzneimittel bei  
Menschen oder Tieren sowie die Verwendung des osmotischen Arzneimittelfrei-  
setzungssystems zur Herstellung eines Arzneimittels zur Behandlung und/oder  
Prävention von Erkrankungen bei Menschen und Tieren.

Osmotische Arzneimittelfreisetzungssysteme sind grundsätzlich im Stand der Technik  
bekannt. Dabei wird im allgemeinen ein osmotischer Druck als Energiequelle ausge-  
nutzt, einen Arzneimittelwirkstoff mit kontrollierter Geschwindigkeit an das umgeben-  
de Medium abzugeben. Daher nennt man solche Systeme auch osmotische Pumpen.  
Eine weitgehend vollständige Übersicht über die osmotischen Arzneimittelfrei-  
setzungssysteme findet sich in Journal of Controlled Release 35 (1995) 1-21. Danach  
unterscheidet man prinzipiell zwischen Mehrkammersystemen und Einkammer-  
systemen. Das Einkammersystem besteht in seiner einfachsten Form aus einer kon-  
ventionellen Tablette, die aus der Hülle einer semipermeablen Membran mit einer  
Austrittsöffnung und einem Kern, in der der Wirkstoff in fester Form vorliegt, besteht.  
Nach der oralen Verabreichung dringt Wasser durch die semipermeable Membran in  
den Kern ein, der Wirkstoff löst sich auf und wird durch eine Austrittsöffnung  
abgegeben (US-Patent No. 3.845.770). Dieses Prinzip eignet sich jedoch nur für sehr  
gut wasserlösliche Wirkstoffe, da nur diese einen ausreichend hohen osmotischen  
Druck erzeugen können. Speziell für schwerlösliche Wirkstoffe wurden daher so-  
genannte Doppelkammersysteme („Push-Pull“-Systeme) entwickelt (US-Patent Nr.  
4.111.202, Europäische Patentanmeldung Nr. 52 917). Die Herstellung solcher Zwei-  
kammersysteme ist jedoch technisch sehr aufwendig. Das Einkammersystem besitzt  
daher einen prinzipiellen Vorteil gegenüber den Mehrkammersystemen. Um die Vor-  
teile des Einkammersystems bei schwerlöslichen Arzneimitteln dennoch zu nutzen,  
wurden zur Erzielung ausreichend hoher osmotischer Drücke im Innern der Tablette

Einkammersysteme vorgeschlagen, deren Kern aus dem Wirkstoff und bestimmten polymeren Quellmitteln besteht, die beim Hinzutreten von Wasser durch die äußere semipermeable Membran aufquellen und zusammen mit dem darin teilweise suspendierten Wirkstoff aus der Öffnung freigesetzt werden. Der Auswahl bestimmter polymerer Quellmittel kommt bei diesem System eine entscheidende Bedeutung zu, da wie  
5 in der EP-A-0 277 092 bereits beschrieben, bestimmte Quellmittel wie z.B. Polyvinylpyrrolidon, Polyethylenoxid oder Polymethacrylat einen so hohen Quelldruck erzeugen, daß es nach kurzer Zeit zu einer vollständigen Aufspaltung der semipermeablen Hüllmembran kommt und der Wirkstoff in kurzer Zeit freigesetzt wird, anstatt, wie  
10 gewünscht, verzögert bzw. kontrolliert freigesetzt zu werden. Die EP-A-0 277 092 trifft zur Lösung dieses Problems daher eine bestimmte Auswahl hydrophiler polymerer Quellmittel, nämlich eine Mischung aus einem Vinylpyrrolidon-Vinylacetat-Copolymer und einem Ethylenoxidhomopolymer.

15 Die WO 96/40080 beansprucht in generischer Form osmotische Einkammersysteme, die einen Kern aus einem pharmazeutischen Wirkstoff, einem wasserlöslichen osmotischen Mittel und einem wasserquellbaren Polymer umfassen. Wie jedoch bereits in der EP-A-0 277 092 dargelegt wird, sind nicht alle polymeren hydrophilen Quellmittel für diese Einkammersysteme geeignet, und eine sorgfältige Auswahl muß getroffen  
20 werden, um die gewünschte kontrollierte Freisetzung des Wirkstoffes aus dem Einkammersystem zu gewährleisten. In den konkreten Ausführungsformen der WO 96/40080 werden als wasserquellbare Polymere u.a. Polyethylenoxid und Cellulose bzw. deren Derivate verwendet.

25 Ein osmotisches Arzneimittelfreisetzungssystem mit kontrollierter, d.h. im allgemeinen mit verzögerter Freisetzung, das aus einem Einkammersystem besteht, sollte grundsätzlich eine möglichst vollständige Freisetzung des Wirkstoffes ermöglichen, ohne daß es während der Freisetzung zu einem Aufreißen der Austrittsöffnung und somit zu unkontrollierter Wirkstofffreisetzung kommt. Bei den Einkammersystemen besteht  
30 jedoch häufig das Problem, daß ein nicht unerheblicher Anteil des Wirkstoffs in der Tablette verbleibt, da der im Innern der Tablette erzeugte osmotische Druck nicht ausreicht, den Wirkstoff vollständig freizusetzen. So besitzen die oben beschriebenen

Systeme den Nachteil, daß sie den Wirkstoff nicht vollständig aus der Hüllmembran durch die Austrittsöffnung abgeben, so daß ein relativ hoher Anteil des Wirkstoffs nicht absorbiert wird und ungenutzt ausgeschieden wird. Wird jedoch auf der anderen Seite ein wasserquellbares Polymer verwendet, das einen sehr hohen osmotischen Druck erzeugt, kann dies zum Aufreißen oder gar zur vollständigen Sprengung der  
5 Tablette führen, so daß eine verzögerte, kontrollierte Freisetzung nicht erreicht wird.

Häufig weisen die osmotischen Arzneimittelfreisetzungssysteme des Stands der Technik auch das Problem auf, daß die unbeschichteten Tablettenkerne eine ungenügende mechanische Festigkeit aufweisen, was die nachfolgende Lackierung erschwert.  
10

Grundsätzlich sollte ein osmotisches Arzneimittelfreisetzungssystem leicht herstellbar sein, aus preiswerten und pharmakologisch gut verträglichen Stoffen zusammengesetzt sein und es ermöglichen, ein günstiges Freisetzungsprofil des Wirkstoffs zu erreichen.  
15

Es wurde nun überraschend gefunden, daß eine Kombination zweier bestimmter hydrophiler wasserquellbarer Polymere in bestimmten Gewichtsanteilen als Kernbestandteile besonders geeignet ist, die oben beschriebenen gewünschten Eigenschaften eines osmotischen Einkammer-Arzneimittelfreisetzungssystems, das einen pharmazeutischen Wirkstoff, insbesondere ein Dihydropyridin umfaßt, zu erreichen. Die Erfinder der vorliegenden Erfindung fanden, daß die Kombination aus dem Heteropolysaccharid Xanthan und einem Vinylpyrrolidon-Vinylacetat-Copolymer als wasserquellbare Polymere in bestimmten Gewichtsmengen zu einer weitgehend vollständigen Freisetzung eines Wirkstoffes aus der Hülle führt, ohne daß es dabei zu einem Aufreißen der Öffnung und unkontrollierter Wirkstofffreisetzung kommt.  
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Ohne an eine Theorie gebunden zu sein, wird angenommen, daß das Xanthan in Kombination mit dem Vinylpyrrolidon-Vinylacetat-Copolymer insbesondere deshalb sehr günstige Freisetzungseigenschaften bewirkt, da es strukturviskose Lösungen bildet, deren Viskosität beim Fließen unter dem Einfluß zunehmender Schubspannung  
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abnimmt. Dies erlaubt offenbar eine besonders gleichförmige Freisetzung des Wirkstoffs aus der Austrittsöffnung, ohne daß es zum Einreißen der Membran kommt, und dabei wird der Wirkstoff über einen relativ langen Zeitraum gleichförmig und weitgehend vollständig freigesetzt.

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Xanthan als wasserquellbares Polymer besitzt darüberhinaus gegenüber den in der EP-A-0 277 092 und der WO 96/40080 verwendeten Polyethylenoxiden den Vorteil der leichteren Handhabbarkeit, da es nicht den sogenannten TOMS-Effekt (Herabsetzung des Reibungswiderstands) aufweist. Ein weiterer Vorteil der Verwendung des Xanthans gegenüber der Verwendung von Polyethylenoxiden als wasserquellbare Polymere besteht darin, daß Polyethylenoxide in der Regel nur mit organischen Lösungsmitteln feucht granuliert werden (s. z.B. Beispiele der EP-A-0 277 092), so daß die Herstellung unter Explosionsschutz erfolgen muß, oder es wird trocken tablettiert (WO 96/40080), so daß die bekannten Nachteile der Trockentablettierung, wie schlechte Fließfähigkeit der Mischung der Kernbestandteile, Staubentwicklung sowie eine geringere Härte des Tablettenkerns auftreten.

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Die vorliegende Erfindung überkommt die oben beschriebenen Probleme des Stands der Technik mit der Bereitstellung eines osmotischen Arzneimittelfreisetzungssystem, daß besteht aus:

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- einer Hülle aus einem wasserdurchlässigen, für die Komponenten des Kerns undurchlässigen Material, die mindestens eine Öffnung aufweist, und
- einem Kern, enthaltend
  - 15 bis 35 Gew.-% eines pharmazeutischen Wirkstoffs
  - 20 bis 50 Gew.-% Xanthan
  - 10 bis 30 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

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wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydro-



philen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100 % aufaddiert.

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Die Hülle des osmotischen Arzneimittelfreisetzungssystems besteht aus einem wasser-durchlässigen, für die Komponenten des Kerns undurchlässigen Material. Solche Hüllmaterialien sind im Prinzip bekannt und beispielsweise beschrieben in der EP-A-0 277 092. Zur Herstellung der Hülle eignen sich z.B. die literaturbekanntesten polymeren Stoffe, die im Gastrointestinaltrakt nicht metabolisiert werden, d.h. unverändert ausgeschieden werden (s. US-Patente Nr. 3.916.899 und Nr. 3.977.404). Beispielsweise können acylierte Cellulosederivate (Celluloseester), die durch Acetylgruppen ein- bis dreifach oder durch Acetylgruppen ein- bis zweifach und einen weiteren von Acetyl verschiedenen Acylrest substituiert sind, verwendet werden, z.B. Celluloseacetat, Cellulosetriacetat, Celluloseacetatethylcarbammat, Celluloseacetatphthalat, Celluloseacetatmethylcarbammat, Celluloseacetatsuccinat, Celluloseacetatdimethylaminoacetat, Celluloseacetatethylcarbonat, Celluloseacetat-chloracetat, Celluloseacetatethyloxalat, Celluloseacetat-methylsulfonat, Celluloseacetatbutylsulfonat, Celluloseacetatpropionat, Celluloseacetatdiethylaminoacetat, Celluloseacetatoctat, Celluloseacetatlaurat, Celluloseacetat-p-toluolsulfonat, Celluloseacetatbutyrat und andere Celluloseacetatderivate sowie Agaracetat und Amyloseacetat. Als semipermeables Membranmaterial eignen sich auch Ethylcellulose und polymere Epoxide, Copolymere aus Alkylenoxid und Alkylglycidylethern, Polyglykole und Polymilchsäurederivate und weitere Derivate davon. Ferner können auch Mischungen von an sich wasserunlöslichen Acrylaten (z.B. ein Copolymerisat von Acrylsäureethylester und Methacrylsäuremethylester) verwendet werden. Auf die Hülle kann bei Bedarf ein Lichtschutzlack aufgebracht werden. Geeignete Materialien für den Lichtschutzlack sind z.B. Polymere, wie Hydroxypropylcellulose, Hydroxypropylmethylcellulose, in Kombination mit geeigneten Weichmachern wie z.B. Polyethylenglykol und Pigmenten wie z.B. Titandioxid oder Eisenoxide.

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Die Mengen und die verwendeten Bestandteile für die Herstellung der Hülle des osmotischen Arzneimittelfreisetzungssystems beeinflussen in bekannter Weise die Eintrittsgeschwindigkeit der gastrointestinalen Flüssigkeit. Grundsätzlich nimmt die Eintrittsgeschwindigkeit der gastrointestinalen Flüssigkeit mit zunehmender Lackmenge ab.

Die Hülle des osmotischen Arzneimittelfreisetzungssystems der vorliegenden Erfindung weist mindestens eine Öffnung bzw. Passage auf, durch die der Wirkstoff zusammen mit den weiteren Kernbestandteilen allmählich austritt. Die Öffnung wird durch Laserbohren, mechanisches Bohren oder z.B. Stanzen in die Hülle eingebracht. Es können ein oder mehrere Öffnungen in der Hülle vorhanden sein. Die Größe der Öffnung beträgt bevorzugt 0,2 bis 1,6 mm, besonders bevorzugt 0,4 bis 1,2 mm. Die Beschaffenheit und die Herstellverfahren der Öffnung sind an sich bekannt und beispielsweise beschrieben in den US-Patenten Nr. 4063064, 4088864 und 3916899 sowie in der EP-B-0277092.

Der Kern des osmotischen Arzneimittelfreisetzungssystems der vorliegenden Erfindung enthält, bzw. besteht im wesentlichen aus den folgenden Bestandteilen:

- 15 bis 35 Gew.-% eines pharmazeutischen Wirkstoffs
- 20 bis 50 Gew.-% Xanthan
- 10 bis 30 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

Bevorzugt besteht der Kern aus:

- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
- 25 bis 40 Gew.-% Xanthan
- 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

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wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

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Weitere auf dem Gebiet der osmotischen Arzneimittelfreisetzungssysteme übliche Bestandteile können enthalten sein, solange ihre Anwesenheit, die Lösung der eingangs beschriebenen Aufgabenstellung nicht beeinträchtigt.

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Bei den im Kern befindlichen pharmazeutischen Wirkstoffen handelt es sich vorzugsweise um schwerlösliche Wirkstoffe mit einer maximalen Löslichkeit von  $\leq 1$  g in 1000 g Wasser, vor allem um solche, die auch noch im Dickdarm resorbiert werden, insbesondere um einen Wirkstoff der an sich bekannten Klasse der Dihydropyridine, wie sie zum Beispiel in der EP-A-0071819 beschrieben sind, z.B. Nifedipin und Nisoldipin. Sie wirken als Calciumantagonisten. Diese werden sowohl als Herz-Kreislaufmittel in der Indikation Bluthochdruck als auch in der Behandlung und Prävention ischämischer Gehirnerkrankungen eingesetzt.

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25 Besonders bevorzugt wird Nifedipin verwendet.

Der Wirkstoff liegt im Kern des osmotischen Arzneimittelfreisetzungssystem der vorliegenden Erfindung in einer Menge von 15 bis 35 Gew.-%, bevorzugt 20 bis 30 Gew.-%, besonders bevorzugt 19 bis 23 Gew.-%, bezogen auf die Gesamtmenge der Kernbestandteile vor.

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Das osmotische Arzneimittelfreisetzungssystem enthält als einen der wesentlichen Bestandteile des Kerns das hydrophile wasserquellbare Polymer Xanthan. Dabei handelt es sich um ein anionisches Heteropolysaccharid, das im Handel beispielsweise unter der Bezeichnung Rhodigel<sup>®</sup> (hergestellt durch Meyhall) erhältlich ist.

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In einer bevorzugten Ausführungsform weist das Xanthan eine Partikelgröße von weniger als 800 µm auf. Eine Partikelgröße von mehr als 800 µm führt in einigen Fällen zu einem verschlechterten Freisetzungsverhalten. In einer besonders bevorzugten Ausführungsform beträgt die Partikelgröße des Xanthans weniger als 500 µm.

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Das Xanthan liegt in einer Menge 20 bis 50 Gew.-%, bevorzugt 25 bis 40 Gew.-% besonders bevorzugt 28 bis 32 Gew.-%, bezogen auf die Gesamtmenge der Kernbestandteile vor.

15

Ein weiterer wesentlicher Bestandteil des Kerns des Arzneimittelfreisetzungssystems der vorliegenden Erfindung ist das Vinylpyrrolidon-Vinylacetat-Copolymer. Dieses Copolymer ist an sich bekannt und kann mit beliebigen Mischungsverhältnissen der Monomere hergestellt werden. Das bevorzugt verwendete kommerziell erhältliche Kollidon<sup>®</sup> VA64 (hergestellt durch BASF) ist z.B. ein 60:40- Copolymerisat. Es weist im allgemeinen einen Gewichtsmittelwert des Molekulargewichts  $M_w$ , bestimmt durch Lichtstreuungsmessungen, von etwa 45.000 bis etwa 70.000 auf. Die Menge des Vinylpyrrolidon-Vinylacetat-Copolymers im Kern des Arzneimittelfreisetzungssystems der vorliegenden Erfindung beträgt 10 bis 30 Gew.-%, bevorzugt 10 bis 20 Gew.-%, besonders bevorzugt 15 bis 20 Gew.-%, bezogen auf das Gesamtgewicht der Kernbestandteile. Daraus ergibt sich ein bevorzugtes Gewichtsverhältnis von Xanthan zum Vinylpyrrolidon-Vinylacetat-Copolymer von 5 : 1 bis 2 : 3.

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Bevorzugt enthält das osmotische Arzneimittelfreisetzungssystem der vorliegenden Erfindung lediglich Xanthan und das Vinylpyrrolidon-Vinylacetat-Copolymer als wasserquellbare Polymere als Kernbestandteile.

In einer besonders bevorzugten Ausführungsform der Erfindung enthält das osmotische Arzneimittelfreisetzungssystem mindestens einen osmotisch aktiven Zusatz und/oder mindestens einen pharmazeutisch annehmbaren Zusatzstoff.

5 Dabei ist ein osmotisches Arzneimittelfreisetzungssystem bevorzugt, dessen Kern enthält:

- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
- 25 bis 40 Gew.-% Xanthan
- 10 - 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
- 10 bis 30 Gew.-% einer osmotisch aktiven Substanz,
- 8 bis 20 Gew.-% mindestens eines pharmazeutisch annehmbaren Zusatzstoffes,

wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen  
15 sind und die Summe der Kernbestandteile zu 100% aufaddiert.

Obwohl es bevorzugt ist, daß das osmotische Arzneimittelfreisetzungssystem der vor-  
liegenden Erfindung lediglich Xanthan und das Vinylpyrrolidon-Vinylacetat-Copoly-  
mer als wasserquellbare Polymere als Kernbestandteile enthält, können bei Bedarf  
20 weitere zusätzliche hydrophile quellbare Polymere im Kern enthalten sein, die z.B.  
ausgewählt werden aus Hydroxypropylcellulose, Hydroxypropyl-methylcellulose,  
Natriumcarboxymethylcellulose, Polyacrylsäuren bzw. deren Salze.

Die gegebenenfalls im Kern vorhandenen weiteren hydrophilen quellbaren Polymere  
25 liegen im Arzneimittelfreisetzungssystem der vorliegenden Erfindung in einer Menge  
vor, bei der die Lösung der eingangs beschriebenen Aufgabenstellung nicht beein-  
trächtigt ist.

Diese hydrophilen wasserquellbaren Polymere, die in der vorliegenden Erfindung ver-  
wendet werden, umfassen jedoch kein Polyethylenoxid (Polyethylenglykol), d.h. der  
30 Kern der Arzneimittelfreizusammensetzung der vorliegenden Erfindung ist frei von  
Polyethylenoxidzusätzen.

Die wahlweise im Kern des Arzneimittelfreisetzungssystems der vorliegenden Erfindung enthaltenen osmotisch aktiven Zusätze sind im Prinzip nicht beschränkt, und alle wasserlöslichen Stoffe, deren Verwendung in der Pharmazie unbedenklich ist, wie z.B. die in Pharmakopöen oder in „Hager“ und „Remington Pharmaceutical Science“ erwähnten wasserlöslichen Hilfsstoffe können verwendet werden. Insbesondere können wasserlösliche Salze von anorganischen oder organischen Säuren oder nicht-ionische organische Stoffe mit großer Wasserlöslichkeit wie z.B. Kohlehydrate, insbesondere Zucker, oder Aminosäuren verwendet werden. Zum Beispiel können die osmotisch aktiven Zusätze ausgewählt werden aus anorganischen Salzen wie Chloriden, Sulfaten, Carbonaten und Bicarbonaten von Alkali- oder Erdalkalimetallen, wie Lithium, Natrium, Kalium, Magnesium, Calcium sowie Phosphate, Hydrogen- oder Dihydrogenphosphate, Acetate, Succinate, Benzoate, Citrate oder Ascorbate davon. Des weiteren können Pentosen, wie Arabinose, Ribose oder Xylose, Hexosen, wie Glucose, Fructose, Galactose oder Mannose, Disaccharide wie Sucrose, Maltose oder Lactose oder Trisaccharide wie Raffinose verwendet werden. Zu den wasserlöslichen Aminosäuren zählen Glycin, Leucin, Alanin oder Methionin. Besonders bevorzugt wird Natriumchlorid verwendet. Diese osmotisch aktiven Zusätze sind bevorzugt in einer Menge von 10 bis 30 Gew.-%, besonders bevorzugt 15 bis 20 Gew.-%, bezogen auf die Gesamtmenge der kernbildenden Bestandteile enthalten.

Desweiteren kann der Kern des osmotischen Arzneimittelfreisetzungssystems der vorliegenden Erfindung einen oder mehrere pharmazeutisch annehmbare Zusatzstoffe enthalten, die ausgewählt werden aus: Pufferstoffen, wie z.B. Natriumbicarbonat, Sprengmitteln, wie z.B. Natriumcarboxymethylstärke, Gleitmitteln, wie z.B. Magnesiumstearat, Tablettierhilfsmitteln, Schutzkolloiden, wie z.B. in der EP-B-0277092, S. 5, Z. 10-25 beschrieben, Weichmachern, wie z.B. in der EP-B-0277092, S. 5, Z. 29-32 beschrieben, Tensiden, wie z.B. in der EP-B-0277092, S. 5, Z. 33-44 beschrieben, Trägermaterialien, wie z.B. in der EP-B-0277092, S. 5, Z. 45-47 beschrieben.

In einer ganz besonders bevorzugten Ausführungsform der vorliegenden Erfindung umfaßt der Kern:

- 19 bis 23 Gew.-% eines pharmazeutischen Wirkstoffs
- 5 - 28 bis 32 Gew.-% Xanthan
- 15 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
- 15 bis 20 Gew.-% Natriumchlorid
- 5 bis 7 Gew.-% Natriumbicarbonat
- 6 bis 9 Gew.-% Natriumcarboxymethylstärke
- 10 - <1 Gew.-% Magnesiumstearat

wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

- 15 Das osmotische Arzneimittelfreisetzungssystem der vorliegenden Erfindung kann in verschiedenen Formen wie z.B. in der EP-B-0277092, S. 6, Z. 7-14 beschrieben vorliegen. Bevorzugt liegt es in Tablettenform vor.

- 20 Die Erfindung betrifft auch ein Verfahren zur Herstellung des erfindungsgemäßen osmotischen Arzneimittelfreisetzungssystems, bei dem die Bestandteile des Kerns miteinander vermischt werden, gegebenenfalls feucht oder trocken granuliert werden, tablettiert werden und der so entstandene Kern mit der Hülle beschichtet wird. Die Feuchtgranulation bewirkt häufig eine bessere Benetzbarkeit der Bestandteile des Tablettenkerns, wodurch die eintretende Gastrointestinalflüssigkeit den Kern besser
- 25 durchdringt, was vielfach zu einer rascheren und vollständigeren Freisetzung des Wirkstoffs führt, so daß die Feuchtgranulation bevorzugt ist.

- 30 Das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem wird zur Behandlung und/oder Prävention von Erkrankungen von Menschen und Tieren, wie z.B. bei Kreislauferkrankungen, Infektionen, Entzündungen, Schmerzzuständen, Asthma, Cancer, Malaria, Thrombosen, Diabetes, Herzrhythmusstörungen, Hypoglycaemien, Mycosen, Depressionen, Störungen des Salz- und Flüssigkeitshaushaltes, Stoff-

wechselstörungen wie z.B. Störungen des Fettstoffwechsels, koronaren Herzerkrankungen, Bluthochdruck, cerebralen Leistungsstörungen und zur Therapie neurologischer Defizite insbesondere nach Subarachnoidalblutung verwendet. Besonders bevorzugt werden die osmotischen Arzneimittelfreisetzungssysteme der vorliegenden Erfindung zur Behandlung von Bluthochdruck und koronaren Herzerkrankungen verwendet.



**Beispiel 1 und 2** (Tabletten mit trocken granulierten Bestandteilen)

## Zusammensetzung

5 **Kern**

	1	2
Nifedipin	36,00 mg	36,00 mg
Xanthan (Rhodigel <sup>®</sup> , Handelsprodukt, Meyhall)	50,96 mg	50,96 mg
Copolyvidon (Kollidon <sup>®</sup> VA64, Handelsprodukt, BASF, Vinylpyrrolidon-Vinylacetat-Copolymer)	29,45 mg	29,45 mg
Natriumchlorid	28,71 mg	28,71 mg
Natriumbicarbonat	10,15 mg	10,15 mg
Natriumcarboxymethylstärke	12,74 mg	12,74 mg
Aerosil	0,85 mg	0,85 mg
Mg-stearat	0,68 mg	0,68 mg

**Hülle (osmotische Membran)**

Celluloseacetat	8,45 mg	11,40 mg
Polyethylenglykol 3350	0,45 mg	0,60 mg
Tbl.-gewicht ca.	178,5 mg	181,6 mg
Tbl-format	6r9	6r9

## Herstellungsverfahren

5 Nifedipin, Kollidon<sup>®</sup> VA64 (70 Gew.% der o.a. Menge), Rhodigel<sup>®</sup> Natriumchlorid und Natriumbicarbonat wurden gemischt und anschließend trocken granuliert. Das Granulat wurde mit Natriumcarboxymethylstärke, dem anteiligen Rest von Kollidon<sup>®</sup> VA64, Aerosil und Magnesiumstearat nachgemischt. Die Mischung wurde anschließend  
10 tablettiert. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Die beschichteten Tabletten wurden anschließend getrocknet. Die entstandenen Tabletten besaßen einen Durchmesser von 6 mm.

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Anschließend wurde eine Öffnung von ca. 800 µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht.

**Beispiel 3 und 4** (Tabletten mit feucht granulierten Bestandteilen)

## Zusammensetzung

5	<u>Kern</u>		
		3	4
	Nifedipin	36,00 mg	36,00 mg
	Xanthan (Rhodigel <sup>®</sup> , Handelsprodukt, Meyhall)	50,96 mg	50,96 mg
	Copolyvidon (Kollidon <sup>®</sup> VA64, Handelsprodukt, BASF,	29,45 mg	29,45 mg
	Vinylpyrrolidon-Vinylacetat-Copolymer)		
	Natriumchlorid	28,71 mg	28,71 mg
	Natriumbicarbonat	10,15 mg	10,15 mg
	Natriumcarboxymethylstärke	12,74 mg	12,74 mg
	Aerosil	0,90 mg	0,90 mg
	Mg-stearat	0,50 mg	0,50 mg
	<u>Hülle (osmotische Membran)</u>		
	Celluloseacetat	7,50 mg	9,40 mg
	Polyethylenglykol 3350	0,40 mg	0,50 mg
	Tbl.-gewicht ca.	177 mg	179 mg
	Tbl-format	6r9	7r10

#### Herstellungsverfahren

- Rhodigel<sup>®</sup>, Natriumchlorid, Natriumbicarbonat und Natriumcarboxymethylstärke wurden gemischt und anschließend mit einer Suspension von Nifedipin und Kollidon<sup>®</sup> VA64 in Wasser feucht granuliert. Das Granulat wurde mit Aerosil und Magnesiumstearat nach-
- 5 gemischt. Die Mischung wurde anschließend tablettiert. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Die beschichteten Tabletten wurden anschließend getrocknet. Die entstandenen Tabletten besaßen einen Durchmesser von 6 mm bzw. 7 mm.
- 10 Anschließend wurden zwei Öffnungen von je ca. 600µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht.

**Vergleichsbeispiel 1** (entsprechend Beispiel 3 der EP-A-0277092):

## Zusammensetzung

5 **Kern**

Nifedipin	50,00 mg
Polyox coagulant	20,00 mg
Copolyvidon (Kollidon <sup>®</sup> VA64, Handelsprodukt, BASF,	18,00 mg
Vinylpyrrolidon-Vinylacetat-Copolymer)	
Natriumchlorid	20,00 mg
Mg-stearat	2,00 mg

**Hülle (osmotische Membran)**

Celluloseacetat	11,20 mg
Polyethylenglykol 4000	1,50 mg
Tbl.-gewicht ca.	122,7 mg
Tbl-format	7r10

#### Herstellungsverfahren

Nifedipin, Polyox coagulant, Kollidon<sup>®</sup> VA64, Natriumchlorid und Magnesiumstearat wurden gemischt. Die Mischung wurde anschließend jedoch zur Vermeidung der Verwendung organischer Lösungsmittel ohne vorherige Granulation direkt tablettiert. Die  
5 Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Es wurde dabei Celluloseacetat Typ 398-10 anstatt Celluloseacetat Typ 320S eingesetzt, um die Verwendung von chlorierten Kohlenwasserstoffen zu vermeiden. Die beschichteten Tabletten wurden anschließend getrocknet. Die entstandenen Tabletten besaßen einen Durchmesser von 7 mm.

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Anschließend wurde eine Öffnung von ca. 800 µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht.

**Vergleichsbeispiel 2** (entsprechend Beispiel 1 der WO-96/40080):

## Zusammensetzung

5 **Kern**

Nifedipin	33,00 mg
Polyox WSR 303	27,50 mg
Polyox WSR N80	55,00 mg
Natriumcarboxymethylstärke	82,50 mg
Lactose	74,25 mg
Mg-stearat	2,75 mg

**Hülle (osmotische Membran)**

Celluloseacetat	12,48 mg
Polyethylenglykol 400	0,78 mg
Saccharose micr.	1,56 mg
Triacetin	0,78 mg
Tbl.-gewicht ca.	291 mg
Tbl-format	9r15

## Herstellungsverfahren

Nifedipin, Polyox WSR 303, Polyox WSR N80, Natriumcarboxymethylstärke, Lactose und Magnesiumstearat wurden gemischt. Die Mischung wurde anschließend tablettiert. Die entstandenen Tablettenkerne waren sehr weich und ließen sich nur schlecht weiterverarbeiten. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Die beschichteten Tabletten wurden anschließend getrocknet. Die entstandenen Tabletten besaßen einen Durchmesser von 9 mm. Anschließend wurde eine Öffnung von ca. 800 µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht. Die in Figur 1 der WO-96/40080 gezeigten Freisetzungsmengen des Beispiels 1 der WO-96/40080 wurden unter den unten angegebenen Testbedingungen nicht gefunden.

Die in den Beispielen und Vergleichsbeispielen hergestellten osmotischen Arzneimittelfreisetzungssysteme wurden auf ihr Freisetzungsverhalten in der „Apparatur 2“ der USP XXIII (The United States Pharmacopeia USP XXIII 1995, Seite 1791 bis 1792) gemäß der Rührflügelmethode untersucht. Dazu wurde die Wirkstofffreisetzung in einer gängigen Freisetzungsvorrichtung der Firma ERWEKA bestimmt. Die Tabletten wurden in Puffer pH=6,8 (10%ig) nach Deutschem Arzneibuch 9. Ausgabe mit Tensidzusatz bei 37°C und 100 Upm inkubiert. Innerhalb von 24 Stunden setzten die Tabletten den Wirkstoff gemäß Tabelle frei. Die Freisetzungsmengen in der Tabelle sind als prozentualer Anteil der freigesetzten Wirkstoffmenge, bezogen auf die gesamte ursprüngliche Wirkstoffmenge im Kern angegeben.



Freisetzung	Beispiel	Beispiel	Beispiel	Beispiel	Vergleichs- beispiel 1	Vergleichs- beispiel 2
	1	2	3	4		
240 min.	12,5%	10%	32,5%	30,8%	5%	13,6%
480 min.	41,7%	30%	67,5%	64,5%	22%	33,6%
720 min.	57,5%	53,3%	76,7%	75,8%	37%	48,2%
960 min.	65%	60,8%	81,7%	80,8%	45%	54,5%
1440 min.	70%	71,7%	87,5%	86,7%	51%	62,7%

Tabelle Freisetzung von Wirkstoff aus Tabletten gemäß Beispiel 1-4 und aus Tabletten der Vergleichsbeispiele 1-2

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Die Ergebnisse zeigen, daß das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem den Wirkstoff im relevanten Zeitintervall - je nach angestrebter Freisetzungsraten - nahezu vollständig freisetzt, wohingegen die osmotischen Arzneimittelfreisetzungssysteme aus dem Stand der Technik den Wirkstoff am Ende der Freisetzung nur unvollständig freisetzen. Dabei ist davon auszugehen, daß nach einem Zeitraum von 24 Stunden eine Freisetzung an absorptionsrelevanten Stellen des Gastrointestinaltrakts nicht mehr stattfindet und die osmotischen Arzneimittelfreisetzungssysteme das Plateau ihrer Freisetzung erreicht haben. Die erfindungsgemäßen Beispiele 1 und 2 einerseits und 3 und 4 andererseits verdeutlichen den Einfluß der Feuchtgranulation im Unterschied zur Trockengranulation. Wie oben dargelegt, bewirkt die Feuchtgranulation häufig eine bessere Benetzbarkeit der Bestandteile des Tablettenkerns, wodurch die eintretende Gastrointestinalflüssigkeit den Kern besser durchdringt, was zu einer rascheren und vollständigeren Freisetzung des Wirkstoffs führt. Die Feuchtgranulation ist daher bevorzugt. Der Einsatz der Feuchtgranulation wird durch die Verwendung der speziellen wasserquellbaren Polymere in dem erfindungsgemäßen osmotischen Arzneimittelfreisetzungssystem, welche im Gegensatz zu den im Stand der Technik verwendeten Polyethylenoxiden keiner organischen Lösungsmittel bedürfen, praktisch erst ermöglicht. Der Vergleich zwischen den erfindungsgemäßen Beispielen 1 und 2 bzw. 3 und 4 zeigt, daß eine höhere Hüllackauftragsmenge am Anfang der Freisetzung zu einer gewissen Verzögerung (Lag-Zeit) führt, und die Freisetzungsraten aufgrund der

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geringeren Eintrittsgeschwindigkeit der Gastrointestinalflüssigkeit verlangsamt wird. Über einen längeren Zeitraum werden jedoch weitgehend unabhängig von der Lackauftragsmenge etwa gleich hohe Freisetzungsmengen in den erfindungsgemäßen Beispielen erzielt.

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Der Vergleich zwischen Beispiel 2 der Erfindung und Vergleichsbeispiel 1 zeigt, daß das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem bei etwa gleicher Lackauftragsmenge und Lackzusammensetzung sowie vergleichbarem Herstellungsverfahren (Trockengranulation bzw. Direkttablettierung) eine deutlich höhere Endfreisetzung bei annähernd gleichen Anfangsfreisetzungsraten aufweist. Dies bedeutet, daß das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem auch zu einem späteren Zeitpunkt noch mit einer relativ hohen Freisetzungsrate den Wirkstoff freisetzt, wenn die Freisetzung des Wirkstoffs des osmotischen Arzneimittelfreisetzungssystems des Vergleichsbeispiels praktisch bereits zum Erliegen gekommen ist. Das bedeutet, daß ein großer Anteil des Wirkstoffs des Vergleichsbeispiels in der Tablette verbleibt und somit ungenutzt ausgeschieden wird. Auch bei Vergleichsbeispiel 2 wird eine niedrige Freisetzungsrate in einem späteren Zeitpunkt der Freisetzung beobachtet.

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**Patentansprüche**

1. Osmotisches Arzneimittelfreisetzungssystem, bestehend aus
- 5 - einer Hülle aus einem wasserdurchlässigen, für die Komponenten des  
Kerns undurchlässigen Material, die mindestens eine Öffnung aufweist,  
und
- einem Kern, enthaltend
- 10 - 15 bis 35 Gew.-% eines pharmazeutischen Wirkstoffs  
- 20 bis 50 Gew.-% Xanthan  
- 10 bis 30 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copoly-  
mers,
- 15 wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen  
Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weite-  
ren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und  
pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf
- 20 das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der  
Kernbestandteile zu 100% aufaddiert.
2. Osmotisches Arzneimittelfreisetzungssystem nach Anspruch 1, das einen Kern  
umfaßt, der enthält:
- 25 - 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs  
- 25 bis 40 Gew.-% Xanthan  
- 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
- 30 wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen  
Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weite-  
ren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und

pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

- 5        3.        Osmotisches Arzneimittelfreisetzungssystem nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß der Kern mindestens einen osmotisch aktiven Zusatz enthält.
- 10        4.        Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß der Kern mindestens einen osmotisch aktiven Zusatz sowie mindestens einen pharmazeutisch annehmbaren Zusatzstoff enthält.
- 15        5.        Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 4, das einen Kern umfaßt, der enthält:
- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
  - 25 bis 40 Gew.-% Xanthan
  - 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
  - 20        -        10 bis 30 Gew.-% einer osmotisch aktiven Substanz,
  - 8 bis 20 Gew.-% mindestens eines pharmazeutisch annehmbaren Zusatzstoffes,
- 25        wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.
- 30        6.        Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der Wirkstoff ein schwerlöslicher Wirkstoff ist.

7. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß der Wirkstoff ein schwerlöslicher Wirkstoff ist, der auch noch im Dickdarm resorbiert wird.
- 5 8. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß der Wirkstoff ein Dihydropyridin ist.
9. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß der Wirkstoff Nifedipin ist.
- 10 10. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß der osmotisch aktive Zusatz Natriumchlorid ist.
- 15 11. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß der pharmazeutisch annehmbare Zusatzstoff ausgewählt wird aus pharmazeutisch annehmbaren Pufferstoffen, pharmazeutisch annehmbaren Gleitmitteln, pharmazeutisch annehmbaren Sprengmitteln sowie pharmazeutisch annehmbaren Tablettierhilfsmitteln.
- 20 12. Osmotisches Arzneimittelfreisetzungssystem nach Anspruch 11, dadurch gekennzeichnet, daß der pharmazeutisch annehmbare Pufferstoff Natriumbicarbonat, das pharmazeutisch annehmbare Gleitmittel Magnesiumstearat ist, das pharmazeutisch annehmbare Sprengmittel Natriumcarboxymethylstärke, und ein pharmazeutisch annehmbares Tablettierhilfsmittel.
- 25 13. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 12, das einen Kern umfaßt, der enthält:
- 30 - 19 bis 23 Gew.-% eines pharmazeutischen Wirkstoffs  
- 28 bis 32 Gew.-% Xanthan  
- 15 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

- 26 -

- 15 bis 20 Gew.-% Natriumchlorid
- 5 bis 7 Gew.-% Natriumbicarbonat
- 6 bis 9 Gew.-% Natriumcarboxymethylstärke
- <1 Gew.-% Magnesiumstearat

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wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

14. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 13, dadurch gekennzeichnet, daß es in Tablettenform vorliegt.
15. Verfahren zur Herstellung des osmotischen Arzneimittelfreisetzungssystems nach irgendeinem der Ansprüche 1 bis 14, dadurch gekennzeichnet, daß die Bestandteile des Kerns miteinander vermischt werden, gegebenenfalls trocken oder feucht granuliert werden, tablettiert werden und der so entstandene Kern mit der Hülle beschichtet wird.
16. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung als Arzneimittel bei Menschen oder Tieren.
17. Verwendung des osmotischen Arzneimittelfreisetzungssystems nach irgendeinem der Ansprüche 1 bis 14 zur Herstellung eines Arzneimittels zur Behandlung von Bluthochdruck, koronaren Herzerkrankungen, cerebralen Leistungsstörungen und zur Therapie neurologischer Defizite nach Subarachnoidalblutung.
18. Verwendung des osmotischen Arzneimittelfreisetzungssystems nach Anspruch 17 zur Herstellung eines Arzneimittels zur Behandlung von Bluthochdruck und koronaren Herzerkrankungen.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/06454

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/44

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 A61K

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 0 277 092 A (CIBA GEIGY AG) 3 August 1988 cited in the application see page 1, line 61 - page 2, line 6 see page 3, line 34-38 see page 3, line 64 - page 4, line 18 see page 4, line 38-42 see example 4 see claims 1,4 ---	1-18
A	EP 0 740 934 A (BAYER AG) 6 November 1996 see page 2, column 1, line 3-6 see page 1, column 2, line 27-38 see page 1, column 2, line 45 see page 2, column 3, line 26-32 see page 2, column 4, line 27-36 see example 11 see claims 1,2,4 --- -/--	1-18

Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

2 March 1999

Date of mailing of the international search report

10/03/1999

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La Gaetana, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/06454

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 40080 A (ANDRX PHARMACEUTICALS INC) 19 December 1996 cited in the application see page 2, line 20-34 see page 5, line 34-35 see example 1 see claims 1,11,12 ---	1-18
A	WO 97 39050 A (MENDELL CO INC EDWARD ;BAICHWAL ANAND R (US)) 23 October 1997 see page 4, line 16-23 see page 5, line 9-14 see page 5, line 23-26 see page 21; tables 1,2 -----	1-18



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/06454

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
EP 0277092	A	03-08-1988	AU 604825 B	03-01-1991
			AU 1023788 A	21-07-1988
			CA 1328403 A	12-04-1994
			DE 3868077 A	12-03-1992
			DK 13688 A	15-07-1988
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			GR 3003734 T	16-03-1993
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			JP 63174922 A	19-07-1988
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			MX 10086 A	01-12-1993
			NO 175564 B	25-07-1994
			PH 25901 A	19-12-1991
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			AU 2680597 A	07-11-1997
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# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen  
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**A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES**  
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**C. ALS WESENTLICH ANGESEHENE UNTERLAGEN**

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 277 092 A (CIBA GEIGY AG) 3. August 1988 in der Anmeldung erwähnt siehe Seite 1, Zeile 61 - Seite 2, Zeile 6 siehe Seite 3, Zeile 34-38 siehe Seite 3, Zeile 64 - Seite 4, Zeile 18 siehe Seite 4, Zeile 38-42 siehe Beispiel 4 siehe Ansprüche 1,4 ---	1-18
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Name und Postanschrift der internationalen 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  La Gaetana, R
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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie <sup>2</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	<p>EP 0 740 934 A (BAYER AG) 6. November 1996  siehe Seite 2, Spalte 1, Zeile 3-6  siehe Seite 1, Spalte 2, Zeile 27-38  siehe Seite 1, Spalte 2, Zeile 45  siehe Seite 2, Spalte 3, Zeile 26-32  siehe Seite 2, Spalte 4, Zeile 27-36  siehe Beispiel 11  siehe Ansprüche 1,2,4  -----</p>	1-18
A	<p>WO 96 40080 A (ANDRX PHARMACEUTICALS INC)  19. Dezember 1996  in der Anmeldung erwähnt  siehe Seite 2, Zeile 20-34  siehe Seite 5, Zeile 34-35  siehe Beispiel 1  siehe Ansprüche 1,11,12  -----</p>	1-18
A	<p>WO 97 39050 A (MENDELL CO INC EDWARD  ;BAICHWAL ANAND R (US)) 23. Oktober 1997  siehe Seite 4, Zeile 16-23  siehe Seite 5, Zeile 9-14  siehe Seite 5, Zeile 23-26  siehe Seite 21; Tabellen 1,2  -----</p>	1-18

# INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP 98/06454

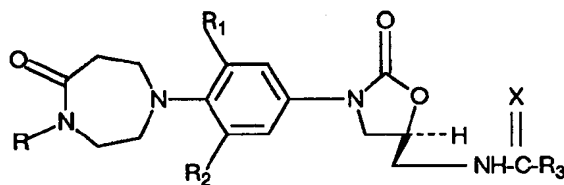
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			KR 9605139 B	22-04-1996
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			CA 2175293 A	03-11-1996
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			AU 6042796 A	30-12-1996
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WO 9739050	A	23-10-1997	US 5773025 A	30-06-1998
			AU 2680597 A	07-11-1997
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07D 413/10, A61K 31/42, C07D 413/14</p>	A1	<p>(11) International Publication Number: <b>WO 99/24428</b> (43) International Publication Date: 20 May 1999 (20.05.99)</p>
<p>(21) International Application Number: PCT/US98/22639 (22) International Filing Date: 30 October 1998 (30.10.98) (30) Priority Data: 60/065,376 12 November 1997 (12.11.97) US (71) Applicant (for all designated States except US): PHARMACIA &amp; UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): HESTER, Jackson, B., Jr. [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). (74) Agent: PHARMACIA &amp; UPJOHN COMPANY; Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, 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, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>

(54) Title: OXAZOLIDINONE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS



## (57) Abstract

A compound of Formula (I) or a pharmaceutically acceptable salt thereof, which is antimicrobial agents, effective against various human and veterinary pathogens, including gram positive aerobic organisms, gram negative organisms, and anaerobic organisms.

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## OXAZOLIDINONE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS

## BACKGROUND OF THE INVENTION

The present invention relates to novel oxazolidinone compounds or  
5 pharmaceutically acceptable salts thereof, and pharmaceutical agents that contain them as  
active ingredients for preventing or treating infectious diseases. The compounds are  
unique oxazolidinones having a hexahydro-1,4-diazepin-5-one substituent.

More specifically, novel oxazolidinone compounds of the present invention  
relates to useful antimicrobial agents, effective against various human and veterinary  
10 pathogens, including gram positive aerobic organisms such as multiply-resistant  
*staphylococci* and *streptococci*, gram negative organisms such as *H. influenzae* and *M.*  
*catarrhalis* as well as anaerobic organisms such as *bacteroides* and *clostridia* species,  
and acid-resistant organisms such as *Mycobacterium tuberculosis* and *Mycobacterium*  
*avium*.

15

## INFORMATION DISCLOSURE

International Publication No. 97/27188 discloses piperazine-3-one analogs which  
are homologs of the invention.

International Publication No. WO93/23384 discloses oxazolidinones containing a  
20 substituted diazine (piperazine) moiety and their uses as antimicrobials.

International Publication No. WO93/09103 discloses substituted aryl and  
heteroaryl-phenyl-oxazolidinones useful as antimicrobials.

International Publication No. WO90/02744 discloses 5'-indolinyl-5-  
amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5-  
25 midomethyloxazolidinones, and 3-(nitrogen substituted)-phenyl-5-  
amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patents 5,547,950,  
4,801,600, J. Med. Chem., 32, 1673-81 (1989); J. Med. Chem., 33, 2569-78 (1990);  
Tetrahedron, 45, 1323-26 (1989); and J. Med. Chem., 35, 1156 (1992).

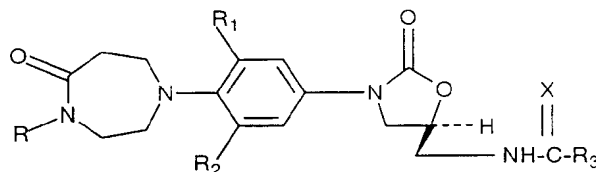
30 European Patent Publication 352,781 discloses phenyl and pyridyl substituted  
phenyl oxazolidinones.

European Patent Publication 316,594 discloses 3-substituted styryl  
oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and pyridylmethyl substituted phenyl oxazolidinones.

### SUMMARY OF THE INVENTION

5 The present invention provides an oxazolidinone derivative represented by the general structural Formula I or a pharmaceutically acceptable salt thereof



10

I

or a pharmaceutically acceptable salt thereof wherein:

R is H, C<sub>2-6</sub> alkenyl, C<sub>2-7</sub> alkynyl, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted with one or two of the following:

- a) F,
- 15 b) Cl,
- c) CF<sub>3</sub>,
- d) -OH,
- e) C<sub>1-4</sub> alkoxy,
- f) -CH<sub>2</sub>C(=O)C<sub>1-4</sub> alkyl,
- 20 g) -OC(=O)N(R<sub>4</sub>)<sub>2</sub>,
- h) C<sub>1-4</sub> alkyl S(O)<sub>n</sub>, (wherein n is 0 to 2),
- i) -CN,
- j) carboxy,
- k) -C<sub>1-4</sub> alkoxy carbonyl,
- 25 l) -C(=O)N(R<sub>4</sub>)<sub>2</sub>,
- m) -N(R<sub>4</sub>)SO<sub>2</sub>C<sub>1-4</sub> alkyl,
- n) -N(R<sub>4</sub>)C(=O)C<sub>1-4</sub> alkyl,
- o) -N(R<sub>4</sub>)C(=O)N(R<sub>4</sub>)<sub>2</sub>,
- p) -N(R<sub>4</sub>)C(=O)C<sub>1-4</sub> alkoxy,
- 30 q) aryl, or



r) Het;

aryl is phenyl, optionally substituted with one or two of the following:

- 5 a) F,  
 b) Cl,  
 c) Br,  
 d) -CF<sub>3</sub>,  
 e) CN,  
 f) C<sub>1-3</sub> alkoxy, or  
 g) C<sub>1-3</sub> alkylthio;

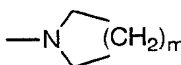
10 Het is a 5- or 6-membered heteroaromatic moiety having 1-3 N, O or S atoms, optionally substituted with the following:

- a) F,  
 b) Cl,  
 c) C<sub>1-3</sub> alkoxy,  
 15 d) C<sub>1-3</sub> alkylthio, or  
 e) CN;

R<sub>1</sub> and R<sub>2</sub> are independently H, F, or Cl;

R<sub>3</sub> is

- 20 a) C<sub>1-6</sub> alkyl, optionally substituted with one to three F or one to two Cl,  
 b) C<sub>1-6</sub> alkoxy,  
 c) amino,  
 d) C<sub>1-6</sub> alkylamino,  
 e) C<sub>1-6</sub> dialkylamino  
 f) C<sub>3-6</sub> cycloalkyl,  
 25 g) C<sub>1-6</sub> alkylthio, or

h)  (wherein m is 0, 1, 2, 3 or 4);

R<sub>4</sub> is

- 30 a) H, or  
 b) C<sub>1-3</sub> alkyl; and

X is O or S.

The present invention also provides an antimicrobial agent or pharmaceutical composition that contains the oxazolidinone compound or a pharmaceutically acceptable salt thereof as an active ingredient. The antimicrobial agent containing the active ingredient of the present invention can be used for treatment or prevention of infectious diseases.

#### DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula I as structurally disclosed above are useful antimicrobials. Typically, as further explained below, the compounds can be administered as antibacterial agents in a dosage range of from about 0.1 to 100 mg/kg or preferably from about 3.0 to about 50 mg/kg of body weight per day.

In the structural formula shown above 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<sub>i</sub>-C<sub>j</sub> defines the number of carbon atoms present from the integer "i" to the integer "j" inclusive.

The term "C<sub>1-6</sub> alkyl" used herein refers to an alkyl group having one to six carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and isomeric forms thereof; preferably methyl, ethyl, propyl and isomeric forms thereof.

The term "C<sub>2-6</sub> alkenyl" refers to at least one double bound alkenyl group having two to six carbon atoms such as, for example, vinyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl and isomeric forms thereof, preferably an alkenyl group having 2 to 6 carbon atoms, and more preferably an alkenyl group having 2 to 4 carbon atoms.

The term "C<sub>2-7</sub> alkynyl" refers to at least one triple bond alkynyl group having two to seven carbon atoms such as, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl and their isomeric forms thereof.

The term "C<sub>1-6</sub> alkylamino" refers to an alkyl group having one to six carbon atoms attached to an amino moiety.

The term "C<sub>1-6</sub> dialkylamino" refers to two alkyl groups having one to six carbon atoms attached to an amino moiety.

The term "C<sub>1-4</sub> alkoxy" refers to an alkyl group having one to four carbon atoms attached an oxygen atom of hydroxyl group such as, for example, methoxy, ethoxy,

propoxy, butoxy and isomeric forms thereof, preferably an alkoxy group having 1 to 2 carbon atoms.

The term "C<sub>1-6</sub> alkylthio" refers to an alkyl group having one to six carbon atoms attached a thio moiety such as, for example, methylthio, ethylthio, propylthio and isomeric forms thereof, preferably an alkylthio group having 1 to 2 carbon atoms.

The term "C<sub>3-6</sub> cycloalkyl" refers to three to six carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and isomeric forms thereof.

The term "aryl" refers to an phenyl moiety optionally substituted with one or two F, Cl, Br, -CF<sub>3</sub>, -CN, -C<sub>1-3</sub> alkoxy, or -C<sub>1-3</sub> alkylthio;

The term "Het" refers to a 5- or 6-membered heteroaromatic moiety having one to three atoms selected from the group consisting of O, N or S atoms such as, for example, furan, thiophene, pyrrole, pyrazole, triazoles, oxazole, thiazole, isothiazole, oxadiazoles, oxathiazole, pyridine, pyridazine, pyrimidine, pyrazine, piperazine and triazines all of which can optionally be substituted with one substituent selected from the group consisting of F, Cl, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> alkylthio or CN.

The compounds of the present invention can be converted to their salts according to conventional methods.

Pharmaceutically acceptable salts means acid addition salts useful for administering the compounds of this invention and these include hydrochloride, hydrobromide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, succinate, tartrate, citrate, 2-hydroxyethyl sulfonate, fumarate and the like when a basic group is present. These salts may be in hydrated form. Some of the compounds of this invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts".

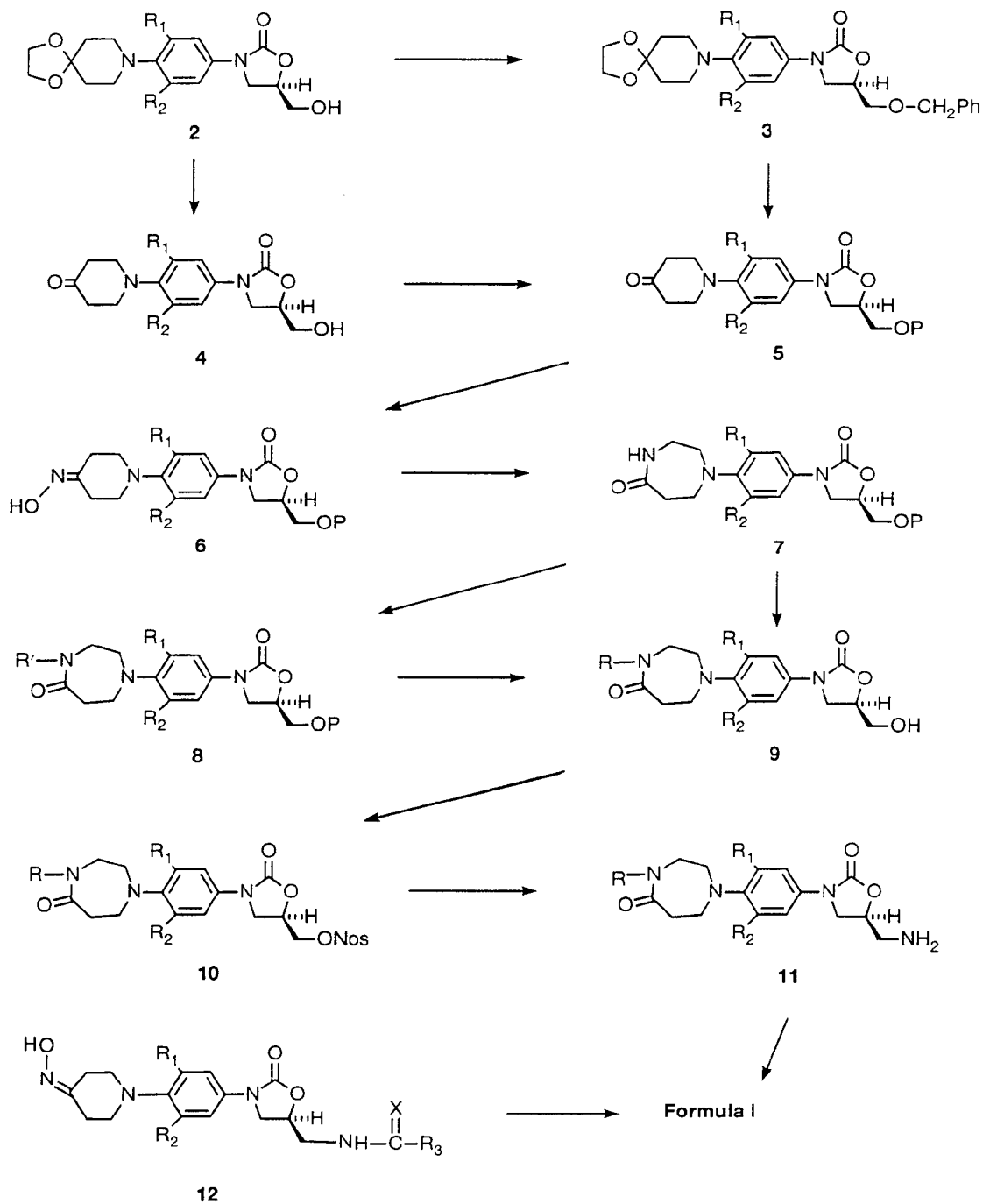
Due to the configuration at C-5 of the oxazolidinone ring of compounds as represented in the structure of Formula I the compounds of this invention may exist in geometric, optical and other isomeric forms and this invention embraces any of these isomers. The racemic mixture and enantiomers are all believed to be useful as an antibacterial. Regardless, the preferred absolute configuration at C-5 of the oxazolidinone ring of compounds is as represented in the structure of Formula I. This absolute configuration is called (S) under the Cahn-Ingold-Prelog nomenclature system. It is believed that a majority of the pharmacological activity resides in this (S)-enantiomer to produce the antibacterial effect.

Compounds of Formula I can be prepared as shown in Scheme I where P represents an alcohol protecting group such as benzyl or *tert*-butyldimethylsilyl. Structure 2 of this scheme are prepared according to the methods outlined in Example 1, Step 1 and 2. In Scheme I, the alcohols of 2 are protected as benzyl ethers. In a suitable procedure for this reaction, a solution of the alcohol 2 in a solvent such as Et<sub>2</sub>O or THF is allowed to react first with sodium hydride at 0-25 °C and then with benzyl bromide and tetrabutylammonium iodide at 0-25 °C to give structure 3. The ethylene ketal of 3 can then be removed with an acidic catalyst such as *p*-toluenesulfonic acid in acetone (as described in Example 1, Step 2) to give structure 5 where P is benzyl. Alternatively the ketal of 2 can be removed, the resulting structure 4 is allowed to react with *tert*-butyldimethylsilyl chloride and imidazole in DMF or *tert*-butyldimethylsilyl chloride and triethyl amine in methylene chloride to give structure 5 where the alcohol protecting group (P) is *tert*-butyldimethylsilyl. Ketone 5 is then allowed to react with hydroxylamine hydrochloride and sodium acetate in methanol-methylene chloride to give oxime 6 (see Example 1, Step 3). The Beckmann rearrangement of structure 6 is carried out with *p*-toluenesulfonyl chloride and sodium carbonate in aqueous acetone at 20-40 °C to give structure 7. For compounds of Formula I where R is not hydrogen, compounds 7 can be alkylated with R'Y where Y is Br, I, CH<sub>3</sub>SO<sub>3</sub> or *p*-CH<sub>3</sub>PhSO<sub>3</sub> and R' is an appropriate alkyl substituent. In one method for this alkylation compounds of structure 7 are allowed to react with sodium hydride and R'Y in a solvent such as DMF at 0-25 °C to give 8. Alternatively, structure 7 can react with R'Y, potassium hydroxide and tetrabutylammonium bromide in THF or acetonitrile at 20-50 °C to give 8. Deprotection of the alcohols 7 or 8 provide structure 9. When P is a benzyl ether, this can be accomplished by hydrogenolysis with hydrogen and a palladium catalyst in ethanol or with ammonium formate and a palladium catalyst in methanol at 10-30 °C. The *tert*-butyldimethylsilyl protecting group can be removed under acidic conditions or with fluoride ion. This deprotection can be carried out, for example, with trifluoroacetic acid in methylene chloride at 25 °C or with tetrabutylammonium fluoride in THF at 25 °C to give alcohol 9. Transformation of the alcohol 9 to the amine 11 can be carried out as described in Example 1, Step 1. Alternatively, the reaction of 9 with *m*-nitrobenzenesulfonyl chloride and triethylamine in methylene chloride at 5-25 °C will give the *m*-nitrobenzenesulfonate 10 which will react with ammonium hydroxide in THF or acetonitrile -isopropanol at 30-60 °C to give the amine 11. The reaction of compound

**11** with acyl halides, anhydrides, isocyanates, isothiocyanates or dithioesters provides compounds of Formula I.

Compounds of Formula I where R is hydrogen and X is oxygen are conveniently prepared by allowing compounds **12** to react with p-toluenesulfonyl chloride and sodium carbonate in aqueous acetone at 20-40 °C (see Example 1, Step 4).

Scheme I



The compounds of the invention are useful for the treatment of microbial infections in humans and other warm blooded animals by either parenteral, oral, or topical administration.

The term "treatment" as used herein means partial or total lessening of symptoms of a disease which a patient suffers from; the term "prevention" as used herein means  
5 partial or total avoidance of symptoms of a disease in a patient who, according to a doctor's diagnosis, may suffer from the disease or a related state unless the preventive measure is taken.

The pharmaceutical compositions of this invention may be prepared by combining  
10 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 and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent,  
15 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  
20 compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is made by employing conventional techniques in unit dosage form containing effective amounts of the active component,  
25 that is, the compound of Formula I according to this invention.

The quantity of active component, that is the compound of Formula I, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component  
30 will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting bacterial infections in humans and other animals that have been diagnosed with bacterial infections, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or

topically 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 mg/kg, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula I are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a 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 a few. 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. 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.

As a topical treatment, an effective amount of a compound of Formula I is admixed in a pharmaceutically acceptable gel or cream vehicle that can be applied to the patient's skin at the area of treatment. Preparation of such creams and gels is well known in the art and can include penetration enhancers.

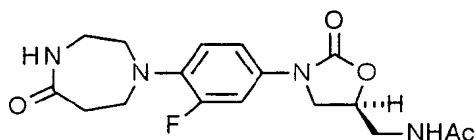
The compounds of this invention are useful antimicrobial agents, effective against various human and veterinary pathogens, including gram positive aerobic organisms such



as multiply-resistant *staphylococci* and *streptococci*, gram negative organisms such as *H. influenzae* and *M. catarrhalis* as well as anaerobic organisms such as *bacteroides* and *clostridia* species, and acid-resistant organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

5 In order to more fully illustrate the nature of the invention and the manner of practice the same, the following experimental examples are presented, but they should not be taken as limitations.

10 EXAMPLE 1 Preparation of (S)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.



15 Step 1: Preparation of (S)-N-[3-(3-fluoro-4-piperidin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide :

Diisopropylethylamine (15.7 ml) and 3,4-difluoronitrobenzene (5.0 ml) are added successively to an ethyl acetate solution (70 ml) of piperidine (5.77 g) and the mixture is stirred at room temperature for 2 days. Water is added to the reaction solution and the separating ethyl acetate layer are washed with water and brine, dried over anhydrous sodium sulfate. The solvent is evaporated to afford a nitro compound (10.1 g) in a yield of 100%. Palladium on carbon (10%, 1.0 g) is added to an ethyl acetate solution (101 ml) of the nitro compound (10.1 g) and the mixture is stirred at room temperature for 4 hours under hydrogen atmosphere. The palladium on carbon is filtered off and the filtrate is concentrated under vacuum to yield an amine (8.75 g, 100%). Sodium hydrogencarbonate (5.0 g) and benzyloxycarbonyl chloride (8.4 ml) are added successively to a tetrahydrofuran (THF) solution (100 ml) of the amine (8.75 g), and the mixture is stirred at room temperature for 14 hours. Water is added to the reaction solution and the separating THF layer is washed with water and brine, dried over anhydrous sodium sulfate. The solvent is evaporated and the residue is purified by silica gel column chromatography (solvent: ethyl acetate/hexane/chloroform = 1/6/4) to afford a benzyl carbamate (14.5 g) in a yield of 98%. Butyl lithium (1.6 M hexane solution: 5.2

ml) is added to a THF solution (24 ml) of the benzyl carbamate (2.75 g) at -78 C and the mixture is stirred for 5 min. At the same temperature, (R)-(-)-glycidyl butyrate (1.25 ml) is added to the stirred solution and the mixture is stirred for 14 hours while the temperature is raised slowly to room temperature. Water is added to the reaction solution and the separating THF layer is washed with water and brine, dried over anhydrous sodium sulfate. The solvent is evaporated and the residue is purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 3/1) to afford an alcohol (2.20 g) in a yield of 89%. Tosyl chloride (2.85 g) is added to a pyridine solution (8 ml) of the alcohol (2.20 g) and the mixture is stirred at room temperature for 6 h. Water (32 ml) is added to the reaction solution and the mixture is stirred for 1 hour. The resulting precipitate is collected by filtration and washed with water, followed by drying under vacuum at room temperature to afford a tosylate (3.28 g) in a yield of 98%. Sodium azide (3.80 g) is added to a dimethylformamide (DMF) solution (23 ml) of the tosylate (3.28 g) at room temperature and the mixture is stirred at 65 C for 5.5 hours. After the reaction mixture is cooled to room temperature, water is added and the mixture is extracted with ethyl acetate; the organic layer is concentrated under vacuum. The resulting residue is dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate. The solvent is evaporated and the residue is purified by silica gel column chromatography (solvent: ethyl acetate/hexane = 1/1) to afford an azide (2.20 g) in a yield of 94%. Acetic anhydride (0.65 ml) and pyridine (1.0 ml) are added to an ethyl acetate solution (19 ml) of the azide (2.20 g) at room temperature; after addition of palladium on carbon (10%, 0.22 g), the mixture is stirred at room temperature for 6 hours under 1 atm hydrogen atmosphere. The palladium on carbon is filtered off and the filtrate is washed with water and brine, dried over anhydrous sodium sulfate. The solvent is evaporated and the residue is purified by silica gel column chromatography (solvent: acetone/hexane = 1/1) to afford the title compound.

Step 2: Preparation of (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide.

Using a commercially available 1,4-dioxo-8-aza-spiro[4.5]decane, (S)-N-{3-[4-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide is synthesized by the same method as in Step 1. To an acetone solution (70 ml) of this compound (3.79 g), water (20 ml) and p-toluenesulfonic acid monohydrate (3.66 g) are added successively and the mixture is heated under reflux for 3 hours. After

the reaction mixture is cooled to room temperature, acetone is distilled off and the aqueous layer is neutralized with triethylamine. The solution is extracted with methylene chloride and the organic layer is washed with brine, dried over anhydrous sodium sulfate. The solvent is evaporated and the residue is purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1 - 25/1) to afford the title compound .

Step 3: Preparation of (*S*)-N-{3-[3-fluoro-4-(4-hydroxyimino-piperidin-1-yl)-phenyl]-2-oxo oxazolidin-5-ylmethyl}-acetamide.

Sodium acetate (517 mg) and hydroxylamine hydrochloride (219 mg) are successively added to a methanol-methylene chloride solution (10-10 ml) of 1.00 g of the product of Step 2, and the mixture is stirred at room temperature for 2 days. The solvent is evaporated and the residue is dissolved in methanol, followed by addition of a silica gel (8 g). Methanol is evaporated and the residue is purified by silica gel column chromatography (solvent: chloroform/methanol = 50/1 - 25/1) to afford the title compound.

Step 4: Preparation of (*S*)-N-[[3-[3-Fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

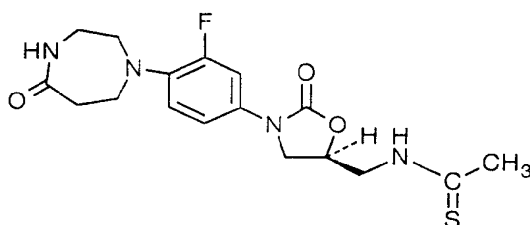
A stirred mixture of the compound of product of Step 3 (0.200 g, 0.549 mmol) in acetone (5.3 mL), under nitrogen, is treated first with 5% aqueous sodium carbonate (5.3 mL) and then, dropwise during 3minutes with a solution of *p*-toluenesulfonyl chloride (0.16 g, 0.82 mmol) in acetone (2.7 mL). Initially this mixture is a two phase solution; however, after about 25minutes a precipitate began to form. It is kept at ambient temperature (23 °C) for 4 hours and filtered. The filtrate is concentrated under reduced pressure to remove acetone and the aqueous residue is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract is dried (MgSO<sub>4</sub>) and concentrated to give a small amount of crude product. Most of the product is in the aqueous layer which is concentrated in vacuo. The residue is combined with the crude product from the CH<sub>2</sub>Cl<sub>2</sub> extract and chromatographed on silica gel with mixtures of MeOH-NH<sub>4</sub>OH-CH<sub>2</sub>Cl<sub>2</sub> that continued 3-5% MeOH and 0.3-0.5% NH<sub>4</sub>OH. The product is crystallized from MeOH-EtOAc to give the title compound. mp 140-146 °C;

MS *m/z* (relative intensity) 364 (M<sup>+</sup>, 96.1), 320 (100), 306 (6.7), 294 (10.9), 236 (41.8);

HRMS calcd for C<sub>17</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>4</sub>; 364.1547 (M<sup>+</sup>); found 364.1545;

<sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 1.81 (s, 3H), 2.57 (m, 2H), 3.07 (m, 4H), 3.24 (m, 2H), 3.38 (t, 2H), 3.67 (d, d, 1H), 4.06 (t, 1H), 4.68 (m, 1H), 7.08 (t, 1H), 7.13 (d, d, 1H), 7.45 (d, d, 1H), 7.65 (t, 1H), 8.21 (t, 1H).

5 EXAMPLE 2: Preparation of (*S*)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide.



10 Step 1: Preparation of (*S*)-[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl *tert*-butyldimethylsilyl ether.

A stirred solution of 10.6 g (0.03 mol) of (*S*)-[3-[4-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol, the intermediate of formula 2  
 15 (Scheme 1) for the preparation of (*S*)-N-{3-[3-fluoro-4-(4-oxopiperidin-1-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-acetamide (Example 1, Step 2), in acetone (230 mL) is treated with water (65 mL) and *p*-toluenesulfonic acid monohydrate (11.4 g, 0.06 mol), refluxed under nitrogen for 5 hours and kept at ambient temperature (24 °C) for 18 hours. It is then concentrated in vacuo to remove acetone. The aqueous residue is neutralized  
 20 with sodium bicarbonate and extracted with ethyl acetate; the extract is washed with saturated sodium bicarbonate, water and dilute sodium chloride, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give the ketone, a compound of formula 4 (Scheme 1). A stirred solution of the ketone and triethylamine (12.5 mL, 0.09 mol) in methylene chloride (100 mL) is treated with *tert*-butyldimethylsilyl chloride (6.03 g, 0.04 mol) and kept under nitrogen at  
 25 ambient temperature for 23 hours. Additional *tert*-butyldimethylsilyl chloride (3.0 g) is added and the mixture is kept at ambient temperature for an additional 20 hours. Additional triethylamine (3.0 mL) and *tert*-butyldimethylsilyl chloride (3.0 g) are again added and the mixture is kept at ambient temperature for 4 days, diluted with methylene chloride, washed with water and dilute sodium chloride, dried (Na<sub>2</sub>SO<sub>4</sub>) and  
 30 concentrated. Chromatography of the residue on silica gel with mixtures of acetone-

heptane that contained 20-30% acetone gave 7.72 g of the *tert*-butyldimethylsilyl (TBDMS) ether, a compound of formula 5 (Scheme 1) where P is TBDMS. A stirred solution of the TBDMS ether (7.27 g, 17.2 mmol) in methanol (150 mL) is treated dropwise with a solution of hydroxylamine hydrochloride (1.44 g, 0.021 mol) and sodium acetate (1.72 g, 0.021 mol) in water (15 mL) and kept at ambient temperature for 20 hours. The mixture is concentrated under reduced pressure. A solution of the residue, a white solid, in methylene chloride is washed with water and dilute sodium chloride, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give 7.25 g of the oxime, a compound of formula 6 (Scheme 1). A stirred solution of the oxime in acetone (165 mL), under nitrogen, is treated with 5% aqueous sodium carbonate (165 mL) and then dropwise during 20 minutes with a solution of *p*-toluenesulfonyl chloride (4.92 g, 0.0258 mol) in acetone (80 mL). The mixture is kept at ambient temperature for 18 hours and then concentrated under reduced pressure. A solution of the residue in methylene chloride is washed with water and dilute sodium chloride, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography of the residue on silica gel with 3% methanol - 0.3% ammonium hydroxide-methylene chloride gave 5.98 g of the titled compound.

Step 2: Preparation of (*S*)-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]amine.

An ice cold, stirred mixture of the product of Example 2, Step 1 (0.22 g, 0.50 mmol) in tetrahydrofuran (THF; 15 mL), under nitrogen, is treated dropwise during 2 minutes, with a 1M solution of tetrabutylammonium fluoride in THF (1.5 mL). The mixture is kept in the ice bath for 10 minutes and at ambient temperature (24 °C) for 1 hour 25 minutes, diluted with ethyl acetate, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography of the residue on silica gel with mixtures of methanol-methylene chloride containing 3-6% methanol gave 0.15 g of the alcohol, a compound of formula 9 (Scheme 1) where R is hydrogen: MS(ES) *m/z* 324 ( $\text{M}+\text{H}^+$ ). A stirred suspension of the alcohol (0.15 g, 0.46 mmol) in methylene chloride (15 mL) and THF (8 mL), under nitrogen, is treated with triethylamine (0.5 mL, 1.4 mmol) and then portionwise during 1 minute at ambient temperature, with 0.14 g (0.56 mmol) of *m*-nitrobenzenesulfonyl chloride. The mixture is stirred for 90 minutes, mixed with additional methylene chloride (10 mL) to give a solution and kept at ambient temperature for 1 hour. It is then kept for several days at -11 °C, diluted with methylene chloride, washed with saturated sodium bicarbonate, water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and

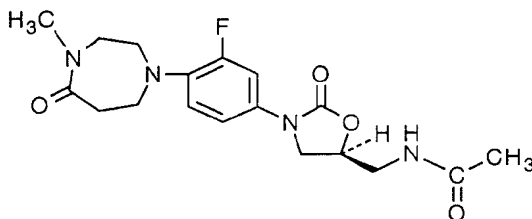
concentrated to give 0.21 g of the *m*-nitrobenzenesulfonate, a compound of formula 10 (Scheme 1). A stirred mixture of the *m*-nitrobenzenesulfonate (0.21 g, 0.44 mmol), acetonitrile (10 mL), 2-propanol (10 mL) and 29% ammonium hydroxide (10 mL) is warmed at 45-50 °C under a Dry Ice-acetone condenser for 4.5 hours and kept at ambient temperature for 18 hours. Additional ammonium hydroxide (5 mL) is added and the mixture is warmed at 45-50 °C for 4.5 hours, kept at ambient temperature for 1 hour, treated with 5 mL of ammonium hydroxide and kept at ambient temperature for 18 hours. It is then concentrated to give a yellow solid which is chromatographed on silica gel with mixtures of methanol-methylene chloride containing 5-7.5% methanol followed by 8% methanol-0.2% ammonium hydroxide-methylene chloride to give the titled product.

Step 3: Preparation of (*S*)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide.

A stirred solution of 0.12 g of the product of Example 2, Step 2 and 0.40 mL of triethylamine in a mixture of methylene chloride (10 mL) and methanol (10 mL), under nitrogen, is treated with ethyl dithioacetate (0.05 mL) and kept at ambient temperature for 145 hours. Additional 0.05 mL portions of ethyl dithioacetate are added after 24, 31 and 49 hours; additional triethylamine (1.0 mL) is also added after 49 hours. The mixture is concentrated to a small volume, diluted with ethyl acetate, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with 3.5% methanol-methylene chloride gave 0.061 g of the titled product.

<sup>1</sup>H NMR [300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] δ 2.42 (s, 3H), 2.56 (m, 2H), 3.07 (m, 4H), 3.24 (m, 2H), 3.76 (dd, 1H), 3.87 (m, 2H), 4.11 (t, 1H), 4.91 (m, 1H), 7.12 (m, 2H), 7.46 (dd, 1H), 7.67 (broad s, 1H), 10.35 (broad s, 1H).

EXAMPLE 3: Preparation of (*S*)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-4-methyl-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide.



30

Step 1: Preparation of (*S*)-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-4-methyl-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]amine.

A mixture of 0.63 g (1.4 mmol) of the product of Example 2, Step 2, methyl iodide (0.093 mL) and THF (40 mL) is added dropwise during 12 minutes, under nitrogen, to a stirred mixture of powdered potassium hydroxide (0.12 g) and tetrabutylammonium bromide (0.096 g) in THF (10 mL) and kept at ambient temperature for 20 hours. It is then diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with mixtures of acetone-methylene chloride that contained 10-40% acetone gave 0.46 g (71%) of the methylated product, a compound of formula 8 (Scheme 1) where R' is methyl. An ice cold, stirred mixture of this product (0.17 g, 0.38 mmol) and THF (12 mL), under nitrogen, is treated dropwise with a 1M solution of tetrabutylammonium fluoride in THF (1.2 mL). It is kept in the ice bath for 15 minutes and at ambient temperature for 3 hours, mixed with ice water and extracted with ethyl acetate. The extract is washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated to give 0.15 g of the alcohol, a compound of formula 9 (Scheme 1). A stirred, ice cold solution of the alcohol (0.52 g, 1.5 mmol) and triethylamine (0.60 mL) in methylene chloride (45 mL) is treated portionwise during 5 minutes with *m*-nitrobenzenesulfonyl chloride (0.42 g). The mixture is kept in the ice bath for 15 minutes and at ambient temperature for 3 hours, diluted with methylene chloride, washed with saturated sodium bicarbonate, water and brine, dried (MgSO<sub>4</sub>) and concentrated to give the *m*-nitrobenzenesulfonate, a compound of formula 10 (Scheme 1). A stirred mixture of this product, acetonitrile (35 mL), 2-propanol (35 mL) and concentrated ammonium hydroxide (35 mL) is kept at 45-50 °C under a Dry Ice-acetone condenser for 4.5 hours and at ambient temperature for 20 hours. Additional ammonium hydroxide (6 mL) is added and the mixture is kept at 45-50 °C for 5.5 hours and at ambient temperature for 18 hours. The mixture is then concentrated under reduced pressure to remove the organic solvents and the aqueous residue is extracted first with ethyl acetate and then methylene chloride. The extracts are washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with mixtures of methanol-methylene chloride containing 7.5-10% methanol gave the titled compound.

Step 2: Preparation of (*S*)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-4-methyl-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

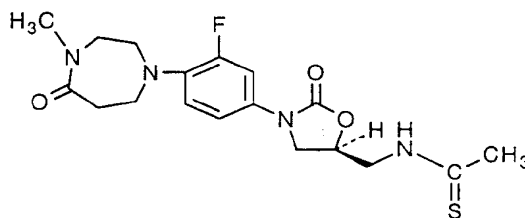
A stirred, ice cold mixture of 0.10 g (0.30 mmol) of the product of Example 3, Step 1, and pyridine (1.74 mL), under nitrogen, is treated dropwise with acetic anhydride (0.57 mL, 6.04 mmol) and kept in the ice bath for 15 minutes and at ambient temperature for 3.5 hours. It is then concentrated in vacuo; the residue is mixed with ice water and saturated sodium bicarbonate and extracted with ethyl acetate. The extract is washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. Crystallization of the residue from ethyl acetate-methanol gave 0.053 g of the titled compound.

mp 203-204 °C.

MS(ES) *m/z* 379 (M+H<sup>+</sup>), 401 (M+Na<sup>+</sup>).

Anal. calcd for C<sub>18</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>4</sub>: C, 57.13; H, 6.13; N, 14.81. Found: C, 57.05; H, 6.23; N, 14.85.

EXAMPLE 4 Preparation of (*S*)-N-[[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-4-methyl-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioacetamide.



An ice cold, stirred solution of 0.18 g (0.535 mmol) of the product of Example 3, Step 1 and triethylamine (0.21 mL) in THF (8 mL) and methylene chloride (10 mL) is treated with a solution of ethyl dithioacetate (0.074 mL, 0.64 mmol) in THF (2 mL). The mixture is kept at ambient temperature for 20 hours, treated with one drop of additional ethyl dithioacetate and kept at ambient temperature for 7 hours. It is then concentrated under a stream of nitrogen. The residue is mixed with methylene chloride, washed with saturated sodium bicarbonate, water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography of the residue on silica gel with mixtures of methanol-methylene chloride containing 2-4% methanol and crystallization of the product from ethyl acetate gave 0.13 g of the titled compound. mp 157-158 °C.

Anal. calcd for C<sub>18</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub>S: C, 54.81; H, 5.88; N, 14.20. Found: C, 54.83; H, 5.93; N, 14.11.



## EXAMPLE 5 MIC Test Method

The *in vitro* MICs of test compounds are determined by a standard agar dilution method. A stock drug solution of each analog is prepared in the preferred solvent, usually DMSO:H<sub>2</sub>O (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<sup>4</sup> to 10<sup>5</sup> 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 Table I.

TABLE I

Example No.	SAUR <sup>a</sup> 9213 MIC	SEPI <sup>b</sup> 12084 MIC	EFAE <sup>c</sup> 9217 MIC	SPNE <sup>d</sup> 9912 MIC	HINF <sup>e</sup> 30063 MIC	MCAE <sup>f</sup> 30610 MIC
1	4	1	4	0.5	8	8
3	4	1	4	1	32	8
4	1	<0.5	1	<0.5	8	2

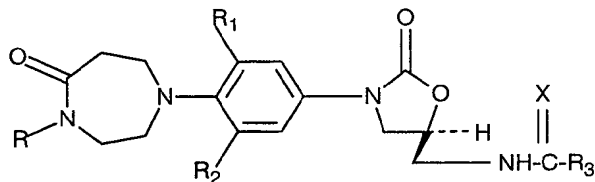
20

- a) *S. aureus*, culture 9213
- b) *S. epidermidis*, culture 12084
- c) *E. faecalis*, culture 9217
- d) *S. pneumoniae*, culture 9912
- e) *H. influenzae*, culture 30063
- f) *M. catarrhalis*, culture 30610

25

## CLAIMS

1. A compound of Formula I:



5

I

or a pharmaceutically acceptable salt thereof wherein:

R is H, C<sub>2-6</sub> alkenyl, C<sub>2-7</sub> alkynyl, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted with one or two of the following:

- 10 a) F,  
 b) Cl,  
 c) CF<sub>3</sub>,  
 d) -OH,  
 e) C<sub>1-4</sub> alkoxy,  
 15 f) -CH<sub>2</sub>C(=O)C<sub>1-4</sub> alkyl,  
 g) -OC(=O)N(R<sub>4</sub>)<sub>2</sub>,  
 h) C<sub>1-4</sub> alkyl S(O)<sub>n</sub>, (wherein n is 0, 1 or 2),  
 i) -CN,  
 j) carboxy,  
 20 k) -C<sub>1-4</sub> alkoxycarbonyl,  
 l) -C(=O)N(R<sub>4</sub>)<sub>2</sub>,  
 m) -N(R<sub>4</sub>)SO<sub>2</sub>C<sub>1-4</sub> alkyl,  
 n) -N(R<sub>4</sub>)C(=O)C<sub>1-4</sub> alkyl,  
 o) -N(R<sub>4</sub>)C(=O)N(R<sub>4</sub>)<sub>2</sub>,  
 25 p) -N(R<sub>4</sub>)C(=O)C<sub>1-4</sub> alkoxy,  
 q) aryl, or  
 r) Het;

aryl is phenyl, optionally substituted with one or two of the following:

- a) F,  
 30 b) Cl,

- c) Br,  
 d) -CF<sub>3</sub>,  
 e) CN,  
 f) C<sub>1-3</sub> alkoxy, or  
 5 g) C<sub>1-3</sub> alkylthio;

Het is a 5- or 6-membered heteroaromatic moiety having 1-3 N, O or S atoms, optionally substituted with the following:

- a) F,  
 b) Cl,  
 10 c) C<sub>1-3</sub> alkoxy,  
 d) C<sub>1-3</sub> alkylthio, or  
 e) CN;

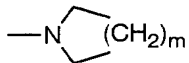
R<sub>1</sub> and R<sub>2</sub> are independently

- a) H,  
 15 b) F, or  
 c) Cl;

R<sub>3</sub> is

- a) C<sub>1-6</sub> alkyl, optionally substituted with one to three F or one to two Cl,  
 b) C<sub>1-6</sub> alkoxy,  
 20 c) amino,  
 d) C<sub>1-6</sub> alkylamino,  
 e) C<sub>1-6</sub> dialkylamino  
 f) C<sub>3-6</sub> cycloalkyl,  
 g) C<sub>1-6</sub> alkylthio, or

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- h)  (wherein m is 0, 1, 2, 3 or 4);

R<sub>4</sub> is

- a) H, or  
 b) C<sub>1-3</sub> alkyl; and  
 30 X is O or S.

2. A compound of Claim 1 wherein X is O.

3. A compound of Claim 1 wherein X is S.
4. A compound of Claim 1 wherein R is H.
5. A compound of Claim 1 wherein R is C<sub>1-4</sub> alkyl.
6. A compound of Claim 1 wherein R<sub>3</sub> is C<sub>1-4</sub> alkyl, optionally substituted with one to three F or one to two Cl.
7. The compound of Claim 1 wherein Formula I is the S-enantiomer.
8. A compound of Claim 1 which is
- (a) (S)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
- (b) (S)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide,
- (c) (S)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-4-methyl-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, or
- (d) (S)-N-[[3-[3-fluoro-4-(1,2,3,4,6,7-hexahydro-4-methyl-5-oxo-1,4-diazepin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide.
9. A method for treating microbial infections in human comprising administering to a patient in need thereof an effective amount of a compound of Formula I as shown in Claim 1.
10. A pharmaceutical composition comprising a compound of Formula I as shown in Claim 1 and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/22639

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D413/10 A61K31/42 C07D413/14

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 A61K

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 97 27188 A (ZENECA LTD ) 31 July 1997 cited in the application see claims ---	1-10
Y	WO 95 25106 A (UPJOHN CO ) 21 September 1995 see claims ---	1-10
Y	WO 93 23384 A (UPJOHN CO ) 25 November 1993 cited in the application see claims ---	1-10
Y	WO 95 14684 A (UPJOHN CO ) 1 June 1995 see claims -----	1-10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- "P" document published prior to the international filing date but later than the priority date claimed

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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
- "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.
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Date of the actual completion of the international search

Date of mailing of the international search report

4 February 1999

12/02/1999

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Authorized officer  
  
Henry, J

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/22639

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
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			NZ 274966	A 26-01-1998
			US 5652238	A 29-07-1997
			ZA 9407885	A 09-04-1996

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/22639

## 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.: 9  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 9 is 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 APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>C07D 413/10, A61K 31/38, 31/42</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 99/29688</b></p> <p>(43) International Publication Date: 17 June 1999 (17.06.99)</p>									
<p>(21) International Application Number: PCT/US98/24526</p> <p>(22) International Filing Date: 23 November 1998 (23.11.98)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/067,830</td> <td>5 December 1997 (05.12.97)</td> <td>US</td> </tr> <tr> <td>60/089,498</td> <td>16 June 1998 (16.06.98)</td> <td>US</td> </tr> <tr> <td>60/100,185</td> <td>14 September 1998 (14.09.98)</td> <td>US</td> </tr> </table> <p>(71) Applicant (for all designated States except US): PHARMACIA &amp; UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): POEL, Toni-Jo [US/US]; 304 Anderson, Wayland, MI 49348 (US). MARTIN, Joseph, P., Jr. [US/US]; 6749 North 32nd Street, Richland, MI 49093 (US). BARBACHYN, Michael, R. [US/US]; 32 Viola Drive, East Hampton, CT 06424 (US).</p> <p>(74) Agent: YANG, Lucy, X.; Pharmacia &amp; Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p>		60/067,830	5 December 1997 (05.12.97)	US	60/089,498	16 June 1998 (16.06.98)	US	60/100,185	14 September 1998 (14.09.98)	US	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, 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, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
60/067,830	5 December 1997 (05.12.97)	US									
60/089,498	16 June 1998 (16.06.98)	US									
60/100,185	14 September 1998 (14.09.98)	US									
<p>(54) Title: S-OXIDE AND S,S-DIOXIDE TETRAHYDROTHIOPYRAN PHENYLOXAZOLIDINONES</p>											
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(I)</p> </div> <div style="text-align: center;"> <p>(II)</p> </div> </div>											
<p>(57) Abstract</p> <p>The present invention provides compounds of formula (I) and formula (II) useful as antimicrobial agents wherein R<sub>1</sub> is methyl, ethyl, cyclopropyl, or dichloromethyl; R<sub>2</sub> and R<sub>3</sub> are independently hydrogen or fluoro; R<sub>4</sub> is ethyl or dichloromethyl. The invention also relates to a novel assay for determining the inhibitory activity of oxazolidinones to human monoamine oxidase.</p>											



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S-OXIDE AND S,S-DIOXIDE TETRAHYDROTHIOPYRAN  
PHENYLOXAZOLIDINONES

FIELD OF THE INVENTION

5           The present invention relates to sulfur oxidized tetrahydrothiopyran  
N-phenyloxazolidinone compounds in which the phenyloxazolidinone moiety is  
linked with a thiopyran ring through a carbon-carbon bond. The invention also  
relates to a novel assay for determining the inhibitory activity of oxazolidinones to  
human monoamine oxidase.

10

BACKGROUND OF THE INVENTION

The oxazolidinone antibacterial agents are a novel synthetic class of  
antimicrobials with potent activity against a number of human and veterinary  
pathogens, including gram-positive aerobic bacteria such as multiply-resistant  
15 staphylococci and streptococci, gram-negative aerobic bacteria such as *H. influenzae*  
and *M. catarrhalis*, as well as anaerobic organisms such as bacteroides and  
clostridia species, acid-fast organisms such as *Mycobacterium tuberculosis* and  
*Mycobacterium avium*. It is also known that as a chemical compound class,  
oxazolidinones inhibit monoamine oxidase (MAO), the enzyme responsible for  
20 preventing acute blood pressure elevation by the endogenous and dietary amine,  
tyramine. Accordingly, there is a demand to discover oxazolidinone antibiotics  
which possess minimum MAO inhibitory activity to eliminate the related side effects  
from potential drug-drug interactions. There is also currently an interest in  
developing a high throughput screening assay to determine the MAO inhibitory  
25 activity of oxazolidinone antibiotics.

INFORMATION DISCLOSURE

International Publication No. WO 97/09328; pending U.S. application, Serial  
No. 08/696,313, discloses phenyloxazolidinones having a C-C bond to 4-8 membered  
30 heterocyclic rings, which generically covers the compounds of the present  
application.

International Publication No. WO 97/30995 discloses antibiotic oxazolidinone  
derivatives.

Other references that disclose aromatic heterocycles attached to a  
35 phenyloxazolidinone include European Patent Publication No. 0352 781 A2,  
International Publication No. WO 9309103-A1 and U.S. Patent Nos. 5,130,316,

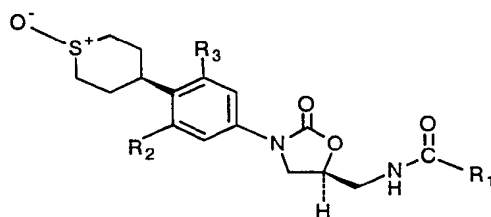
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Additional references of general interest include: Castagnoli Jr. et al.,  
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 15 Radiochemical Assay for Monoamine Oxidase Activity - Problems and Pitfalls",  
*Biochemical Pharmacology*, Vol. 46, No. 8, pp. 1311-1316 (1993).

#### SUMMARY OF THE INVENTION

In one aspect, the present invention is a compound of formula I

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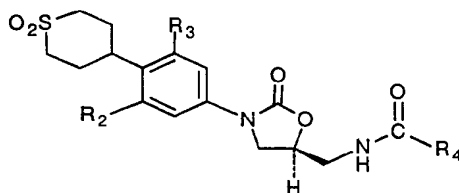
I

or pharmaceutically acceptable salts thereof wherein R<sub>1</sub> is methyl, ethyl, cyclopropyl,  
 or dichloromethyl; R<sub>2</sub> and R<sub>3</sub> are the same or different and are  
 hydrogen or fluoro. The formula I of the invention embraces both *trans*- and *cis*-  
 isomers.

30

In another aspect, the present invention is a compound of formula II

35



II

or pharmaceutically acceptable salts thereof wherein R<sub>2</sub> and R<sub>3</sub> are the same as defined above; R<sub>4</sub> is ethyl or dichloromethyl.

Preferably, in the above formula I, R<sub>1</sub> is methyl or ethyl.

Preferably, in the above formula II, R<sub>4</sub> is ethyl.

5 Also preferably, compounds of formulas I and II are mono-fluoro compounds.

Preferred compounds of the present invention are:

- a. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
- b. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,
- 10 c. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide,
- d. [4(S)-cis]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
- 15 e. (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,
- f. (S)-(-)-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
- g. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,
- 20 h. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide, or
- i. [4(S)-trans]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

25 More preferred is compound [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

In still another aspect, the present invention provides a method of assaying an oxazolidinone antibiotic's MAO inhibitory activity, which comprises the steps of

- a) incubating an oxazolidinone with a monoamine oxidase in a buffer
- 30 solution having pH value from about 7.0 to about 7.5;
- b) adding 1-methyl-4-(1-methyl-2-pyrrolyl)-1,2,3,6-tetrahydropyridine into said incubating solution; and
- c) determining the monoamine oxidase inhibitory activity of said oxazolidinone.

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#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides sulfur oxidized tetrahydrothiopyran phenyloxazolidinone of formula I and formula II as defined above. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens as disclosed above. In particular, it has been discovered that, while  
5 oxazolidinones as a chemical compound class are inhibitors of human monoamine oxidase A (MAO A) and monoamine oxidase B (MAO B), the compounds of the present invention have unexpectedly weak MAO inhibitory activity, which indicates that these compounds possess the capacity to minimize or eliminate potential drug-drug interactions since strong inhibition of monoamine oxidase can result in  
10 altered clearance rates for other compounds normally metabolized by it, including several pharmaceuticals.

The present invention also provides a novel spectrophotometric assay for determining the ability of an oxazolidinone to inhibit human monoamine oxidases. MAO A and MAO B are membrane bound flavoproteins localized in the outer  
15 mitochondrial membrane. The two enzymes prefer different substrate in catalyzing the oxidative deamination of biogenic and xenobiotic amines. Historically, MAO enzymes have been assayed by radioactive end point (discontinuous) methods using two different substrates. These methods have been criticized because as commonly practiced, they lack the proof of linearity of the reaction time course under  
20 prevailing assay conditions. The use of these methods are also inadequate due to their cumbersome nature when screening a large number of compounds in a short period of time. The methods involve multiple processing steps including solvent extraction of reaction products. These steps lead to inaccuracies in the resulting data. See: Matthew J. Krueger, et al., "An Examination of the Reliability of the  
25 Radiochemical Assay for Monoamine Oxidases A and B", *Analytical Biochemistry*, Vol. 214, pp. 116-123 (1993); Keith F. Tipton, et al., "Commentary - The Radiochemical Assay for Monoamine Oxidase Activity - Problems and Pitfalls", *Biochemical Pharmacology*, Vol. 46, No. 8, pp. 1311-1316 (1993).

We have now developed a continuous, visible, high throughput screening  
30 spectrophotometric assay of MAO based on a colored product of oxidation of a chromogenic substrate, 1-methyl-4-(1-methyl-2-pyrrolyl)-1,2,3,6-tetrahydropyridine. The assay works equally well with MAO-A and MAO-B. It is sensitive, linear and tolerant of the low turbidity level introduced by the solubilized and partially purified MAO A and MAO B. The reaction product is stable for many hours and the reaction  
35 rates for both enzymes are linear functions of time and enzyme concentration. The assay has been successfully adapted to a microtiterplate format, therefore, it can

provide information on thousands of tested oxazolidinone compounds in a short period of time. Even in the microtiterplate screening format, accurate information concerning the linearity of the reaction rate under prevailing assay conditions is obtained.

5 In addition, while evaluation of oxazolidinone compounds' MAO inhibitory activity is the most important utility of this assay, the present invention can be used to detect any inhibitor of MAO enzymes.

For the purpose of the present invention, the term "pharmaceutically acceptable salts" refers to salts useful for administering the compounds of this  
10 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.

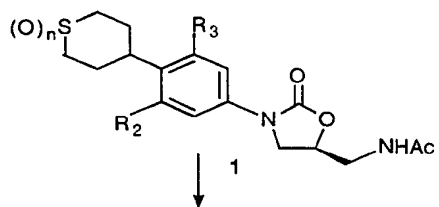
Compounds of the present invention may be prepared in accordance to  
15 Schemes I and II following methodology known to those skilled in the art. Briefly, as shown in Scheme I, hydrolysis of the N-acetyl oxazolidinone **1** with hydroxylamine hydrochloride, for instance, provides the amine **2**. Treatment of structure **2** with an acid chloride or anhydride in the presence of a base affords N-acetyl oxazolidinone **3**, wherein n is 1 or 2, and R is R<sub>1</sub> or R<sub>4</sub> as defined above.  
20 Structure **1** in which n is 2 can be obtained according to the procedures disclosed in International Publication No. WO 97/09328; structure **1** in which n is 1 can be prepared as shown in Scheme II.

Compound **4** in Scheme II, which can be obtained according to the procedures disclosed in International Publication No. WO 97/09328, may be reduced to the  
25 corresponding cis- and trans-sulfoxides **6** and **7** by catalytic hydrogenation in the presence of an appropriate catalyst and a suitable solvent, as depicted in route a. Alternatively, sulfide **5**, which may be isolated as a by-product in the reduction shown in route a or synthesized by the reduction of **6** or **7** with a sulfonic acid-sodium iodide system, can be oxidized with an appropriate oxidizing agent such  
30 NaIO<sub>4</sub> or meta-chloroperoxybenzoic acid in an appropriate solvent to provide **6** and **7**, as depicted in route b of Scheme II. The isomeric mixture of **6** and **7** can be separated by chromatography.

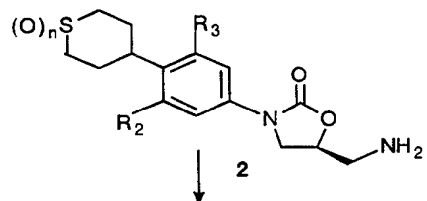
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## SCHEME I

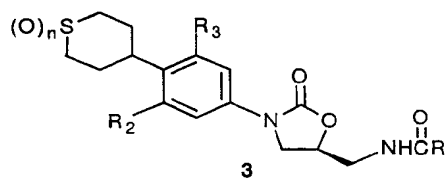
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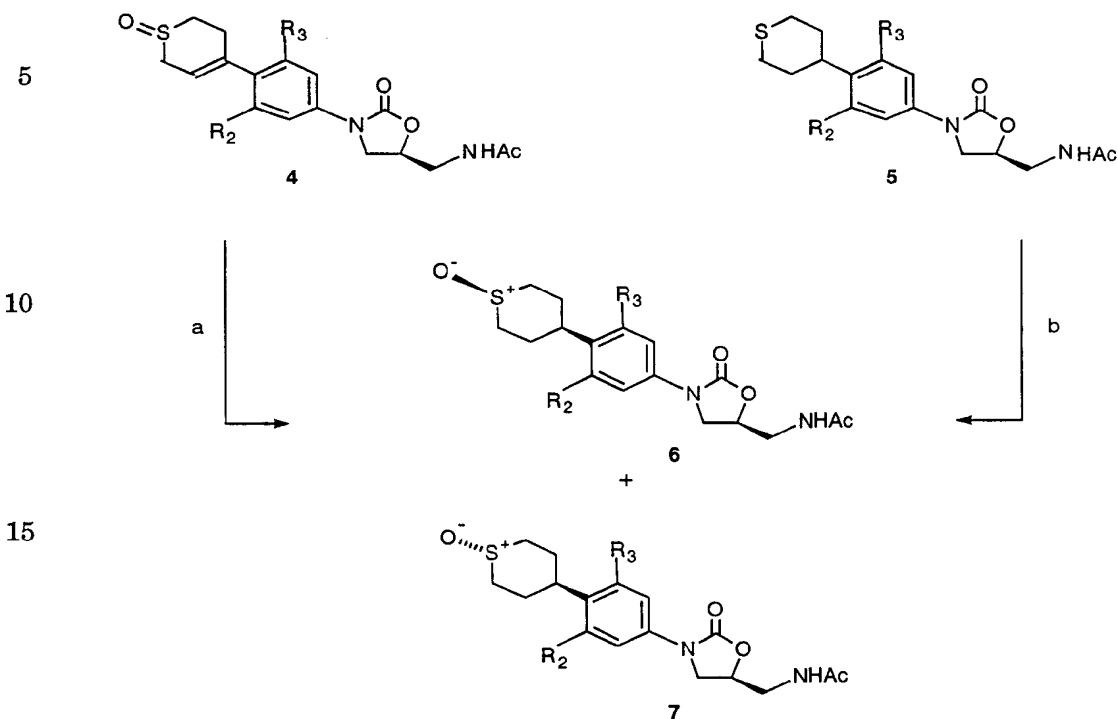
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## SCHEME II



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

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formulas I and II of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipient 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  
5 amounts of the active component, that is, the compounds of formula I or II according to this invention.

The quantity of active component, that is the compound of formula I or II according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application,  
10 the potency of the particular compound and 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  
15 administered orally, topically, transdermally, 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  
20 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  
25 upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of formulas I and II according to this invention are  
30 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 II as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as,  
35 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 compounds according to formula I or II 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 formulas I and II according to this invention are advantageously administered orally in solid and liquid dosage forms.

10 The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The in vitro activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That  
15 Grow Aerobically", 3rd. ed., published 1993 by the National Committee for Clinical Laboratory Standards, Villanova, Pennsylvania, USA. The activity of compounds of this invention against *Staphylococcus aureus* and *H. influenzae* is shown in Table 1.

The continuous spectrophotometric assay for measuring MAO activity is based on a colored oxidation product of the chromogenic substrate, 1-methyl-4-(1-methyl-2-pyrrolyl)-1,2,3,6-tetrahydropyridine, by MAO enzymes. The product is stable for many days at room temperature. The conversion of the substrate to the oxidation product is followed continuously from the moment of mixing of the MAO enzyme with the substrate and the initial reaction rate curve is directly observed. The bright yellow-green oxidation product has a peak absorption at 421 nm with a  
25 broad band that can be measured between 390 nm to 440 nm. Thus, the assay can be performed on the least sophisticated spectrophotometric equipment. The substrate itself is colorless; and does not spontaneously convert to product under conditions of the assay; thus, there is no interfering background rate.

The assay is sensitive, which allows accurate rate measurements at very low  
30 levels of change in the substrate concentration (<1%). The sensitivity of the assay permits measurements to be made on very low concentrations of the MAO enzymes, whether pure or in tissue homogenates. The assay is not susceptible to background interference from biologically derived materials all of which absorb between 210-350 nm.

35 The assay shows a linear reaction rate over a wide range of MAO enzymes, of the substrate, and of oxazolidinones concentrations and over a considerable portion

of the progress curve at any substrate or enzyme concentration. For example, the assay shows a linear reaction rate at final oxazolidinone's concentration from about 1 mM to about 1 nM; at any concentration of the enzymes which is sufficient to produce an absorbance change of 0.0005-0.05/minute at 421 nm; and at the substrate's concentration from about 10  $\mu$ M to about 10 mM. The reaction rate is also linear over long time intervals (up to 90 minutes) even at low enzyme concentrations. These properties permit a highly accurate rate determination as a function of substrate concentration, enzyme concentration or oxazolidinone inhibitor concentration.

10 The assay may be carried out in a buffer solution which does not adversely affect the reaction and provides a pH value at a range from about 7.0 to 7.5. The preferred buffer solution is sodium phosphate. The preferred pH value for assay is about 7.3. Further, the assay is preferably conducted at a temperature from about 25 °C to about 40 °C. The most preferred assay temperature is about 37 °C.

15 The chromogenic substrate 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine can be prepared as described in N. Castagnoli Jr. et al., *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996) and the references cited within. The substrate is prepared as a 10-15 mM stock solution in 50 mM sodium phosphate. The solution is kept on ice or frozen and are typically diluted 1/10-1/100 by 50 mM sodium phosphate (pH = 7-7.5) at the time of assay.

20 Human placental MAO A is solubilized and purified as described in N. Castagnoli Jr. et al., *J. Med Chem.* Vol. 39, pp. 4756-4761 (1996) and J. I. Salach et al., *J. of Bio. Chem.*, Vol. 260, p. 13199 (1985). The human placental MAO A is obtained as a concentrated solution (5 nmols per ml). Bovine liver MAO B is purified as described N. Castagnoli Jr. et al., *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996) and J. I. Salach et al., *Methods Enzymol.*, Vol. 142, pp 627-623 (1987). The bovine liver MAO B is obtained as a concentrated solution (8 nmols per ml). Working stocks of the enzyme solutions are made by 1/50 dilution of initial stocks into 50 mM sodium phosphate and optionally 10% glycerol. The solutions are kept on ice until final dilution into the assay. Alternatively, the frozen MAO enzymes may be diluted 800-3200 fold into the 50 mM sodium phosphate buffer immediately before use. This method is useful when screening a large number of oxazolidinones.

35 Oxazolidinones are prepared in DMSO at a concentration of 50 mM. Serial dilutions of the 50 mM stock solution are made in DMSO to form additional stock solutions ranging from 20 mM to 0.3125 mM. The stock solutions are then frozen until use. The stocks are diluted 1/100 into the final enzyme assay volume at the

time of assay.

Typically, the enzyme, along with an oxazolidinone inhibitor, are preincubated for approximately 15 minutes in the sodium phosphate buffer prior to assay. The reactions are started by addition of the substrate. Initial velocities are generally collected over an interval of one to sixty minutes.

The assay functions well in the spectrophotometer cuvette for evaluating single oxazolidinone's MAO inhibitory activity. The assay has also been successfully adapted to operate in high throughput microtiterplate format (i.e., 96, 384 and 1536 well plate readers). Hundreds of assays can be run simultaneously. Assay volumes are 250  $\mu$ L and the wells have an effective path length of 0.75 cm. Generally, the final composition of the assay in the microtiterplate comprises 0.05 mM sodium phosphate (pH = 7.3), oxazolidinone having concentration ranging up to 500  $\mu$ M, 1% DMSO, 80 $\mu$ M substrate (MAO A) or 200 $\mu$ M substrate (MAO B), and sufficient enzyme to produce an absorbance change from 0.0005 to 0.050 per minute at 421 nm. The reaction is run at 37 °C, and rapid temperature equilibration of the assay solution is achieved by preincubating the plate and stock solutions at about 37 °C. The reaction is followed by recording the increase in absorbance at 421 nm. The oxidation product has an extinction coefficient of 25,000  $M^{-1} cm^{-1}$  at 420. See: N. Castagnoli Jr. et al., *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996). Initial rates are determined by linear regression of the progress curves over an absorbance change of 0.06-0.12 at 421 nm. This range represents a substrate consumption of approximately 5% in the assay. The percentage inhibition of an oxazolidinone is determined from the following equation

$$\% \text{ Inhibition} = 100 \left\{ 1 - \frac{[\text{rate}(I) - \text{rate}(\text{negative control})]}{[\text{rate}(\text{positive control}) - \text{rate}(\text{negative control})]} \right\}$$

In the above equation, the term "negative control" refers to a complete assay with 1% of DMSO but no MAO enzyme. The term "positive control" refers to a complete assay with 1% of DMSO but no inhibitor. The term "rate (I)" refers to the reaction rate under a complete assay conditions. The term "rate (negative control)" refers to the reaction rate under the negative control condition. The term "rate (positive control)" refers to the reaction rate the under position control condition. In the case where a single oxazolidinone's MAO inhibitory activity is evaluated in the microtiterplate screening format, two replicates of positive control assay and two replicates of negative control assay are run to produce averaged control rates. In

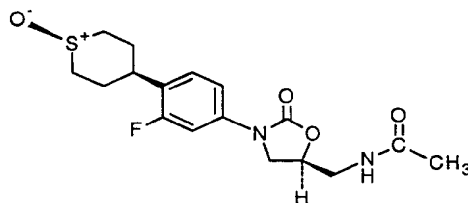
the case where microtiterplate format is used to derive an inhibitory constant (K<sub>i</sub>) for an oxazolidinone inhibitor, each plate contains four to eight wells without inhibitor (positive control). These rates are averaged to produce the mean uninhibited control rate for the plate. Each inhibitor is tested at six to eight  
 5 concentrations. Inhibitory percentage at each concentration is established relative to the uninhibited control rate. Since oxazolidinones are competitive inhibitors of MAO enzymes, the dissociation constant K<sub>i</sub> is calculated from the initial velocity data using the following equation:

$$10 \quad \% \text{Inhibition} = 100[I] / ([I] + K_i (1 + [S]/K_{m(s)}))$$

See I. H. Segel, *Enzyme Kinetics.*, Vol. 957, p.105, (1975). Wiley Interscience. NY, NY. In this equation, [S] refers to the concentration of the chromogenic substrate; [I] refers to the concentration of an oxazolidinone inhibitor; and K<sub>m(s)</sub> refers to the  
 15 dissociation constant of the substrate for the MAO enzyme. In practice, the data points from the inhibitor experiment are fit to the equation by non-linear least squares regression analysis. The K<sub>i</sub> parameter and its standard error are estimated by the regression procedure. A low K<sub>i</sub> value indicates that the tested inhibitor possesses a tight binding ability to MAO enzyme, thus, it is a strong MAO inhibitor.

20 The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

EXAMPLE 1 Preparation of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-  
 25 2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

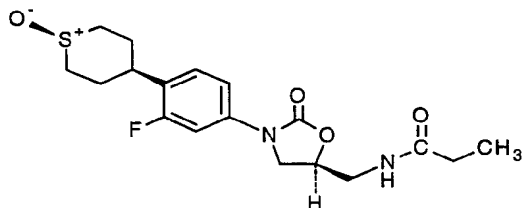


30 A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide (4.50 g, can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) and platinum  
 35 oxide (697 mg) in methanol (164 mL) is shaken 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 the title compound, mp 203 - 204 °C.

**EXAMPLE 2** Preparation of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.

10



15 Step 1: Preparation of [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone.

A mixture of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 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 hours and at ambient temperature for 16

20 hours, 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

25 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 the title compound, mp 159 - 161 °C.

30 Step 2: Preparation of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.

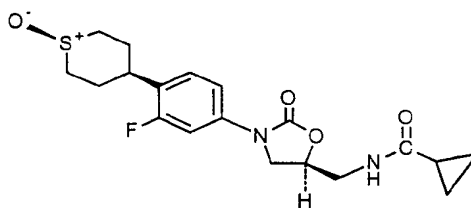
A solution of [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 2, Step 1, 150 mg), propionic anhydride (62  $\mu$ L) and pyridine (75  $\mu$ L) in methylene chloride is stirred under a

35 nitrogen atmosphere for 66 hours, during which time additional propionic anhydride (12  $\mu$ L) is added. The reaction mixture is then diluted with water (15 mL) and

extracted with methylene chloride (2 x 20 mL), and the combined 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 chromatographed on silica gel (230 - 400 mesh, 35 g), eluting with a gradient of methanol/methylene chloride (3/97 - 5/95). Pooling and concentration of those fractions with an  $R_f = 0.51$  by TLC (methanol/chloroform, 10/90) and recrystallization from methylene chloride/diethyl ether gives the title compound, mp 212 - 214 °C (dec.).

**EXAMPLE 3** Preparation of [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl] cyclopropane-carboxamide.

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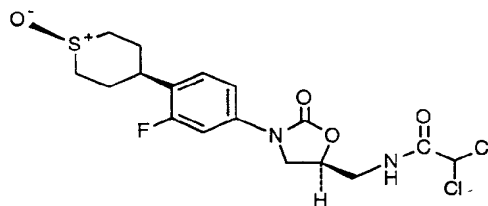


A solution of [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 2, Step 1, 250 mg) and triethylamine (0.16 mL) in methylene chloride (3.1 mL) at 0 °C under a nitrogen atmosphere is treated with cyclopropanecarbonyl chloride (73  $\mu$ L) and stirred at 0 °C for 2 hours. The reaction mixture is then diluted with methylene chloride (25 mL), washed with water (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, 40 g), eluting with methanol/methylene chloride (5/95). Pooling and concentration of these fractions with an  $R_f = 0.65$  by TLC (methanol/chloroform, 10/90) followed by trituration with methylene chloride/diethyl ether (50/50) and filtration gives the title compound, mp 242 - 243 °C (dec.).

**EXAMPLE 4** Preparation of [4(S)-cis]-2,2-dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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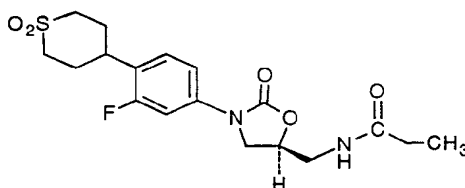


Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting dichloroacetyl chloride for cyclopropanecarbonyl chloride, the title compound is obtained, mp 198 - 200 °C (dec.).

10

EXAMPLE 5 Preparation of (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.

15



Step 1: Preparation of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone.

20

Following the general procedure of EXAMPLE 2, Step 1, and making non-critical variations but substituting (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) for [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 194 °C (dec.).

25

Step 2: (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide

Following the general procedure of EXAMPLE 2, Step 2, and making non-critical variations but substituting (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 5, Step 1) for [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone and allowing for a reaction time of 2 hours, the title compound is obtained, mp 200 - 201 °C.

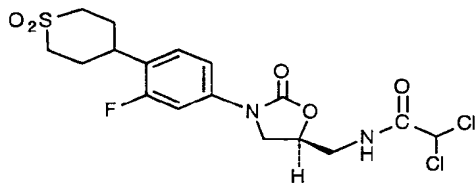
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EXAMPLE 6 Preparation of (S)-(-)-2,2-dichloro-N-[[3-[3-fluoro-4-(tetrahydro-



1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide.

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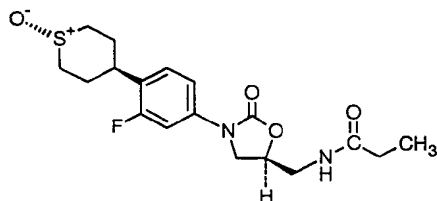


Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting dichloroacetyl chloride for cyclopropanecarbonyl chloride and (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 5, Step 1) for [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone and chromatographing the crude product with methanol/chloroform (2/98), the title compound is obtained, mp 136-137 °C (dec.).

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EXAMPLE 7 Preparation of [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]propionamide.

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25 Step 1: Preparation of (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide.

Following the general procedure of EXAMPLE 1, and making non-critical variations but pooling and concentrating those fractions from the chromatography with an  $R_f = 0.67$  by TLC (methanol/chloroform, 10/90), the title compound is obtained, mp 202 - 205 °C. Anal. Calcd for  $C_{17}H_{21}FN_2O_3S$ : C, 57.94; H, 6.01; N, 7.95; S, 9.10. Found: C, 57.95; H, 5.98; N, 7.94; S, 8.97.

Step 2: Preparation of [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide.

A slurry of (S)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide (EXAMPLE 7, Step 1, 2.50 g) in methylene chloride (35 mL) at 0 °C under a nitrogen atmosphere is treated with MCPBA (2.16 g, <85%

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pure, <10.64 mmol) in two portions. The resulting mixture is allowed to warm to ambient temperature and is stirred for 20 hours, during which time additional MCPBA (360 mg, <85% pure, <1.77 mmol) is added. The reaction is then diluted with methylene chloride (50 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), the aqueous phase is reextracted with methanol/methylene chloride (2 x 50 mL, 5/95), and the combined organic phase is washed with saline (25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude reaction mixture is chromatographed on silica gel (230-400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3.5/96.5 - 5/95), and those fractions with an  $R_f = 0.42$  by TLC (methanol/chloroform, 10/90) are pooled and concentrated to give a mixture of the *cis* and *trans* sulfoxide products. Subsequent purification by HPLC (Chiralcel OD column, ethanol eluent) followed by trituration with methylene chloride/diethyl ether (50/50) gives the title compound, mp 211 - 212 °C.

15 Step 3: Preparation of [4(S)-*trans*]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone.

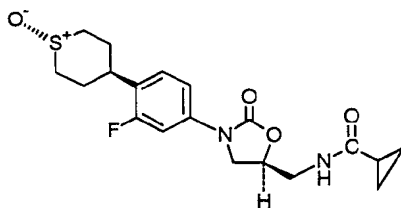
Following the general procedure of EXAMPLE 2, Step 1, and making non-critical variations but substituting [4(S)-*trans*]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide for [4(S)-*cis*]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 138 - 140 °C.

20 Step 4: Preparation of [4(S)-*trans*]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.

Following the general procedure of EXAMPLE 2, Step 2, and making non-critical variations but substituting [4(S)-*trans*]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone for [4(S)-*cis*]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, the title compound is obtained, mp 200 - 202 °C (dec.).

30 EXAMPLE 8 Preparation of [4(S)-*trans*]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropane-carboxamide.

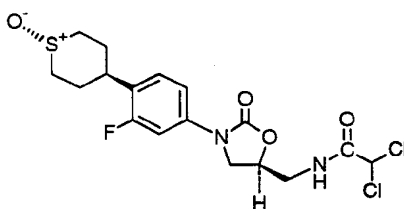
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Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting [4(S)-trans]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone for [4(S)-cis]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, the title compound is obtained, mp 189 - 191 °C.

EXAMPLE 9 Preparation of [4(S)-trans]-2,2-dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting dichloroacetyl chloride for cyclopropanecarbonyl chloride and [4(S)-trans]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone for [4(S)-cis]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, the title compound is obtained, mp 206 - 208 °C (dec.).

EXAMPLE 10 Evaluation of Oxazolidinones' Inhibitory Activity to Human MAO-A

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The solubilized and purified forms of human MAO-A and the substrate are obtained from Dr. Neal Castagnoli Jr's lab in Department of Chemistry, Virginia Technical University, Blacksburg, Virginia.

Preparation of buffer solutions: sodium phosphate was prepared as a 50 mM stock solution, pH = 7.3 at 37 °C. Preparation of the testing compounds: stock solutions (50 mM) of the test compounds were prepared in DMSO. Serial dilutions of

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the 50 mM stocks were made in DMSO to form additional stock solutions ranging from 20 mM to 0.3125 mM. These stocks were then frozen until needed. The stocks were diluted 1/100 into the final enzyme assay volume at the time of assay. A 10 mM stock solution of the chromogenic substrate was prepared in the 50 mM phosphate buffer, aliquoted and then frozen until time of use.

Enzyme Assay- Initial velocity assays were run in a SPECTRAmax 250 microplate spectrophotometer (Molecular Devices Corp., Sunnyvale, CA.). The final composition of the assay solution comprises 0.05 M sodium phosphate (pH = 7.3), 80  $\mu$ M substrate, inhibitor concentrations ranging up to 500  $\mu$ M, 1% DMSO, and sufficient enzyme to produce an absorbance change at 421 nm of 0.0005-0.005/minute. The reactions were run at 37 °C. The reaction was followed by recording the increase in absorbance at 421 nm. Inhibitors were pre-incubated with the MAO A in the reaction mixture for 15 minutes prior to starting the reaction.  $K_i$  values were determined from the initial velocity data using the above equation.

The results are also shown in Table 1.

TABLE 1

In vitro activities against *S. aureus* UC® No. 9213 and gram-negative bacteria  
*H. influenzae* 30063, and inhibitory activity data of human MAO A.

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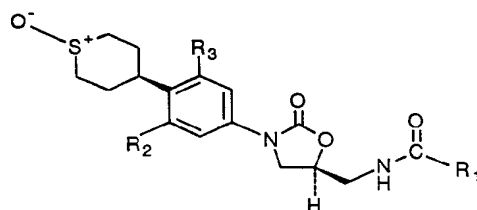
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Example No.	MIC ( $\mu\text{g/mL}$ ) <i>S. aureus</i> (UC 9213)	MIC ( $\mu\text{g/mL}$ ) H. <i>influenzae</i> 30063	Ki ( $\mu\text{M}$ )
1	4	8	648
2	8	16	>3000
3	8	16	734
4	2	8	2570
5	4	8	3000
6	2	2	>3000
7	4	4	905
8	8	16	>3000
9	1	2	396

## CLAIMS

1. A compound of formula I

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I

or pharmaceutically acceptable salts thereof wherein:

R<sub>1</sub> is

- a) methyl,  
 b) ethyl,  
 15 c) cyclopropyl, or  
 d) dichloromethyl;

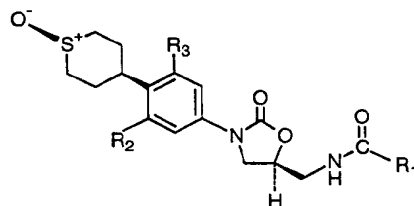
R<sub>2</sub> and R<sub>3</sub> are the same or different and are

- a) hydrogen, or  
 b) fluoro.

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2. A compound of claim 1 wherein R<sub>1</sub> is methyl.  
 3. A compound of claim 1 wherein R<sub>2</sub> is fluoro; R<sub>3</sub> is hydrogen.  
 25 4. A compound of formula I in claim 1 which is

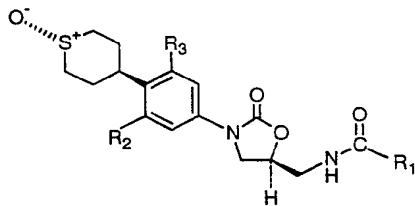
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5. A compound of formula I in claim 1 which is

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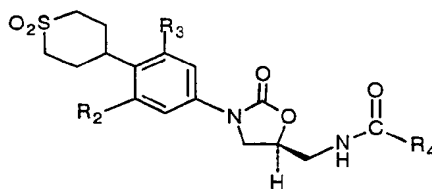
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6. A compound of claim 1 which is
- a. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
  - 10 b. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,
  - c. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide,
  - d. [4(S)-cis]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.
  - 15 e. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,
  - f. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide, or
  - 20 g. [4(S)-trans]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

7. A compound of formula II

25



30

II

or pharmaceutically acceptable salts thereof wherein

$R_2$  and  $R_3$  are the same or different and are

- a) hydrogen, or
- b) fluoro;
- 35  $R_4$  is
- a) ethyl, or

- b) dichloromethyl.
8. A compound of claim 7 wherein R<sub>2</sub> is fluoro; R<sub>3</sub> is hydrogen.
- 5 9. A compound of claim 7 which is
- a. (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide, or
- b. (S)-(-)-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.
- 10
10. A use of a compound of Formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament to treat microbial infections in patients comprising:
- administering to a patient in need thereof an effective amount of a compound of
- 15 Formula I as shown in claim 1.
11. A use of a compound of Formula II or pharmaceutically acceptable salts thereof for the preparation of a medicament for treating microbial infections in patients comprising:
- 20 administering to a patient in need thereof an effective amount of a compound of Formula II as shown in claim 7.
12. The use of claim 10 wherein said compound of Formula I is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.
- 25
13. The use of claim 11 wherein said compound of Formula II is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.
14. The use of claim 10 wherein said compound is administered in an amount of
- 30 from about 0.1 to about 100 mg/kg of body weight/day.
15. The use of claim 11 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.
- 35 16. A method of assaying compounds which may have monoamine oxidase inhibitory activity comprising the steps of :



- a) incubating a potential inhibitor with a monoamine oxidase in a buffer solution having pH value from about 7.0 to about 7.5;
- b) adding 1-methyl-4-(1-methyl-2-pyrrolyl)-1,2,3,6-tetrahydropyridine into said incubating solution; and
- 5 c) determining the monoamine oxidase inhibitory activity of said oxazolidinone.
17. The method of claim 16 wherein said inhibitor is an oxazolidinone antibiotic.
- 10 18. The method of claim 16 wherein said buffer solution is a phosphate solution.
19. The method of claim 16 wherein the pH value of said buffer solution is about 7.3.
- 15 20. The method of claim 16 wherein the length of incubation is about 15 minutes.
- 21 The method of claim 16 wherein said monoamine oxidase is monoamine oxidase A.
- 20 22. The method of claim 16 wherein said monoamine oxidase is monoamine oxidase B.
23. The method of claim 16 wherein said oxazolidinone is in a final concentration of from about 1 mM to about 1 nM.
- 25 24 The method of claim 16 wherein said MAO enzyme is sufficient to produce an absorbance change of 0.0005-0.05/minute at 421 nM.
25. The method of claim 16 wherein said substrate is in a concentration of from about 50  $\mu$ M to about 500  $\mu$ M.
- 30 26. The method of claim 16 wherein said assaying is performed in a spectrophotometer.
- 35 27. The method of claim 16 wherein said assaying is performed in a microtiterplate spectrophotometer.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24526

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07D413/10 A61K31/38 A61K31/42

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 <sup>o</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 09328 A (PHARMACIA & UPJOHN CO.) 13 March 1997 cited in the application see page 1, line 30 - page 3, line 31 see page 13, line 16 - line 21 see page 13, line 26 - line 35 see examples 49-51,54,55,63-65 see page 95, formula 52 ---	1,7,10, 11
A	WO 97 30995 A (ZENECA LTD.) 28 August 1997 cited in the application see claims 1,10,11; tables A,B --- -/--	1,7,10, 11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

<sup>o</sup> Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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

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"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

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Date of the actual completion of the international search

24 March 1999

Date of mailing of the international search report

06/04/1999

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Hass, C

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# INTERNATIONAL SEARCH REPORT

Int'l. Application No  
PCT/US 98/24526

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 0 352 781 A (E. I. DU PONT DE NEMOURS AND CO.) 31 January 1990 cited in the application see claims 1,11,12; examples; tables & US 4 948 801 A cited in the application & US 5 130 316 A cited in the application & US 5 254 577 A cited in the application -----	1,7,10, 11
A	WO 93 09103 A (THE UPJOHN CO.) 13 May 1993 cited in the application see abstract; claim 1 -----	1,7,10, 11
A	US 5 523 403 A (M. R. BARBACHYN) 4 June 1996 see column 40, line 13 - column 41, line 50; claim 1; table 1 -----	1,7,10, 11

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Information on patent family members

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information on patent family members

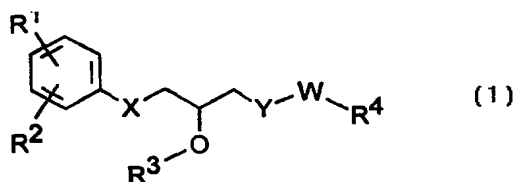
International Application No

PCT/US 98/24526

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		SK 74695 A	11-10-1995
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		ZA 9307791 A	20-05-1995
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**PCT**WELTORGANISATION FÜR GEISTIGES EIGENTUM  
Internationales BüroINTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE  
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

<b>(51) Internationale Patentklassifikation<sup>6</sup> :</b> <b>C07D 413/14, 413/12, 295/26, C07C 257/18, A61K 31/41, 31/495, 31/155</b>	<b>A1</b>	<b>(11) Internationale Veröffentlichungsnummer: WO 99/31092</b>  <b>(43) Internationales Veröffentlichungsdatum:</b> 24. Juni 1999 (24.06.99)
<b>(21) Internationales Aktenzeichen:</b> PCT/EP98/07673 <b>(22) Internationales Anmeldedatum:</b> 27. November 1998 (27.11.98)  <b>(30) Prioritätsdaten:</b> 197 55 268.4 12. Dezember 1997 (12.12.97) DE  <b>(71) Anmelder (für alle Bestimmungsstaaten ausser US):</b> MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE).  <b>(72) Erfinder; und</b> <b>(75) Erfinder/Anmelder (nur für US):</b> DORSCH, Dieter [DE/DE]; Königsberger Strasse 17A, D-64372 Ober-Ramstadt (DE). JURASZYK, Horst [DE/DE]; Kleiner Ring 14, D-64342 Seeheim (DE). WURZIGER, Hanns [DE/DE]; Greinstrasse 7b, D-64291 Darmstadt (DE). GANTE, Joachim [DE/DE]; Stormstrasse 4, D-64291 Darmstadt (DE). MEDERSKI, Werner [DE/DE]; Am Ohlenberg 29, D-64390 Erzhausen (DE). BUCHSTALLER, Hans-Peter [DE/DE]; Heinrichstrasse 54, D-64331 Weiterstadt (DE). ANZALI, Soheila [DE/DE]; Am Alten Berg 13, D-64342 Seeheim (DE). BERNOTAT-DANIELOWSKI, Sabine [DE/DE]; Liebigstrasse 5, D-61231 Bad Neuheim (DE). MELZER, Guido [DE/DE]; Mörikestrasse 6, D-65719 Hofheim (DE).	<b>(81) Bestimmungsstaaten:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, 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), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches 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, GW, ML, MR, NE, SN, TD, TG).  <b>Veröffentlicht</b> <i>Mit internationalem Recherchenbericht.</i> <i>Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	

**(54) Title:** BENZAMINE DERIVATIVES**(54) Bezeichnung:** BENZAMIDINDERIVATE ALS KOAGULATIONSFAKTOR-XA-HEMMER**(57) Abstract**

The invention relates to novel compounds of formula (1) wherein X, Y, W, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the meaning cited in Claim 1. The inventive compounds are inhibitors of coagulation factor Xa and can be used in prophylaxis and/or therapy for thromboembolic diseases.

**(57) Zusammenfassung**

Neue Verbindungen der Formel (1), worin X, Y, W, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die in Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.

**LEDIGLICH ZUR INFORMATION**

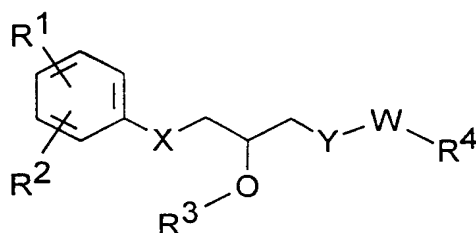
Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

<b>AL</b>	Albanien	<b>ES</b>	Spanien	<b>LS</b>	Lesotho	<b>SI</b>	Slowenien
<b>AM</b>	Armenien	<b>FI</b>	Finnland	<b>LT</b>	Litauen	<b>SK</b>	Slowakei
<b>AT</b>	Österreich	<b>FR</b>	Frankreich	<b>LU</b>	Luxemburg	<b>SN</b>	Senegal
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<b>BB</b>	Barbados	<b>GH</b>	Ghana	<b>MG</b>	Madagaskar	<b>TJ</b>	Tadschikistan
<b>BE</b>	Belgien	<b>GN</b>	Guinea	<b>MK</b>	Die ehemalige jugoslawische Republik Mazedonien	<b>TM</b>	Turkmenistan
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<b>BG</b>	Bulgarien	<b>HU</b>	Ungarn	<b>ML</b>	Mali	<b>TT</b>	Trinidad und Tobago
<b>BJ</b>	Benin	<b>IE</b>	Irland	<b>MN</b>	Mongolei	<b>UA</b>	Ukraine
<b>BR</b>	Brasilien	<b>IL</b>	Israel	<b>MR</b>	Mauretanien	<b>UG</b>	Uganda
<b>BY</b>	Belarus	<b>IS</b>	Island	<b>MW</b>	Malawi	<b>US</b>	Vereinigte Staaten von Amerika
<b>CA</b>	Kanada	<b>IT</b>	Italien	<b>MX</b>	Mexiko		
<b>CF</b>	Zentralafrikanische Republik	<b>JP</b>	Japan	<b>NE</b>	Niger	<b>UZ</b>	Usbekistan
<b>CG</b>	Kongo	<b>KE</b>	Kenia	<b>NL</b>	Niederlande	<b>VN</b>	Vietnam
<b>CH</b>	Schweiz	<b>KG</b>	Kirgisistan	<b>NO</b>	Norwegen	<b>YU</b>	Jugoslawien
<b>CI</b>	Côte d'Ivoire	<b>KP</b>	Demokratische Volksrepublik Korea	<b>NZ</b>	Neuseeland	<b>ZW</b>	Zimbabwe
<b>CM</b>	Kamerun			<b>PL</b>	Polen		
<b>CN</b>	China	<b>KR</b>	Republik Korea	<b>PT</b>	Portugal		
<b>CU</b>	Kuba	<b>KZ</b>	Kasachstan	<b>RO</b>	Rumänien		
<b>CZ</b>	Tschechische Republik	<b>LC</b>	St. Lucia	<b>RU</b>	Russische Föderation		
<b>DE</b>	Deutschland	<b>LI</b>	Liechtenstein	<b>SD</b>	Sudan		
<b>DK</b>	Dänemark	<b>LK</b>	Sri Lanka	<b>SE</b>	Schweden		
<b>EE</b>	Estland	<b>LR</b>	Liberia	<b>SG</b>	Singapur		

## BENZAMIDINDERIVATE ALS KOAGULATIONSFAKTOR-XA-HEMMER

Die Erfindung betrifft Verbindungen der Formel I

5

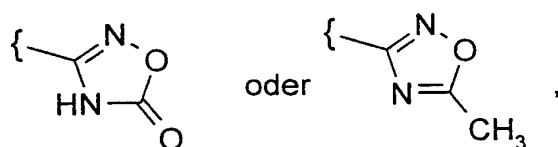


10

worin

R<sup>1</sup> -C(=NH)-NH<sub>2</sub>, das auch einfach durch -COA,  
-CO-[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-Ar, -COOA, -OH oder durch eine konven-  
tionelle Aminoschutzgruppe substituiert sein kann,

15



20

R<sup>2</sup> H, A, OR<sup>5</sup>, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, Hal, NR<sup>5</sup>COA, NHCOAr,  
NH<sub>2</sub>SO<sub>2</sub>A, NH<sub>2</sub>SO<sub>2</sub>Ar, COOR<sup>5</sup>, CON(R<sup>5</sup>)<sub>2</sub>, CONHAr, COR<sup>5</sup>,  
COAr, S(O)<sub>n</sub>A oder S(O)<sub>n</sub>Ar,

25

R<sup>3</sup> R<sup>5</sup> oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>,

R<sup>3</sup> und X zusammen auch -CO-N- unter Ausbildung eines 5-Rings,  
wobei R<sup>3</sup> -C=O und X N bedeutet,

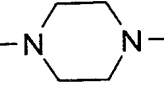
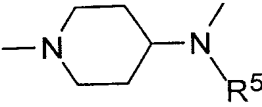
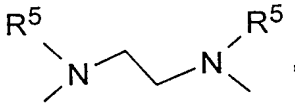
30

R<sup>4</sup> A, Cycloalkyl, -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar, -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het oder  
-CR<sup>5</sup>=CR<sup>5</sup>-Ar,

35

R<sup>5</sup> H, A oder Benzyl,



- X O, NR<sup>5</sup> oder CH<sub>2</sub>,
- 5 Y O, NR<sup>5</sup>, N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-Ar, N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-Het,  
 N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>, ,
- 10 , ,
- N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-CON(R<sup>5</sup>)<sub>2</sub>, N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-CONR<sup>5</sup>Ar oder  
 N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-CONAr<sub>2</sub>,
- 15 W eine Bindung, -SO<sub>2</sub>-, -CO-, -COO- oder -CONR<sup>5</sup>-,
- A Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH<sub>2</sub>-Gruppen  
 durch O- oder S-Atome oder durch -CR<sup>5</sup>=CR<sup>5</sup>-Gruppen  
 20 und/oder 1-7 H-Atome durch F ersetzt sein können,
- Ar unsubstituiertes oder ein-, zwei- oder dreifach durch R<sup>1</sup>, A,  
 Ar', OR<sup>5</sup>, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, Hal, NHCOA, NHCOAr', NHSO<sub>2</sub>A,  
 25 NHSO<sub>2</sub>Ar', COOR<sup>5</sup>, CON(R<sup>5</sup>)<sub>2</sub>, CONHAr', COR<sup>5</sup>, COAr',  
 S(O)<sub>n</sub>A oder S(O)<sub>n</sub>Ar substituiertes Phenyl oder Naphthyl,
- Ar' unsubstituiertes oder ein-, zwei- oder dreifach durch R<sup>1</sup>, A,  
 OR<sup>5</sup>, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, Hal, NHCOA, COOR<sup>5</sup>, CON(R<sup>5</sup>)<sub>2</sub>,  
 30 COR<sup>5</sup>, oder S(O)<sub>n</sub>A substituiertes Phenyl oder Naphthyl,
- Het ein- oder zweikerniges unsubstituiertes oder ein- oder mehr-  
 35 fach durch Hal, A, Ar', OR<sup>5</sup>, COOR<sup>5</sup>, CN, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>,  
 NHCOA, NHCOAr' und/oder Carbonylsauerstoff substituier-

tes gesättigtes oder ungesättigtes heterocyclisches Ringsystem, welches eines, zwei, drei oder vier gleiche oder verschiedene Heteroatome wie Stickstoff, Sauerstoff und Schwefel enthält,

5

Hal	F, Cl, Br oder I,
m	0, 1, 2, 3 oder 4,
n	0, 1 oder 2 bedeutet,

10

sowie deren Salze.

Gegenstand der Erfindung sind auch die optisch aktiven Formen, die Racemate, die Diastereomeren sowie die Hydrate und Solvate dieser Verbindungen.

15

Der Erfindung lag die Aufgabe zugrunde, neue Verbindungen mit wertvollen Eigenschaften aufzufinden, insbesondere solche, die zur Herstellung von Arzneimitteln verwendet werden können.

20

Es wurde gefunden, daß die Verbindungen der Formel I und ihre Salze bei guter Verträglichkeit sehr wertvolle pharmakologische Eigenschaften besitzen. Insbesondere zeigen sie Faktor Xa inhibierende Eigenschaften und können daher zur Bekämpfung und Verhütung von thromboembolischen Erkrankungen wie Thrombose, myocardialem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens eingesetzt werden.

25

Aromatische Amidinderivate mit antithrombotischer Wirkung sind z.B. aus der EP 0 540 051 B1 bekannt. Cyclische Guanidine zur Behandlung thromboembolischer Erkrankungen sind z.B. in der WO 97/08165 beschrieben. Aromatische Heterocyclen mit Faktor Xa inhibitorischer Aktivität sind z.B. aus der WO 96/10022 bekannt.

30

35

Der antithrombotische und antikoagulierende Effekt der erfindungsgemäßen Verbindungen wird auf die inhibierende Wirkung gegenüber der aktivierten Gerinnungsprotease, bekannt unter dem Namen Faktor Xa, oder auf die Hemmung anderer aktivierter Serinproteasen wie Faktor VIIa, Faktor IXa oder Thrombin zurückgeführt.

Faktor Xa ist eine der Proteasen, die in den komplexen Vorgang der Blutgerinnung involviert ist. Faktor Xa katalysiert die Umwandlung von Prothrombin in Thrombin. Thrombin spaltet Fibrinogen in Fibrinmonomere, die nach Quervernetzung elementar zur Thrombusbildung beitragen. Eine Aktivierung von Thrombin kann zum Auftreten von thromboembolischen Erkrankungen führen. Eine Hemmung von Thrombin kann jedoch die in die Thrombusbildung involvierte Fibrinbildung inhibieren.

Die Messung der Inhibierung von Thrombin kann z.B. nach der Methode von G. F. Cousins et al. in *Circulation* **1996**, *94*, 1705-1712 erfolgen.

Eine Inhibierung des Faktors Xa kann somit verhindern, daß Thrombin gebildet wird.

Die erfindungsgemäßen Verbindungen der Formel I sowie ihre Salze greifen durch Inhibierung des Faktors Xa in den Blutgerinnungsprozeß ein und hemmen so die Entstehung von Thromben.

Die erfindungsgemäßen Verbindungen der Formel I können weiterhin Inhibitoren der Gerinnungsfaktoren Faktor VIIa, Faktor IXa und Thrombin der Blutgerinnungskaskade sein.

Die Inhibierung des Faktors Xa durch die erfindungsgemäßen Verbindungen und die Messung der antikoagulierenden und antithrombotischen Aktivität kann nach üblichen in vitro- oder in vivo-Methoden ermittelt werden. Ein geeignetes Verfahren wird z.B. von J. Hauptmann et al. in *Thrombosis and Haemostasis* **63**, 220-223 (1990) beschrieben.

Die Messung der Inhibierung von Faktor Xa kann z.B. auch nach der Methode von T. Hara et al. in *Thromb. Haemostas.* **71**, 314-319 (1994) erfolgen.

Der Gerinnungsfaktor VIIa initiiert nach Bindung an Tissue Faktor den extrinsischen Teil der Gerinnungskaskade und trägt zur Aktivierung des Faktors X zu Faktor Xa bei. Eine Inhibierung von Faktor VIIa verhindert somit die Entstehung des Faktors Xa und damit eine nachfolgende  
5 Thrombinbildung.

Die Inhibierung des Faktors VIIa durch die erfindungsgemäßen Verbindungen und die Messung der antikoagulierenden und antithrombotischen Aktivität kann nach üblichen in vitro- oder in vivo-Methoden ermittelt werden. Ein übliches Verfahren zur Messung der Inhibierung von Faktor VIIa wird z.B. von H. F. Ronning et al. in *Thrombosis Research* **1996**, *84*, 73-81  
10 beschrieben.

Die Verbindungen der Formel I können als Arzneimittelwirkstoffe in der Human- und Veterinärmedizin eingesetzt werden, insbesondere zur Bekämpfung und Verhütung von thromboembolischen Erkrankungen wie  
15 Thrombose, myocardialem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens.

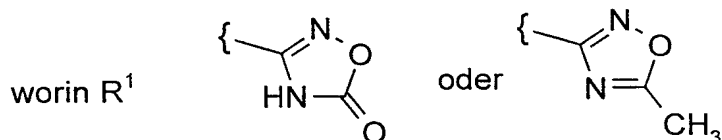
Gegenstand der Erfindung sind die Verbindungen der Formel I und ihre Salze sowie ein Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1 sowie ihrer Salze, dadurch gekennzeichnet, daß man  
20

- a) sie aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt, indem man  
25
- i) eine Amidinogruppe aus ihrem Oxadiazolderivat durch Hydrogenolyse freisetzt,  
30
  - ii) eine konventionelle Aminoschutzgruppe durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel durch Wasserstoff ersetzt oder  
eine durch eine konventionelle Schutzgruppe geschützte Aminogruppe in Freiheit setzt,  
35

oder

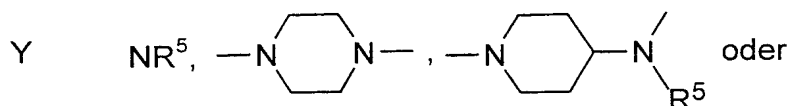
b) zur Herstellung von Verbindungen der Formel I,

5

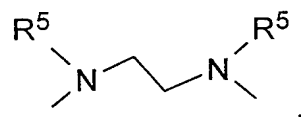


10

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



15



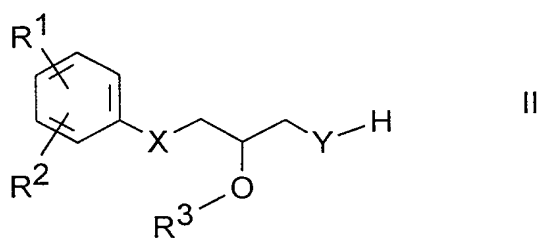
W -SO<sub>2</sub>- oder -CO- bedeuten,

20

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

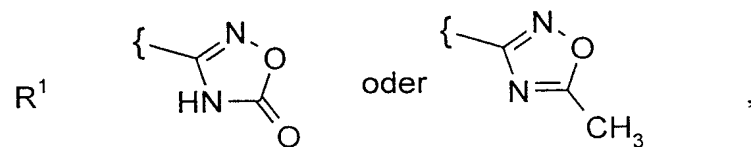
eine Verbindung der Formel II

25



30

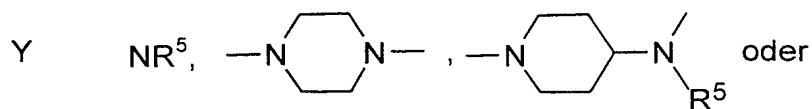
worin



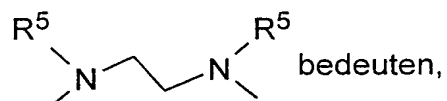
35

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

- 7 -



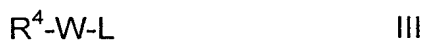
5



und  $\text{R}^2$  und  $\text{R}^5$  die in Anspruch 1 angegebenen Bedeutungen haben,

mit einer Verbindung der Formel III

10



worin

W  $-\text{SO}_2-$  oder  $-\text{CO}-$  bedeutet,

15

$\text{R}^4$  die in Anspruch 1 angegebene Bedeutung hat,

und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell  
abgewandelte OH-Gruppe bedeutet,

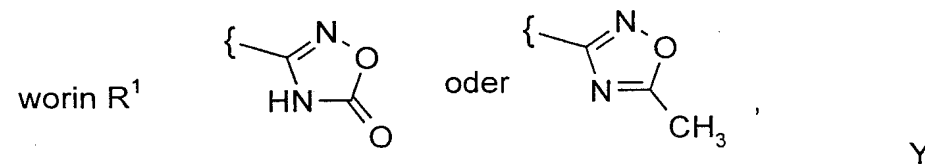
20

umsetzt,

oder

25

c) zur Herstellung von Verbindungen der Formel I,



30

$\text{R}^3$  und X zusammen  $-\text{CO-N}-$  unter Ausbildung eines 5-Rings,

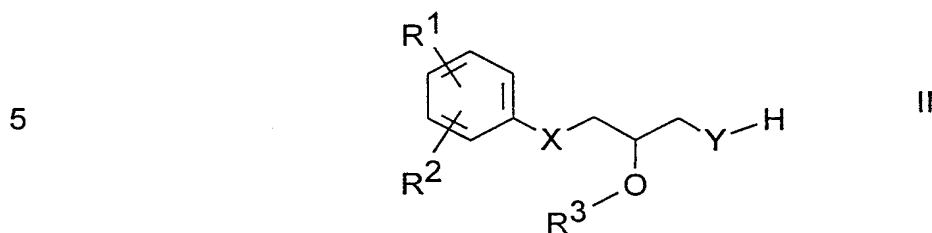
Y O,

W eine Bindung bedeuten,

35

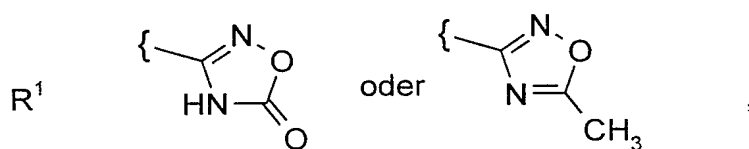
und  $\text{R}^2$  und  $\text{R}^4$  die in Anspruch 1 angegebenen Bedeutungen haben,

eine Verbindung der Formel II



worin

10



15

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,  
 Y O bedeuten,  
 und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat,

mit einer Verbindung der Formel IV

20



worin

W eine Bindung bedeutet,

25

und R<sup>4</sup> die in Anspruch 1 angegebene Bedeutung hat,

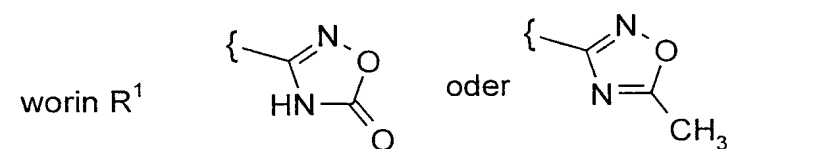
umsetzt,

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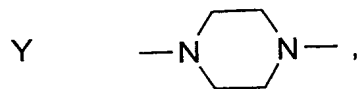
oder

d) zur Herstellung von Verbindungen der Formel I,

35



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



5

W eine Bindung,

R<sup>4</sup> -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het,

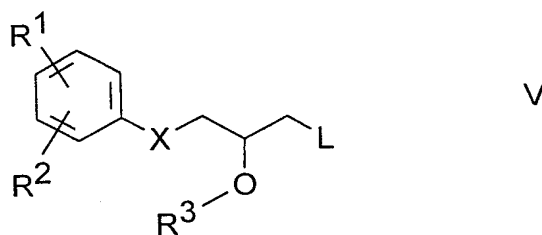
10

m 0 bedeuten,

und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat,

eine Verbindung der Formel V

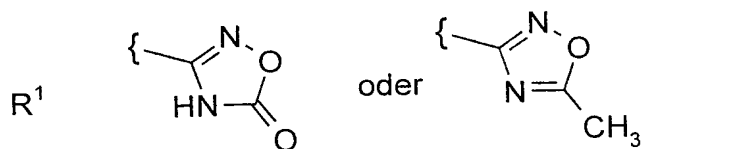
15



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worin

25



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

30

und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell  
abgewandelte OH-Gruppe bedeutet,

und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat,

mit einer Verbindung der Formel VI

35

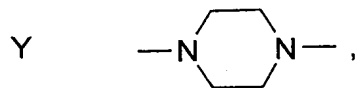




worin

W eine Bindung,

5



R<sup>4</sup> -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het und

10

m 0 bedeuten,

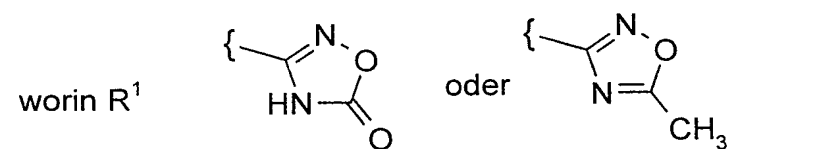
umsetzt,

oder

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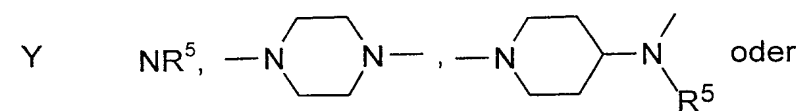
e) zur Herstellung von Verbindungen der Formel I,

20

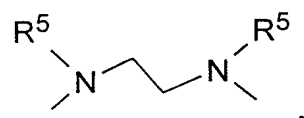


R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

25



30



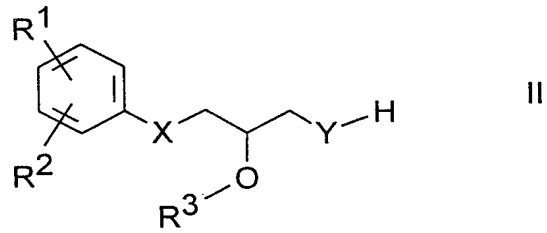
W -CONH- bedeuten,

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

35

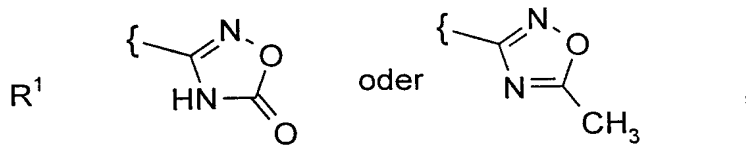
eine Verbindung der Formel II

5



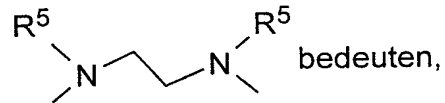
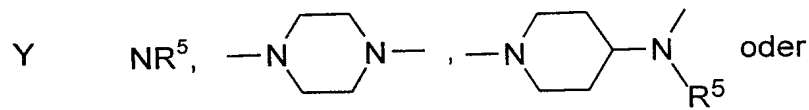
worin

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R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

15



20

und R<sup>2</sup> und R<sup>5</sup> die in Anspruch 1 angegebene Bedeutung haben,

mit einer Verbindung der Formel VII

25



worin

R<sup>4</sup> die in Anspruch 1 angegebene Bedeutung hat,

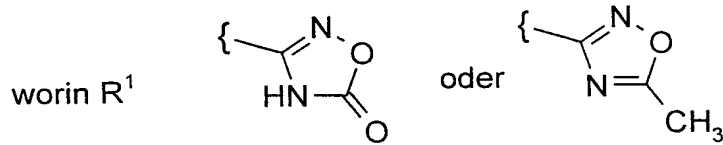
30

umsetzt,

oder

f) zur Herstellung von Verbindungen der Formel I,

35



5

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

Y N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>,

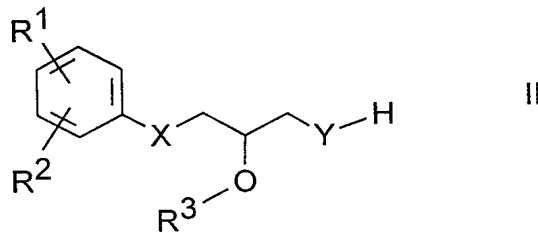
W SO<sub>2</sub> bedeuten,

10

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

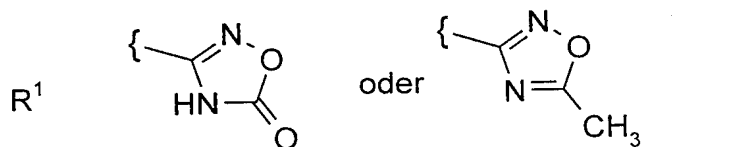
eine Verbindung der Formel II

15



20

worin



25

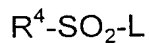
R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,  
bedeuten,

Y N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>

und R<sup>2</sup> und R<sup>5</sup> die in Anspruch 1 angegebene Bedeutung haben,

30

mit einer Verbindung der Formel VIII



VIII

worin

35

L Cl, Br, I oder eine freie oder reaktionsfähig funktionell abgewandelte OH-Gruppe bedeutet,

und R<sup>4</sup> die in Anspruch 1 angegebene Bedeutung hat,

5

umsetzt,

oder

10 g) zur Herstellung von Verbindungen der Formel I,

worin

15 X NH und  
R<sup>3</sup> H bedeutet,

und R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, Y und W die in Anspruch 1 angegebenen Bedeutungen haben,

20 sie aus ihren Oxazolidinonderivaten durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt,

oder

25 h) zur Herstellung von Verbindungen der Formel I,

worin R<sup>1</sup> -C(=NH)-NH<sub>2</sub> bedeutet,

eine Cyangruppe in eine Amidinogruppe umwandelt,

30

oder

i) in einer Verbindung der Formel I einen oder mehrere Rest(e) Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und/oder R<sup>4</sup> in einen oder mehrere Rest(e) R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und/oder R<sup>4</sup> umwandelt,

35

indem man beispielsweise

i) eine Estergruppe zu einer Carboxygruppe hydrolysiert,

5 ii) eine Nitrogruppe reduziert,

iii) eine Aminogruppe acyliert,

und/oder

10

k) eine Base oder Säure der Formel I in eines ihrer Salze umwandelt.

Für alle Reste, die mehrfach auftreten, wie z.B.  $R^5$ , gilt, daß deren Bedeutungen unabhängig voneinander sind.

15

Vor- und nachstehend haben die Reste bzw. Parameter L, W, X, Y,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , m und n die bei den Formeln I bis VIII angegebenen Bedeutungen, falls nicht ausdrücklich etwas anderes angegeben ist.

20

Solvate bedeutet Additionsverbindungen mit z.B. organischen inerten Lösungsmitteln, wie z.B. mit Alkoholen wie Methanol, Ethanol oder Propanol.

In den vorstehenden Formeln bedeutet A Alkyl, ist linear oder verzweigt, und hat 1 bis 20, vorzugsweise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 oder

25

12 C-Atome. A bedeutet vorzugsweise Methyl, weiterhin Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, sek.-Butyl oder tert.-Butyl, ferner auch Pentyl, 1-, 2- oder 3-Methylbutyl, 1,1-, 1,2- oder 2,2-Dimethylpropyl, 1-Ethylpropyl, Hexyl, 1-, 2-, 3- oder 4-Methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- oder 3,3-Dimethylbutyl, 1- oder 2-Ethylbutyl, 1-Ethyl-1-methylpropyl, 1-Ethyl-2-methylpropyl, 1,1,2- oder 1,2,2-Trimethylpropyl, Heptyl, Octyl, Nonyl oder Decyl.

30

A bedeutet weiterhin z.B. Trifluormethyl, Pentafluorethyl, Allyl oder Crotyl.

$OR^5$  bedeutet OH, OA oder Benzyloxy, wobei OA vorzugsweise Methoxy, Ethoxy, Propoxy, Butyloxy oder Hexyloxy bedeutet.

35

Cycloalkyl bedeutet vorzugsweise Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Cycloheptyl. Cycloalkyl bedeutet z.B. auch den Rest eines bicyclischen Terpens, wie z.B. 3-Menthyl, besonders bevorzugt ist der Campher-10-yl-Rest.

5

COR<sup>5</sup> ist Acyl und bedeutet vorzugsweise Formyl, Acetyl, Propionyl, ferner auch Butyryl, Pentanoyl oder Hexanoyl.

Hal bedeutet vorzugsweise F, Cl oder Br, aber auch I.

10

R<sup>2</sup> bedeutet vorzugsweise H, Fluor, Chlor, Brom, Iod, Hydroxy, Methoxy, Ethoxy, Propoxy, Nitro, Amino, Methylamino, Dimethylamino, Ethylamino, Diethylamino, Acetamido, Sulfonamido, Methylsulfonamido, Phenylsulfonamido, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Phenylsulfinyl, Phenylsulfonyl, Cyan, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, ferner auch Acyl oder Benzoyl. Insbesondere bedeutet R<sup>2</sup> H.

15

R<sup>3</sup> bedeutet vorzugsweise A, Benzyl, CH<sub>2</sub>COOH oder CH<sub>2</sub>COOA, insbesondere jedoch H.

20

R<sup>4</sup> bedeutet vorzugsweise z.B. A, Cycloalkyl, Ar, CH<sub>2</sub>Ar, CH<sub>2</sub>CH<sub>2</sub>Ar, CH<sub>2</sub>Het, CH<sub>2</sub>CH<sub>2</sub>Het oder CH=CH-Ar.

R<sup>5</sup> bedeutet H, A oder Benzyl, insbesondere jedoch H.

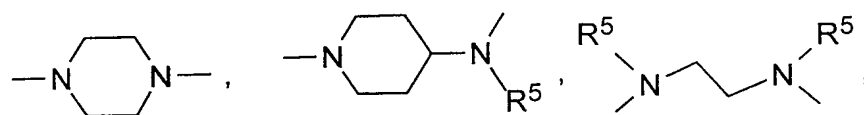
25

X bedeutet O, NH, NA oder N-Benzyl, ferner auch CH<sub>2</sub>.

R<sup>3</sup> und X bedeuten zusammen auch -CO-N-, wobei mit der -CH<sub>2</sub>-CH-O-Einheit ein Fünfring gebildet wird.

Y bedeutet vorzugsweise z.B. O, NH, N-Methyl, N-Ethyl, N-Ar, N-CH<sub>2</sub>-Ar, N-Het, N-CH<sub>2</sub>-Het, N-COOA, N-CH<sub>2</sub>-COOA, N-CH<sub>2</sub>-COOH, N-CH<sub>2</sub>-COOBenzyl,

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35

NCH<sub>2</sub>-CONH<sub>2</sub>, NCH<sub>2</sub>-CONHA, NCH<sub>2</sub>-CONA<sub>2</sub>, NCH<sub>2</sub>-CONR<sup>5</sup>Ar oder

$\text{NCH}_2\text{-CONAr}_2$ .

W bedeutet vorzugsweise z.B. eine Bindung,  $-\text{SO}_2-$  oder  $-\text{CO}-$ , ferner auch  $-\text{COO}-$  oder  $-\text{CONH}-$ .

5 Ar bedeutet vorzugsweise unsubstituiertes Phenyl oder Naphthyl, weiterhin vorzugsweise z.B. durch A, Fluor, Chlor, Brom, Iod, Hydroxy, Methoxy, Ethoxy, Propoxy, Butoxy, Pentyloxy, Hexyloxy, Benzyloxy, Phenethyloxy, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Phenylsulfinyl, Phenylsulfonyl, Nitro, Amino, Methylamino, Ethylamino, Dimethylamino, Diethylamino, Formamido, Acetamido, Propionylamino, Butyrylamino, Methylsulfonamido, Ethylsulfonamido, Propylsulfonamido, Butylsulfonamido, Phenylsulfonamido, (4-Methylphenyl)-sulfonamido, Carboxymethoxy, Carboxyethoxy, Methoxycarbonylmethoxy, Methoxycarbonylethoxy, Hydroxymethoxy, Hydroxyethoxy, Methoxyethoxy, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Cyan, Phenylaminocarbonyl, Acyl oder Benzoyl mono-, di- oder trisubstituiertes Phenyl oder Naphthyl, ferner auch Biphenyl.

20 Ar bedeutet daher bevorzugt z.B. o-, m- oder p-Tolyl, o-, m- oder p-Ethylphenyl, o-, m- oder p-Propylphenyl, o-, m- oder p-Isopropylphenyl, o-, m- oder p-tert.-Butylphenyl, o-, m- oder p-Hydroxyphenyl, o-, m- oder p-Nitrophenyl, o-, m- oder p-Aminophenyl, o-, m- oder p-(N-Methylamino)-phenyl, o-, m- oder p-Acetamidophenyl, o-, m- oder p-Methoxyphenyl, o-, m- oder p-Ethoxyphenyl, o-, m- oder p-Carboxyphenyl, o-, m- oder p-Methoxycarbonylphenyl, o-, m- oder p-(N,N-Dimethylamino)-phenyl, o-, m- oder p-(N-Ethylamino)-phenyl, o-, m- oder p-(N,N-Diethylamino)-phenyl, o-, m- oder p-Acetylphenyl, o-, m- oder p-Formylphenyl, o-, m- oder p-Fluorphenyl, o-, m- oder p-Bromphenyl, o-, m- oder p-Chlorphenyl, o-, m- oder p-Methylsulfonylphenyl, o-, m- oder p-(Phenylsulfonamido)-phenyl, o-, m- oder p-(Methylsulfonamido)-phenyl, o-, m- oder p-Methylthiophenyl, weiter bevorzugt 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Difluorphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Dichlorphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Dibromphenyl, 2,4- oder 2,5-Dinitrophenyl, 2,5- oder 3,4-Dimethoxyphenyl, 3-Nitro-4-chlorphenyl, 3-Amino-4-chlor-, 2-Amino-3-chlor-, 2-Amino-4-chlor-, 2-Amino-5-chlor- oder 2-Amino-6-chlorphenyl, 2-Nitro-4-N,N-dimethylamino- oder 3-Nitro-4-N,N-dimethylaminophenyl, 2,3-Diaminophenyl,

2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- oder 3,4,5-Trichlorphenyl, 2,4,6-Trimethoxyphenyl, 2-Hydroxy-3,5-dichlorphenyl, p-Iodphenyl, 3,6-Dichlor-4-aminophenyl, 4-Fluor-3-chlorphenyl, 2-Fluor-4-bromphenyl, 2,5-Difluor-4-bromphenyl, 3-Brom-6-methoxyphenyl, 3-Chlor-6-methoxyphenyl, 3-Chlor-4-acetamidophenyl, 3-Fluor-4-methoxyphenyl, 3-Amino-6-methylphenyl, 3-Chlor-4-acetamidophenyl oder 2,5-Dimethyl-4-chlorphenyl.

Ar bedeutet ganz besonders bevorzugt unsubstituiertes oder ein-, zwei- oder dreifach durch Amino, OR<sup>5</sup>, Hal, CN, Alkyl mit 1-10 C-Atomen, CF<sub>3</sub>, CH<sub>3</sub>SO<sub>2</sub>, OCF<sub>3</sub>, Acetamido, -C(=NH)-NH<sub>2</sub>, Methoxycarbonyl oder Ethoxycarbonyl substituiertes Phenyl, weiterhin einfach durch Hal, Dimethylamino oder Alkoxy mit 1-6 C-Atomen substituiertes Naphthyl sowie unsubstituiertes Biphenyl.

Ar' bedeutet insbesondere z.B. Phenyl oder Naphthyl, ferner bevorzugt z.B. o-, m- oder p-Tolyl, o-, m- oder p-Ethylphenyl, o-, m- oder p-Propylphenyl, o-, m- oder p-Isopropylphenyl, o-, m- oder p-tert.-Butylphenyl, o-, m- oder p-Hydroxyphenyl, o-, m- oder p-Nitrophenyl, o-, m- oder p-Aminophenyl, o-, m- oder p-(N-Methylamino)-phenyl, o-, m- oder p-Acetamidophenyl, o-, m- oder p-Methoxyphenyl, o-, m- oder p-Ethoxyphenyl, o-, m- oder p-Carboxyphenyl, o-, m- oder p-Methoxycarbonylphenyl, o-, m- oder p-(N,N-Dimethylamino)-phenyl, o-, m- oder p-(N-Ethylamino)-phenyl, o-, m- oder p-(N,N-Diethylamino)-phenyl, o-, m- oder p-Acetylphenyl, o-, m- oder p-Formylphenyl, o-, m- oder p-Fluorphenyl, o-, m- oder p-Bromphenyl, o-, m- oder p-Chlorphenyl oder o-, m- oder p-Methylsulfonylphenyl.

Het bedeutet vorzugsweise z.B. 2- oder 3-Furyl, 2- oder 3-Thienyl, 1-, 2- oder 3-Pyrrolyl, 1-, 2, 4- oder 5-Imidazolyl, 1-, 3-, 4- oder 5-Pyrazolyl, 2-, 4- oder 5-Oxazolyl, 3-, 4- oder 5-Isoxazolyl, 2-, 4- oder 5-Thiazolyl, 3-, 4- oder 5-Isotiazolyl, 2-, 3- oder 4-Pyridyl, 2-, 4-, 5- oder 6-Pyrimidinyl, weiterhin bevorzugt 1,2,3-Triazol-1-, -4- oder -5-yl, 1,2,4-Triazol-1-, -3- oder 5-yl, 1- oder 5-Tetrazolyl, 1,2,3-Oxadiazol-4- oder -5-yl, 1,2,4-Oxadiazol-3- oder -5-yl, 1,3,4-Thiadiazol-2- oder -5-yl, 1,2,4-Thiadiazol-3- oder -5-yl, 1,2,3-Thiadiazol-4- oder -5-yl, 3- oder 4-Pyridazinyl, Pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- oder 7-Indolyl, 4- oder 5-Isoindolyl, 1-, 2-, 4- oder 5-Benzimidazolyl, 1-, 3-, 4-, 5-, 6- oder 7-Benzopyrazolyl, 2-, 4-, 5-, 6- oder 7-Benzoxazolyl, 3-,



5 4-, 5-, 6- oder 7- Benzisoxazolyl, 2-, 4-, 5-, 6- oder 7-Benzothiazolyl, 2-, 4-, 5-, 6- oder 7-Benzisothiazolyl, 4-, 5-, 6- oder 7-Benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- oder 8-Chinolyl, 1-, 3-, 4-, 5-, 6-, 7- oder 8-Isochinolyl, 3-, 4-, 5-, 6-, 7- oder 8-Cinnolyl, 2-, 4-, 5-, 6-, 7- oder 8-Chinazolyl, 5- oder 6-Chinoxalyl, 2-, 3-, 5-, 6-, 7- oder 8-2H-Benzo[1,4]oxazinyl, weiter bevorzugt 1,3-Benzodioxol-5-yl, 1,4-Benzodioxan-6-yl, 2,1,3-Benzothiadiazol-4- oder -5-yl oder 2,1,3-Benzoxadiazol-5-yl.

Die heterocyclischen Reste können auch teilweise oder vollständig hydriert sein.

10 Het kann also z. B. auch bedeuten 2,3-Dihydro-2-, -3-, -4- oder -5-furyl, 2,5-Dihydro-2-, -3-, -4- oder 5-furyl, Tetrahydro-2- oder -3-furyl, 1,3-Dioxolan-4-yl, Tetrahydro-2- oder -3-thienyl, 2,3-Dihydro-1-, -2-, -3-, -4- oder -5-pyrrolyl, 2,5-Dihydro-1-, -2-, -3-, -4- oder -5-pyrrolyl, 1-, 2- oder 3-Pyrrolidinyl, Tetrahydro-1-, -2- oder -4-imidazolyl, 2,3-Dihydro-1-, -2-, -3-, -4- oder  
 15 -5-pyrazolyl, Tetrahydro-1-, -3- oder -4-pyrazolyl, 1,4-Dihydro-1-, -2-, -3- oder -4-pyridyl, 1,2,3,4-Tetrahydro-1-, -2-, -3-, -4-, -5- oder -6-pyridyl, 1-, 2-, 3- oder 4-Piperidyl, 2-, 3- oder 4-Morpholyl, Tetrahydro-2-, -3- oder -4-pyranyl, 1,4-Dioxanyl, 1,3-Dioxan-2-, -4- oder -5-yl, Hexahydro-1-, -3- oder -4-pyridazinyl, Hexahydro-1-, -2-, -4- oder -5-pyrimidinyl, 1-, 2- oder 3-  
 20 Piperazinyl, 1,2,3,4-Tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- oder -8-chinolyl, 1,2,3,4-Tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- oder -8-isochinolyl, 2-, 3-, 5-, 6-, 7- oder 8- 3,4-Dihydro-2H-benzo[1,4]oxazinyl, weiter bevorzugt 2,3-Methylenedioxyphenyl, 3,4-Methylenedioxyphenyl, 2,3-Ethylendioxyphenyl, 3,4-Ethylendioxyphenyl, 3,4-(Difluormethylenedioxy)phenyl, 2,3-Dihydro-  
 25 benzofuran-5- oder 6-yl, 2,3-(2-Oxo-methylenedioxy)-phenyl oder auch 3,4-Dihydro-2H-1,5-benzodioxepin-6- oder -7-yl, ferner bevorzugt 2,3-Dihydro-benzofuranyl oder 2,3-Dihydro-2-oxo-furanyl.

30 Het ist unsubstituiert oder ein- oder mehrfach durch Hal, A, Ar', COOR<sup>5</sup>, CN, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, Ar-CONH-CH<sub>2</sub> substituiert.

"Mehrfach" bedeutet zwei-, drei-, vier- oder fünffach.

Het bedeutet ganz besonders bevorzugt unsubstituiertes oder ein- oder mehrfach durch Hal, A, Phenyl, OR<sup>5</sup>, COOR<sup>5</sup>, CN, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, NHCOA, NHCOPhenyl und/oder Carbonylsauerstoff substituiertes Thiazol-2-, 4-  
 35 oder -5-yl, Thiophen-2- oder -5-yl, Chroman-6-yl, Pyridin-2-, 3- oder -4-yl,

Pyrimidin-2- oder -5-yl, Benzothiophen-2-yl, 1,3-Benzodioxol-4- oder 5-yl, 1,4-Benzodioxan-5- oder -6-yl, 2,1,3-Benzothiadiazol-4- oder -5-yl.

5 Die Verbindungen der Formel I können ein oder mehrere chirale Zentren besitzen und daher in verschiedenen stereoisomeren Formen vorkommen. Die Formel I umschließt alle diese Formen.

10 Dementsprechend sind Gegenstand der Erfindung insbesondere diejenigen Verbindungen der Formel I, in denen mindestens einer der genannten Reste eine der vorstehend angegebenen bevorzugten Bedeutungen hat. Einige bevorzugte Gruppen von Verbindungen können durch die folgenden Teilformeln Ia bis Ii ausgedrückt werden, die der Formel I entsprechen und worin die nicht näher bezeichneten Reste die bei der Formel I angegebene Bedeutung haben, worin jedoch

15

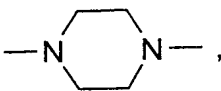
in Ia  $R^2$  H  
bedeutet;

in Ib  $R^3$   $R^5$  oder  $-(CH_2)_m-COOR^5$   
bedeutet;

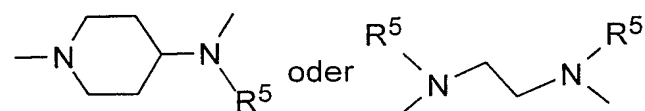
20

in Ic  $R^4$  A, Cycloalkyl,  $-(CH_2)_n-Ar$ ,  $-(CH_2)_m-Het$  oder  $-CH=CH-Ar$   
bedeutet;

25

in Id Y O,  $NR^5$ ,  $N(CH_2)_m-Ar$ ,  $N(CH_2)_m-Het$ ,  
 $N(CH_2)_m-COOR^5$ , 

30

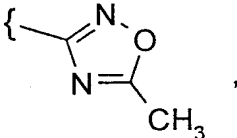


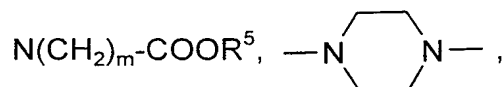
bedeutet;

in Ie A Alkyl mit 1-20 C-Atomen, worin eine oder zwei  $CH_2$ -Gruppen durch  $-CH=CH$ -Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,

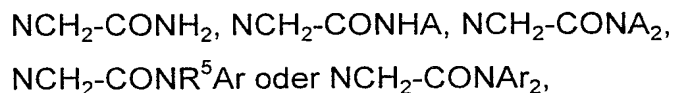
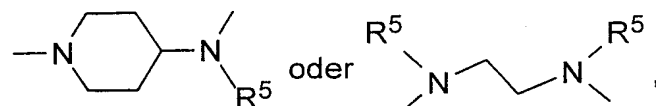
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bedeutet;

5	in lf	Ar	<p>unsubstituiertes oder ein-, zwei- oder dreifach durch <math>R^1</math>, A, Phenyl, <math>OR^5</math>, <math>N(R^5)_2</math>, <math>NO_2</math>, CN, Hal, <math>NHCOA</math>, <math>NHCOPhenyl</math>, <math>NHSO_2A</math>, <math>NHSO_2Phenyl</math>, <math>COOR^5</math>, <math>CON(R^5)_2</math>, <math>CONHPhenyl</math>, <math>COR^5</math>, <math>COPhenyl</math>, <math>S(O)_nA</math> oder <math>S(O)_nAr</math> substituiertes Phenyl oder Naphthyl,</p>
			bedeutet;
	in lg	Ar'	Phenyl,
			bedeutet;
10	in lh	Het	<p>unsubstituiertes oder ein- oder mehrfach durch Hal, A, Phenyl, <math>OR^5</math>, <math>COOR^5</math>, CN, <math>N(R^5)_2</math>, <math>NO_2</math>, <math>NHCOA</math>, <math>NHCOPhenyl</math> und/oder Carbonylsauerstoff substituiertes Thiazol-2-,4- oder -5-yl, Thiophen-2- oder -5-yl, Chroman-6-yl, Pyridin-2-,3- oder -4-yl, Pyrimidin-2- oder -5-yl, Benzothiophen-2-yl, 1,3-Benzodioxol-4- oder 5-yl, 1,4-Benzodioxan-5- oder -6-yl, 2,1,3-Benzothiadiazol-4- oder -5-yl.</p>
15			
20	in li	R <sup>1</sup>	<p>bedeutet;</p> <p><math>-C(=NH)-NH_2</math>, das auch einfach durch <math>-COA</math>, <math>-CO-(CH_2)_m-Ar</math>, <math>-COOA</math>, OH substituiert sein kann,</p>
25			<p>oder</p> 
		R <sup>2</sup>	H,
		R <sup>3</sup>	$R^5$ oder $-(CH_2)_m-COOR^5$ ,
30		R <sup>3</sup> und X	zusammen auch $-CO-N-$ unter Ausbildung eines 5-Rings,
		R <sup>4</sup>	A, Cycloalkyl, $-(CH_2)_mAr$ , $-(CH_2)_mHet$ oder $-CH=CH-Ar$ ,
		R <sup>5</sup>	H, A oder Benzyl,
35		X	O, $NR^5$ oder $CH_2$ ,
		Y	O, $NR^5$ , $N(CH_2)_m-Ar$ , $N(CH_2)_m-Het$ ,



5



10

W  
A

eine Bindung,  $-SO_2-$ ,  $-CO-$ ,  $-COO-$  oder  $-CONH-$ ,  
Alkyl mit 1-20 C-Atomen, worin eine oder zwei  $CH_2-$   
Gruppen durch  $-CH=CH-$ Gruppen und/oder 1-7 H-  
Atome durch F ersetzt sein können,

15

Ar

unsubstituiertes oder ein-, zwei- oder dreifach durch  
 $NH_2$ ,  $OR^5$ , Hal, CN, Alkyl mit 1-10 C-Atomen,  $CF_3$ ,  
 $CH_3SO_2$ ,  $OCF_3$ , Acetamido,  $-C(=NH)-NH_2$ , Methoxy-  
carbonyl oder Ethoxycarbonyl substituiertes Phenyl,  
weiterhin einfach durch Hal, Dimethylamino oder  
Methoxy substituiertes Naphthyl sowie unsubstituier-  
tes Biphenyl.

20

Het

unsubstituiertes oder ein- oder mehrfach durch Hal,  
A, Phenyl,  $OR^5$ ,  $COOR^5$ , CN,  $N(R^5)_2$ ,  $NO_2$ ,  $NHCOA$ ,  
 $NHCOPhenyl$  und/oder Carbonylsauerstoff substitu-  
iertes Thiazol-2-,4- oder -5-yl, Thiophen-2- oder -5-yl,  
Chroman-6-yl, Pyridin-2-,3- oder -4-yl, Pyrimidin-2-  
oder -5-yl, Benzothiophen-2-yl, 1,3-Benzodioxol-4-  
oder 5-yl, 1,4-Benzodioxan-5- oder -6-yl, 2,1,3-  
Benzothiadiazol-4- oder -5-yl.

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bedeutet.

Die Verbindungen der Formel I und auch die Ausgangsstoffe zu ihrer Her-  
stellung werden im übrigen nach an sich bekannten Methoden hergestellt,  
wie sie in der Literatur (z.B. in den Standardwerken wie Houben-Weyl,  
Methoden der organischen Chemie, Georg-Thieme-Verlag, Stuttgart) be-

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schrieben sind, und zwar unter Reaktionsbedingungen, die für die genannten Umsetzungen bekannt und geeignet sind. Dabei kann man auch von an sich bekannten, hier nicht näher erwähnten Varianten Gebrauch machen.

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Die Ausgangsstoffe können, falls erwünscht, auch in situ gebildet werden, so daß man sie aus dem Reaktionsgemisch nicht isoliert, sondern sofort weiter zu den Verbindungen der Formel I umsetzt.

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Verbindungen der Formel I können vorzugsweise erhalten werden, indem man Verbindungen der Formel I aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt.

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Bevorzugte Ausgangsstoffe für die Solvolyse bzw. Hydrogenolyse sind solche, die sonst der Formel I entsprechen, aber anstelle einer oder mehrerer freier Amino- und/oder Hydroxygruppen entsprechende geschützte Amino- und/oder Hydroxygruppen enthalten, vorzugsweise solche, die anstelle eines H-Atoms, das mit einem N-Atom verbunden ist, eine Aminoschutzgruppe tragen, insbesondere solche, die anstelle einer HN-Gruppe eine R'-N-Gruppe tragen, worin R' eine Aminoschutzgruppe bedeutet, und/oder solche, die anstelle des H-Atoms einer Hydroxygruppe eine Hydroxyschutzgruppe tragen, z.B. solche, die der Formel I entsprechen, jedoch anstelle einer Gruppe -COOH eine Gruppe -COOR" tragen, worin R" eine Hydroxyschutzgruppe bedeutet.

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Bevorzugte Ausgangsstoffe sind auch die Oxadiazolderivate, die in die entsprechenden Amidinoverbindungen überführt werden können.

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Die Einführung der Oxadiazolgruppe gelingt z.B. durch Umsetzung der Cyanverbindungen mit Hydroxylamin und Reaktion mit Phosgen, Dialkylcarbonat, Chlorameisensäureester, N,N'-Carbonyldiimidazol oder Acetanhydrid.

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Es können auch mehrere - gleiche oder verschiedene - geschützte Amino- und/oder Hydroxygruppen im Molekül des Ausgangsstoffes vorhanden

sein. Falls die vorhandenen Schutzgruppen voneinander verschieden sind, können sie in vielen Fällen selektiv abgespalten werden.

5 Der Ausdruck "Aminoschutzgruppe" ist allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Aminogruppe vor chemischen Umsetzungen zu schützen (zu blockieren), die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an anderen Stellen des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind insbesondere unsubstituierte oder substituierte Acyl-, Aryl-, Aralkoxymethyl- oder Aralkylgruppen. Da die Aminoschutzgruppen nach der gewünschten Reaktion (oder Reaktionsfolge) entfernt werden, ist ihre Art und Größe im übrigen nicht kritisch; bevorzugt werden jedoch solche mit 1-20, insbesondere 1-8 C-Atomen. Der Ausdruck "Acylgruppe" ist im Zusammenhang mit dem vorliegenden Verfahren in weitestem Sinne aufzufassen. Er umschließt von aliphatischen, araliphatischen, aromatischen oder heterocyclischen Carbonsäuren oder Sulfonsäuren abgeleitete Acylgruppen sowie insbesondere Alkoxycarbonyl-, Aryloxycarbonyl- und vor allem Aralkoxycarbonylgruppen. Beispiele für derartige Acylgruppen sind Alkanoyl wie Acetyl, Propionyl, Butyryl; Aralkanoyl wie Phenylacetyl; Aroyl wie Benzoyl oder Toluyl; Aryloxyalkanoyl wie POA; Alkoxycarbonyl wie Methoxycarbonyl, Ethoxycarbonyl, 2,2,2-Trichlorethoxycarbonyl, BOC (tert.-Butyloxycarbonyl), 2-Iodethoxycarbonyl; Aralkyloxycarbonyl wie CBZ ("Carbobenzoxy"), 4-Methoxybenzyloxycarbonyl, FMOC; Arylsulfonyl wie Mtr. Bevorzugte Aminoschutzgruppen sind BOC und Mtr, ferner CBZ, Fmoc, Benzyl und Acetyl.

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Der Ausdruck "Hydroxyschutzgruppe" ist ebenfalls allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Hydroxygruppe vor chemischen Umsetzungen zu schützen, die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an anderen Stellen des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind die oben genannten unsubstituierten oder substituierten Aryl-, Aralkyl- oder Acylgruppen, ferner auch Alkylgruppen. Die Natur und Größe der Hydroxyschutzgruppen ist nicht kritisch, da sie nach der gewünschten chemischen Reaktion oder Reaktionsfolge wieder entfernt werden; bevorzugt sind Gruppen mit 1-20, insbesondere 1-10 C-Atomen. Beispiele für Hydroxy-

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schutzgruppen sind u.a. Benzyl, p-Nitrobenzoyl, p-Toluolsulfonyl, tert.-Butyl und Acetyl, wobei Benzyl und tert.-Butyl besonders bevorzugt sind.

5 Das In-Freiheit-Setzen der Verbindungen der Formel I aus ihren funktionellen Derivaten gelingt - je nach der benutzten Schutzgruppe - z. B. mit starken Säuren, zweckmäßig mit TFA oder Perchlorsäure, aber auch mit anderen starken anorganischen Säuren wie Salzsäure oder Schwefelsäure, starken organischen Carbonsäuren wie Trichloressigsäure oder Sulfonsäuren wie Benzol- oder p-Toluolsulfonsäure. Die Anwesenheit eines zusätzlichen inerten Lösungsmittels ist möglich, aber nicht immer erforderlich. Als inerte Lösungsmittel eignen sich vorzugsweise organische, beispielsweise Carbonsäuren wie Essigsäure, Ether wie Tetrahydrofuran oder Dioxan, Amide wie DMF, halogenierte Kohlenwasserstoffe wie Dichlormethan, ferner auch Alkohole wie Methanol, Ethanol oder Isopropanol, sowie Wasser. 10 Ferner kommen Gemische der vorgenannten Lösungsmittel in Frage. TFA wird vorzugsweise im Überschuß ohne Zusatz eines weiteren Lösungsmittels verwendet, Perchlorsäure in Form eines Gemisches aus Essigsäure und 70 %iger Perchlorsäure im Verhältnis 9:1. Die Reaktionstemperaturen für die Spaltung liegen zweckmäßig zwischen etwa 0 und etwa 50°, vorzugsweise arbeitet man zwischen 15 und 30° (Raumtemperatur). 20

Die Gruppen BOC, OBut und Mtr können z. B. bevorzugt mit TFA in Dichlormethan oder mit etwa 3 bis 5n HCl in Dioxan bei 15-30° abgespalten werden, die FMOC-Gruppe mit einer etwa 5- bis 50 %igen Lösung von Dimethylamin, Diethylamin oder Piperidin in DMF bei 15-30°. 25

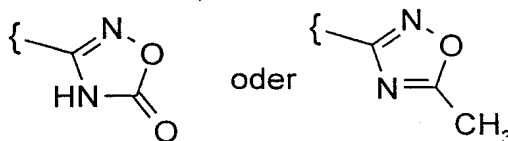
Hydrogenolytisch entfernbare Schutzgruppen (z. B. CBZ, Benzyl oder die Freisetzung der Amidinogruppe aus ihrem Oxadiazolderivat) können z. B. durch Behandeln mit Wasserstoff in Gegenwart eines Katalysators (z. B. eines Edelmetallkatalysators wie Palladium, zweckmäßig auf einem Träger wie Kohle) abgespalten werden. Als Lösungsmittel eignen sich dabei die oben angegebenen, insbesondere z. B. Alkohole wie Methanol oder Ethanol oder Amide wie DMF. Die Hydrogenolyse wird in der Regel bei Temperaturen zwischen etwa 0 und 100° und Drucken zwischen etwa 1 und 200 bar, bevorzugt bei 20-30° und 1-10 bar durchgeführt. Eine Hydrogenolyse der CBZ-Gruppe gelingt z. B. gut an 5 bis 10 %igem Pd/C in Methanol 30 35

oder mit Ammoniumformiat (anstelle von Wasserstoff) an Pd/C in Methanol/DMF bei 20-30°.

Verbindungen der Formel I,

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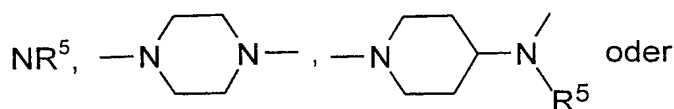
worin R<sup>1</sup>



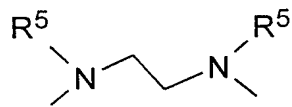
R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

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Y



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W -SO<sub>2</sub>- oder -CO- bedeuten,

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben, können vorzugsweise erhalten werden, indem man Verbindungen der Formel II mit Verbindungen der Formel III umsetzt.

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In den Verbindungen der Formel III bedeutet L vorzugsweise Cl, Br, I oder eine reaktionsfähig abgewandelte OH-Gruppe wie z.B. ein aktivierter Ester, ein Imidazolid oder Alkylsulfonyloxy mit 1-6 C-Atomen (bevorzugt Methylsulfonyloxy) oder Arylsulfonyloxy mit 6-10 C-Atomen (bevorzugt Phenyl- oder p-Tolylsulfonyloxy).

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Die Umsetzung erfolgt in der Regel in einem inerten Lösungsmittel, in Gegenwart eines säurebindenden Mittels vorzugsweise eines Alkali- oder Erdalkalimetall-hydroxids, -carbonats oder -bicarbonats oder eines anderen Salzes einer schwachen Säure der Alkali- oder Erdalkalimetalle, vorzugsweise des Kaliums, Natriums, Calciums oder Cäsiums. Auch der Zusatz einer organischen Base wie Triethylamin, Dimethylanilin, Pyridin oder Chinolin oder eines Überschusses der Aminkomponente der Formel II bzw. des Alkylierungsderivates der Formel III kann günstig sein. Die Reak-

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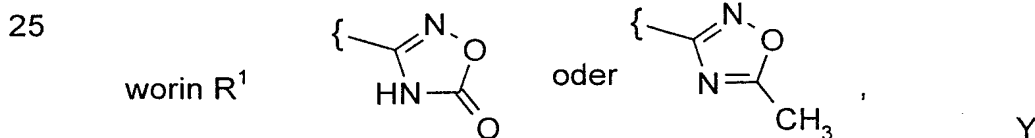


tionszeit liegt je nach den angewendeten Bedingungen zwischen einigen Minuten und 14 Tagen, die Reaktionstemperatur zwischen etwa 0° und 150°, normalerweise zwischen 20° und 130°.

- 5 Als inerte Lösungsmittel eignen sich z.B. Kohlenwasserstoffe wie Hexan, Petrolether, Benzol, Toluol oder Xylol; chlorierte Kohlenwasserstoffe wie Trichlorethylen, 1,2-Dichlorethan, Tetrachlorkohlenstoff, Chloroform oder Dichlormethan; Alkohole wie Methanol, Ethanol, Isopropanol, n-Propanol, n-Butanol oder tert.-Butanol; Ether wie Diethylether, Diisopropylether, 10 Tetrahydrofuran (THF) oder Dioxan; Glykolether wie Ethylenglykolmono-methyl- oder -monoethylether (Methylglykol oder Ethylglykol), Ethylenglykoldimethylether (Diglyme); Ketone wie Aceton oder Butanon; Amide wie Acetamid, Dimethylacetamid, N-Methylpyrrolidon (NMP) oder Dimethylformamid (DMF); Nitrile wie Acetonitril; Sulfoxide wie Dimethylsulfoxid (DMSO); Schwefelkohlenstoff; Carbonsäuren wie Ameisensäure oder Essigsäure; Nitroverbindungen wie Nitromethan oder Nitrobenzol; Ester wie Ethylacetat oder Gemische der genannten Lösungsmittel. 15

Die Ausgangsverbindungen der Formel II und III sind in der Regel bekannt. Sind sie neu, so können aber nach an sich bekannten Methoden hergestellt werden. 20

Verbindungen der Formel I,



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

30 Y O,

W eine Bindung bedeuten,

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

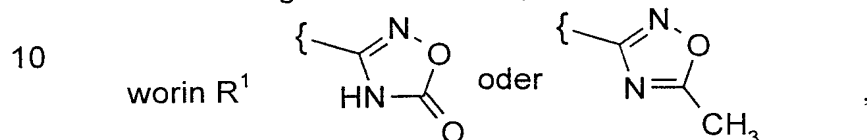
können vorzugsweise erhalten werden, indem man Verbindungen der

35 Formel II, worin Y O bedeutet, mit Verbindungen der Formel IV in einer

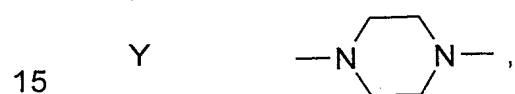
Mitsunobu-Reaktion in Gegenwart von z.B. Triphenylphosphin und Diethylazodicarboxylat in einem inerten Lösungsmittel, umgesetzt.

5 Die Ausgangsverbindungen der Formel II, worin Y O bedeutet, und IV sind in der Regel bekannt. Sind sie neu, so können aber nach an sich bekannten Methoden hergestellt werden.

Verbindungen der Formel I,



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings.



W eine Bindung,

R<sup>4</sup> -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het,

n 0 bedeuten,

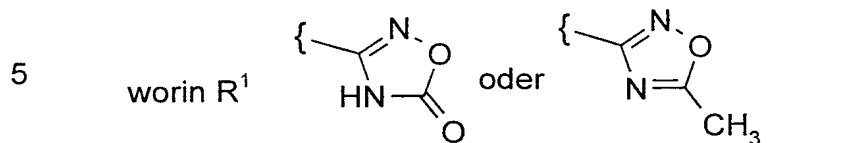
20 und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat, können vorzugsweise erhalten werden, indem man Verbindungen der Formel V mit Verbindungen der Formel VI umsetzt.

25 In den Verbindungen der Formel V bedeutet L vorzugsweise Cl, Br, I oder eine reaktionsfähig abgewandelte OH-Gruppe wie z.B. ein aktivierter Ester, ein Imidazolid oder Alkylsulfonyloxy mit 1-6 C-Atomen (bevorzugt Methylsulfonyloxy) oder Arylsulfonyloxy mit 6-10 C-Atomen (bevorzugt Phenyl- oder p-Tolylsulfonyloxy).

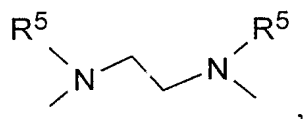
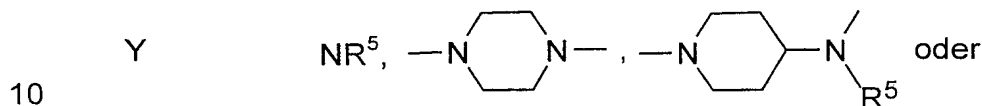
30 Die Umsetzung der Verbindungen der Formel V mit Verbindungen der Formel VI erfolgt vorzugsweise in einem inerten Lösungsmittel und bei Temperaturen wie oben angegeben.

35 Die Ausgangsverbindungen der Formeln V und VI sind in der Regel bekannt. Sind sie neu, so können aber nach an sich bekannten Methoden hergestellt werden.

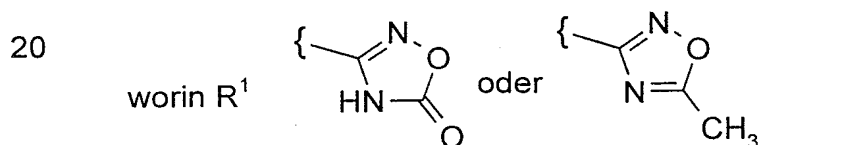
Verbindungen der Formel I,



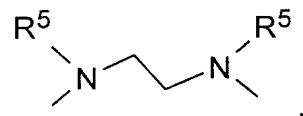
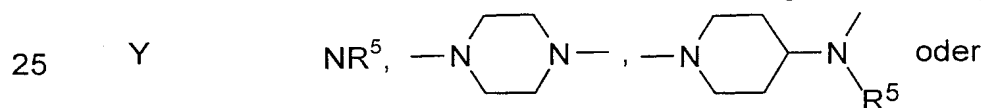
R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



15 W -CONH- bedeuten,  
und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,  
können vorzugsweise erhalten werden, indem man Verbindungen der  
Formel II



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



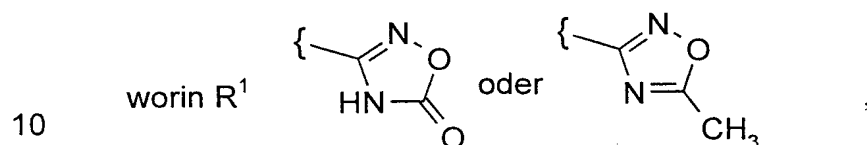
30 W -CONH- bedeuten,  
und R<sup>2</sup> und R<sup>5</sup> die in Anspruch 1 angegebenen Bedeutungen haben,  
mit Verbindungen der Formel VII umsetzt.

35 Die Umsetzung dieser Verbindungen der Formel II, worin W -CONH- be-  
deutet, mit Verbindungen der Formel VII erfolgt vorzugsweise in einem  
inerten Lösungsmittel und bei Temperaturen wie oben angegeben.

Die Ausgangsverbindungen der Formel II, worin W -CONH- bedeutet, und der Formel VII sind in der Regel bekannt. Sind sie neu, so können aber nach an sich bekannten Methoden hergestellt werden.

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Verbindungen der Formel I,



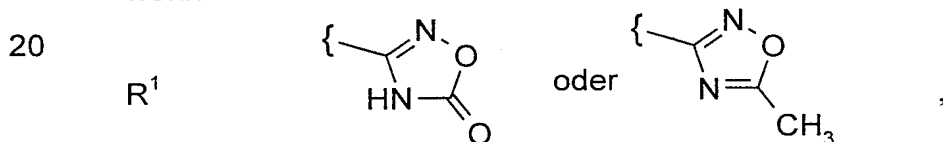
R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

Y N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>,

W SO<sub>2</sub> bedeuten,

15 und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben, können vorzugsweise erhalten werden, indem man Verbindungen der Formel II,

worin



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

25 Y N[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>

und R<sup>2</sup> und R<sup>5</sup> die in Anspruch 1 angegebene Bedeutung haben, mit Verbindungen der Formel VIII umsetzt.

30 In den Verbindungen der Formel VIII bedeutet L vorzugsweise Cl, Br, I oder eine reaktionsfähig abgewandelte OH-Gruppe wie z.B. ein aktivierter Ester, ein Imidazolid oder Alkylsulfonyloxy mit 1-6 C-Atomen (bevorzugt Methylsulfonyloxy) oder Arylsulfonyloxy mit 6-10 C-Atomen (bevorzugt Phenyl- oder p-Tolylsulfonyloxy).

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Die Umsetzung der Verbindungen der Formel II, worin Y

$N[C(R^5)_2]_m-COOR^5$  bedeutet, mit Verbindungen der Formel VIII erfolgt vorzugsweise in einem inerten Lösungsmittel und bei Temperaturen wie oben angegeben.

- 5 Verbindungen der Formel I, worin  
 X NH und  
 R<sup>3</sup> H bedeutet,  
 und R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, Y und W die in Anspruch 1 angegebenen Bedeutungen  
 haben,  
 10 können aus ihren Oxazolidinonderivaten durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit gesetzt werden. Dies geschieht unter Bedingungen wie unter "Schutzgruppenabspaltung" beschrieben.
- 15 Verbindungen der Formel I, worin R<sup>1</sup> -C(=NH)-NH<sub>2</sub> bedeutet, können ferner aus der entsprechenden Cyanverbindung erhalten werden. Die Umwandlung einer Cyangruppe in eine Amidinogruppe erfolgt durch Umsetzung mit z.B. Hydroxylamin und anschließender Reduktion des N-Hydroxyamidins mit Wasserstoff in Anwesenheit eines Katalysators wie  
 20 z.B. Pd/C.  
 Zur Herstellung eines Amidins der Formel I (R<sup>1</sup> = -C(=NH)-NH<sub>2</sub>) kann man an ein Nitril der Formel I (R<sup>1</sup> = CN) auch Ammoniak anlagern. Die Anlagerung erfolgt bevorzugt mehrstufig, indem man in an sich bekannter Weise  
 25 a) das Nitril mit H<sub>2</sub>S in ein Thioamid umwandelt, das mit einem Alkylierungsmittel, z.B. CH<sub>3</sub>I, in den entsprechenden S-Alkyl-imidothioester übergeführt wird, welcher seinerseits mit NH<sub>3</sub> zum Amidin reagiert, b) das Nitril mit einem Alkohol, z.B. Ethanol in Gegenwart von HCl in den entsprechenden Imidoester umwandelt und diesen mit Ammoniak behandelt, oder  
 30 c) das Nitril mit Lithium-bis-(trimethylsilyl)-amid umsetzt und das Produkt anschließend hydrolysiert.

Es ist ferner möglich, eine Verbindung der Formel I in eine andere Verbindung der Formel I umzuwandeln, indem man einen oder mehrere Rest(e) Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und/oder R<sup>4</sup> in einen oder mehrere Rest(e) Y, R<sup>1</sup>, R<sup>2</sup>,  
 35 R<sup>3</sup> und/oder R<sup>4</sup> umwandelt, z.B. indem man eine Aminogruppe acyliert oder Nitrogruppen (beispielsweise durch Hydrierung an Raney-Nickel oder

Pd-Kohle in einem inerten Lösungsmittel wie Methanol oder Ethanol) zu Aminogruppen reduziert.

5 Ester können z.B. mit Essigsäure oder mit NaOH oder KOH in Wasser, Wasser-THF oder Wasser-Dioxan bei Temperaturen zwischen 0 und 100° verseift werden.

10 Ferner kann man freie Aminogruppen in üblicher Weise mit einem Säurechlorid oder -anhydrid acylieren oder mit einem unsubstituierten oder substituierten Alkylhalogenid alkylieren, zweckmäßig in einem inerten Lösungsmittel wie Dichlormethan oder THF und /oder in Gegenwart einer Base wie Triethylamin oder Pyridin bei Temperaturen zwischen -60 und +30°.

15 Eine Base der Formel I kann mit einer Säure in das zugehörige Säureadditionssalz übergeführt werden, beispielsweise durch Umsetzung äquivalenter Mengen der Base und der Säure in einem inerten Lösungsmittel wie Ethanol und anschließendes Eindampfen. Für diese Umsetzung kommen insbesondere Säuren in Frage, die physiologisch unbedenkliche Salze liefern. So können anorganische Säuren verwendet werden, z.B.  
20 Schwefelsäure, Salpetersäure, Halogenwasserstoffsäuren wie Chlorwasserstoffsäure oder Bromwasserstoffsäure, Phosphorsäuren wie Orthophosphorsäure, Sulfaminsäure, ferner organische Säuren, insbesondere aliphatische, alicyclische, araliphatische, aromatische oder heterocyclische  
25 ein- oder mehrbasige Carbon-, Sulfon- oder Schwefelsäuren, z.B. Ameisensäure, Essigsäure, Propionsäure, Pivalinsäure, Diethylelessigsäure, Malonsäure, Bernsteinsäure, Pimelinsäure, Fumarsäure, Maleinsäure, Milchsäure, Weinsäure, Äpfelsäure, Citronensäure, Gluconsäure, Ascorbinsäure, Nicotinsäure, Isonicotinsäure, Methan- oder Ethansulfonsäure,  
30 Ethandisulfonsäure, 2-Hydroxyethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Naphthalin-mono- und -disulfonsäuren, Laurylschwefelsäure. Salze mit physiologisch nicht unbedenklichen Säuren, z.B. Pikrate, können zur Isolierung und /oder Aufreinigung der Verbindungen der Formel I verwendet werden.

35

Andererseits können Verbindungen der Formel I mit Basen (z.B. Natrium- oder Kaliumhydroxid oder -carbonat) in die entsprechenden Metall-, insbesondere Alkalimetall- oder Erdalkalimetall-, oder in die entsprechenden Ammoniumsalze umgewandelt werden.

5 Auch physiologisch unbedenkliche organische Basen, wie z.B. Ethanolamin können verwendet werden.

10 Erfindungsgemäße Verbindungen der Formel I können aufgrund ihrer Molekülstruktur chiral sein und können dementsprechend in verschiedenen enantiomeren Formen auftreten. Sie können daher in racemischer oder in optisch aktiver Form vorliegen.

15 Da sich die pharmazeutische Wirksamkeit der Racemate bzw. der Stereoisomeren der erfindungsgemäßen Verbindungen unterscheiden kann, kann es wünschenswert sein, die Enantiomere zu verwenden. In diesen Fällen kann das Endprodukt oder aber bereits die Zwischenprodukte in enantiomere Verbindungen, durch dem Fachmann bekannte chemische oder physikalische Maßnahmen, aufgetrennt oder bereits als solche bei der Synthese eingesetzt werden.

20 Im Falle racemischer Amine werden aus dem Gemisch durch Umsetzung mit einem optisch aktiven Trennmittel Diastereomere gebildet. Als Trennmittel eignen sich z.B. optisch aktiven Säuren, wie die R- und S-Formen von Weinsäure, Diacetylweinsäure, Dibenzoylweinsäure, Mandelsäure, Äpfelsäure, Milchsäure, geeignet N-geschützte Aminosäuren (z.B. N-Benzoylprolin oder N-Benzolsulfonylprolin) oder die verschiedenen optisch  
25 aktiven Camphersulfonsäuren. Vorteilhaft ist auch eine chromatographische Enantiomerentrennung mit Hilfe eines optisch aktiven Trennmittels (z.B. Dinitrobenzoylphenylglycin, Cellulosetriacetat oder andere Derivate von Kohlenhydraten oder auf Kieselgel fixierte chiral derivatisierte  
30 Methacrylatpolymere). Als Laufmittel eignen sich hierfür wäßrige oder alkoholische Lösungsmittelgemische wie z.B. Hexan/Isopropanol/ Acetonitril z.B. im Verhältnis 82:15:3.

35 Gegenstand der Erfindung ist ferner die Verwendung der Verbindungen der Formel I und/oder ihrer physiologisch unbedenklichen Salze zur Herstellung pharmazeutischer Zubereitungen, insbesondere auf nicht-chem-

ischem Wege. Hierbei können sie zusammen mit mindestens einem festen, flüssigen und/oder halbflüssigen Träger- oder Hilfsstoff und gegebenenfalls in Kombination mit einem oder mehreren weiteren Wirkstoffen in eine geeignete Dosierungsform gebracht werden.

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Gegenstand der Erfindung sind ferner pharmazeutische Zubereitungen, enthaltend mindestens eine Verbindung der Formel I und/oder eines ihrer physiologisch unbedenklichen Salze.

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Diese Zubereitungen können als Arzneimittel in der Human- oder Veterinärmedizin verwendet werden. Als Trägerstoffe kommen organische oder anorganische Substanzen in Frage, die sich für die enterale (z.B. orale), parenterale oder topische Applikation eignen und mit den neuen Verbindungen nicht reagieren, beispielsweise Wasser, pflanzliche Öle, Benzyl-

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alkohole, Alkylenglykole, Polyethylenglykole, Glycerintriacetat, Gelatine, Kohlehydrate wie Lactose oder Stärke, Magnesiumstearat, Talk, Vaseline.

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Zur oralen Anwendung dienen insbesondere Tabletten, Pillen, Dragees, Kapseln, Pulver, Granulate, Sirupe, Säfte oder Tropfen, zur rektalen Anwendung Suppositorien, zur parenteralen Anwendung Lösungen, vorzugsweise ölige oder wässrige Lösungen, ferner Suspensionen, Emulsionen oder Implantate, für die topische Anwendung Salben, Cremes oder Puder. Die neuen Verbindungen können auch lyophilisiert und die erhaltenen Lyophilisate z.B. zur Herstellung von Injektionspräparaten verwendet werden.

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Die angegebenen Zubereitungen können sterilisiert sein und/oder Hilfsstoffe wie Gleit-, Konservierungs-, Stabilisierungs- und/oder Netzmittel, Emulgatoren, Salze zur Beeinflussung des osmotischen Druckes, Puffersubstanzen, Farb-, Geschmacks- und /oder mehrere weitere Wirkstoffe enthalten, z.B. ein oder mehrere Vitamine.

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Die Verbindungen der Formel I und ihre physiologisch unbedenklichen Salze können bei der Bekämpfung und Verhütung von thromboembolischen Erkrankungen wie Thrombose, myocardialem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens verwendet werden.

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Dabei werden die erfindungsgemäßen Substanzen in der Regel vorzugsweise in Dosierungen zwischen etwa 1 und 500 mg, insbesondere zwischen 5 und 100 mg pro Dosierungseinheit verabreicht. Die tägliche Dosierung liegt vorzugsweise zwischen etwa 0,02 und 10 mg/kg Körpergewicht. Die spezielle Dosis für jeden Patienten hängt jedoch von den verschiedensten Faktoren ab, beispielsweise von der Wirksamkeit der eingesetzten speziellen Verbindung, vom Alter, Körpergewicht, allgemeinen Gesundheitszustand, Geschlecht, von der Kost, vom Verabreichungszeitpunkt und -weg, von der Ausscheidungsgeschwindigkeit, Arzneistoffkombination und Schwere der jeweiligen Erkrankung, welcher die Therapie gilt. Die orale Applikation ist bevorzugt.

Vor- und nachstehend sind alle Temperaturen in °C angegeben. In den nachfolgenden Beispielen bedeutet "übliche Aufarbeitung": Man gibt, falls erforderlich, Wasser hinzu, stellt, falls erforderlich, je nach Konstitution des Endprodukts auf pH-Werte zwischen 2 und 10 ein, extrahiert mit Ethylacetat oder Dichlormethan, trennt ab, trocknet die organische Phase über Natriumsulfat, dampft ein und reinigt durch Chromatographie an Kieselgel und /oder durch Kristallisation. Rf-Werte an Kieselgel: Laufmittel: Ethylacetat/Methanol 9:1.

Massenspektrometrie (MS): EI (Elektronenstoß-Ionisation) M<sup>+</sup>

FAB (Fast Atom Bombardment) (M+H)<sup>+</sup>

#### Beispiel 1

Eine Lösung von 100 mg 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-piperazin-1-ylmethyl-oxazolidin-2-on ("A") [erhältlich durch Umsetzung von Methansulfonsäure-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethylester mit 1-tert.-Butoxycarbonylpiperazin und Natriumhydrogencarbonat in Acetonitril; Abspaltung der BOC-Gruppe mit HCl/Dioxan und anschließende Behandlung mit Natriumhydroxidlösung] und 110 mg 2,4,6-Trichlorbenzolsulfonylchlorid in 10 ml Dichlormethan wird mit 400 mg 4-Dimethylaminopyridin auf Polystyrol versetzt und 18 Stunden bei Raumtemperatur gerührt. Man filtriert, entfernt das Lösungsmittel und erhält 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,4,6-trichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on, FAB 586/588.

Analog erhält man durch Umsetzung von "A"

mit 4-Biphenylsulfonylchlorid

5 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-biphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Phenylvinylsulfonylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-phenylvinylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Nitrophenylsulfonylchlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-nitrophenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2,5-Dimethoxyphenylsulfonylchlorid

20 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,5-dimethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Naphthylsulfonylchlorid

25 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Chlor-4-fluorphenylsulfonylchlorid

30 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-chlor-4-fluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit (2-Acetamido-4-methyl-thiazol-5-yl)-sulfonylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-((2-acetamido-4-methyl-thiazol-5-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Cyanphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-cyanphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

35 mit 5-Nitro-2-methylphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(5-nitro-2-methylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit Benzylsulfonylchlorid

5 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-benzylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-2-on;

mit Decylsulfonylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-decylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-2-on;

mit 2-Trifluormethylphenylsulfonylchlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-trifluormethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3-Chlor-4-fluorphenylsulfonylchlorid

20 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-chlor-4-fluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Chlor-2,5-dimethylphenylsulfonylchlorid

25 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-chlor-2,5-dimethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Fluorphenylsulfonylchlorid

30 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-fluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,4-Dibromphenylsulfonylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,4-dibromphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3-Chlorphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-chlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

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mit 2,6-Dichlorphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,6-dichlorophenyl-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,4-Dichlorphenylsulfonylchlorid

5 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,4-dichlorophenyl-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,5-Dichlorphenylsulfonylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,5-dichlorophenyl-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Naphthylcarbonsäurechlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-naphthyl-carbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit Methylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-methylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-2-on;

20 mit 2-Methylsulfonylphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-methylsulfonyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Nitrobenzylsulfonylchlorid

25 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-nitrobenzyl-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit (4-Methoxycarbonyl-3-methoxy-thiophen-2-yl)-sulfonylchlorid

30 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-((4-methoxy-carbonyl-3-methoxy-thiophen-2-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3-Trifluormethylphenylsulfonylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-trifluormethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Trifluormethoxyphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

5 mit (1S)-(Campher-10-yl)-sulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(((1S)-campher-10-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit (1R)-(Campher-10-yl)-sulfonylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(((1R)-campher-10-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit (2,2,5,7,8-Pentamethylchroman-6-yl)-sulfonylchlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-((2,2,5,7,8-pentamethylchroman-6-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Isopropylphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-isopropylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

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mit 4-tert.-Butylphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-tert.-butylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

25 mit 4-Butylphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-butylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,5-Dinitro-4-methoxyphenylsulfonylchlorid

30 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,5-dinitro-4-methoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit Ethylsulfonylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-ethylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-2-on;

mit 4-Nitrophenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-nitrophenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

5 mit 2-Trifluormethoxyphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2,4-Dinitrophenylsulfonylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,4-dinitrophenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit Isopropylsulfonylchlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-isopropylsulfonylpiperazin-1-ylmethyl)-oxazolidin-2-on;

mit 4-Ethylphenylsulfonylchlorid

20 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-ethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Brom-2-trifluormethoxyphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-brom-2-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

25 mit 2,3,4-Trifluorphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,3,4-trifluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,4-Difluorphenylsulfonylchlorid

30 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,4-difluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2,2,2-Trifluorethylsulfonylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,2,2-trifluorethylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3-Nitro-4-methylphenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-nitro-4-methylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

5 mit 2-Nitro-6-chlor-phenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-nitro-6-chlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2,5-Dimethoxyphenylacetylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,5-dimethoxyphenylacetyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,4-Dichlorbenzoylchlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,4-dichlorbenzoyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3-Fluorbenzoylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-fluorbenzoyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

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mit 4-Trifluormethoxybenzoylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-trifluormethoxybenzoyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

25 mit 3-Pyridylcarbonsäurechlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-pyridylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Benzothienylcarbonsäurechlorid

30 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-benzothienylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Chlorphenylacetylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-chlorphenylacetyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 1-Naphthylcarbonsäurechlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(1-naphthyl-carbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

5 mit (1,3-Benzodioxol-5-yl)-carbonsäurechlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-((1,3-benzodioxol-5-yl)-carbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3-Nitrobenzoylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-nitrobenzoyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Biphenylcarbonsäurechlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-biphenylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit Cyclopentylcarbonsäurechlorid

20 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(cyclopentyl-carbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit [5-Chlor-1-(4-methylphenyl)-1H-pyrazol-4-yl]-sulfonylchlorid

25 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[5-chlor-1-(4-methylphenyl)-1H-pyrazol-4-yl]-sulfonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Chlor-phenylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-chlorphenyl-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

30 mit 5,7,7-Trimethyl-2-(1,3,3-trimethylbutyl)-octylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)-octylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Butoxy-5-(1,1-dimethylpropyl)-phenylsulfonylchlorid

35 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[2-butoxy-5-(1,1-dimethylpropyl)-phenylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on;



mit 2-Butoxy-5-(1,1,3,3-tetramethylbutyl)-phenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[2-butoxy-5-(1,1,3,3-tetramethylbutyl)-phenylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-Nitro-4-trifluormethyl-phenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-nitro-4-trifluormethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Brom-2-ethyl-phenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-brom-2-ethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Trifluormethyl-phenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-trifluormethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Trifluormethyl-phenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-trifluormethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 3,4-Difluorphenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,4-difluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 1-Naphthylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(1-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Methoxyphenylsulfonylchlorid  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-methoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Tolylsulfonylchlorid

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-tolylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Propylsulfonylchlorid

5 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-propylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 6-Chlor-2-naphthylsulfonylchlorid

10 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 2-(Naphth-1-yl)-ethylsulfonylchlorid

15 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[2-(naphth-1-yl)-ethylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit Chlorameisensäureisobutylester

20 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(isobutyloxy-carbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on.

## 20 Beispiel 2

Eine Lösung von 100 mg 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,4,6-trichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on in 15 ml Methanol wird mit 100 mg Raney-Nickel und einem Tropfen Essigsäure versetzt und 8 Stunden bei Raumtemperatur hydriert. Der Katalysator wird abfiltriert und das Lösungsmittel entfernt. Man erhält 4-[2-Oxo-5-[4-(2,4,6-trichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl]-benzamidin, Acetat, FAB 546/548.

30 Analog erhält man durch Hydrierung aus den in Beispiel 1 erhaltenen Verbindungen die nachstehenden Benzamidinderivate

4-[2-Oxo-5-[4-(4-biphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl]-benzamidin, Trifluoracetat, FAB 520;

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4-{2-Oxo-5-[4-(2-phenylethylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 472;

5 4-{2-Oxo-5-[4-(2-aminophenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 459;

4-{2-Oxo-5-[4-(2,5-dimethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 504;

10 4-{2-Oxo-5-[4-(2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 494;

4-{2-Oxo-5-[4-(2-chlor-4-fluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 496;

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4-{2-Oxo-5-[4-((2-acetamido-4-methyl-thiazol-5-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 522;

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4-{2-Oxo-5-[4-(2-cyanphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 469;

4-{2-Oxo-5-[4-(5-amino-2-methylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 473;

25

4-{2-Oxo-5-(4-benzylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 458;

4-{2-Oxo-5-(4-decylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 508;

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4-{2-Oxo-5-[4-(2-trifluormethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 512;

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4-{2-Oxo-5-[4-(3-chlor-4-fluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 496;

4-{2-Oxo-5-[4-(4-chlor-2,5-dimethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 506;

5 4-{2-Oxo-5-[4-(2-fluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 462;

4-{2-Oxo-5-[4-(3,4-dibromphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 600/602/604;

10 4-{2-Oxo-5-[4-(3-chlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 478;

4-{2-Oxo-5-[4-(2,6-dichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 512;

15

4-{2-Oxo-5-[4-(3,4-dichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 512;

20 4-{2-Oxo-5-[4-(3,5-dichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 512;

4-{2-Oxo-5-[4-(2-naphthylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 458;

25 4-{2-Oxo-5-(4-methylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-3-yl}-benzamidin, Acetat, FAB 382;

4-{2-Oxo-5-[4-(2-methylsulfonylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 522;

30

4-{2-Oxo-5-[4-(2-aminobenzylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 473;

35 4-{2-Oxo-5-[4-((4-methoxycarbonyl-3-methoxy-thiophen-2-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 538;

4-{2-Oxo-5-[4-(3-trifluormethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 512;

5 4-{2-Oxo-5-[4-(4-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 528;

4-{2-Oxo-5-[4-(((1S)-campher-10-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 518;

10

4-{2-Oxo-5-[4-(((1R)-campher-10-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 518;

15

4-{2-Oxo-5-[4-((2,2,5,7,8-pentamethylchroman-6-yl)-sulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 570;

4-{2-Oxo-5-[4-(4-isopropylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 486;

20

4-{2-Oxo-5-[4-(4-tert.-butylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat;

4-{2-Oxo-5-[4-(4-butylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 500;

25

4-{2-Oxo-5-[4-(3,5-diamino-4-methoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 504;

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4-{2-Oxo-5-(4-ethylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-3-yl}-benzamidin, Acetat, FAB 396;

4-{2-Oxo-5-[4-(4-nitrophenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 459;

35

4-{2-Oxo-5-[4-(2-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 528;

4-{2-Oxo-5-[4-(2,4-diaminophenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 474;

5 4-{2-Oxo-5-(4-isopropylsulfonyl-piperazin-1-ylmethyl)-oxazolidin-3-yl}-benzamidin, Acetat, FAB 410;

4-{2-Oxo-5-[4-(4-ethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 472;

10

4-{2-Oxo-5-[4-(4-brom-2-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 606/608;

4-{2-Oxo-5-[4-(2,3,4-trifluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 498;

15

4-{2-Oxo-5-[4-(3,4-difluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 480;

4-{2-Oxo-5-[4-(2,2,2-trifluorethylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 450;

20

4-{2-Oxo-5-[4-(3-amino-4-methylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 473;

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4-{2-Oxo-5-[4-(2-amino-6-chlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 585;

4-{2-Oxo-5-[4-(2,5-dimethoxyphenylacetyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 482;

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4-{2-Oxo-5-[4-(3,4-dichlorbenzoyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 476;

4-{2-Oxo-5-[4-(3-fluorbenzoyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 426;

35

4-{2-Oxo-5-[4-(4-trifluoromethoxybenzoyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 492;

5 4-{2-Oxo-5-[4-(3-pyridylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 409;

4-{2-Oxo-5-[4-(2-benzothiénylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 463;

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4-{2-Oxo-5-[4-(4-chlorphenylacetyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 456;

4-{2-Oxo-5-[4-(1-naphthylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 458;

15

4-{2-Oxo-5-[4-((1,3-benzodioxol-5-yl)-carbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 452;

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4-{2-Oxo-5-[4-(3-aminobenzoyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 423;

4-{2-Oxo-5-[4-(4-biphenylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 484;

25

4-{2-Oxo-5-[4-(cyclopentylcarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 400;

30

4-{2-Oxo-5-[4-[5-chlor-1-(4-methylphenyl)-1H-pyrazol-4-yl]-sulfonyl]-piperazin-1-ylmethyl}-oxazolidin-3-yl}-benzamidin, Acetat, FAB 558;

4-{2-Oxo-5-[4-(4-chlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 478;

35

4-{2-Oxo-5-[4-[5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)-octylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 620;

4-{2-Oxo-5-[4-[2-butoxy-5-(1,1-dimethylpropyl)-phenylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 586;

5 4-{2-Oxo-5-[4-[2-butoxy-5-(1,1,3,3-tetramethylbutyl)-phenylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 628;

4-{2-Oxo-5-[4-(2-amino-4-trifluormethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat;

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4-{2-Oxo-5-[4-(4-brom-2-ethyl-phenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 550/552;

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4-{2-Oxo-5-[4-(4-trifluormethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 512;

4-{2-Oxo-5-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 528;

20

4-{2-Oxo-5-[4-(isobutyloxycarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 404.

Analog erhält man durch Umsetzung von 3-[3-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-piperazin-1-ylmethyl-oxazolidin-2-on mit 6-Chlor-2-naphthylsulfonylchlorid und anschließender Hydrierung die Verbindung

25

3-{2-Oxo-5-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, F. 118°.

30

Analog erhält man durch Umsetzung von 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-piperazin-1-ylmethyl-oxazolidin-2-on mit 6-Methoxy-2-naphthylsulfonylchlorid und anschließender Hydrierung die Verbindung

35

4-{2-Oxo-5-[4-(6-methoxy-2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin.



Analog erhält man durch Umsetzung von 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-piperazin-1-ylmethyl-oxazolidin-2-on mit 2-Fluorbenzylchlorid und anschließender Hydrierung die Verbindung

5            4-{2-Oxo-5-[4-(2-fluorbenzyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin.

### Beispiel 3

10            Eine Lösung von 100 mg 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2,4,6-trichlorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on in 8 ml Methanol wird mit 3 ml 1N Natronlauge versetzt und 48 Stunden bei 60° gerührt. Nach üblicher Aufarbeitung erhält man 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(2,6-dichlor-4-methoxyphenylsulfonyl)-piperazin-1-yl]-propan-2-ol, FAB 556/558.

15

Analog erhält man

20            aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,4-difluorphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on  
              3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(3-fluor-4-methoxyphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

25            aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(1-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on  
              3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(1-naphthylsulfonyl)-piperazin-1-yl]-propan-2-ol;

30            aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-trifluormethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on  
              3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-trifluormethylphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

35            aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-biphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-biphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

5 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3-trifluormethylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(3-trifluormethylphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

10 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-trifluormethoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-trifluormethoxyphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

15 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-isopropylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

20 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-butylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-butylphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

25 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-methoxyphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

30 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-tolylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-tolylsulfonyl)-piperazin-1-yl]-propan-2-ol;

35 aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(4-propylphenylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(4-propyl-phenylsulfonyl)-piperazin-1-yl]-propan-2-ol;

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-yl]-propan-2-ol;

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(2-phenylvinylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(2-phenylvinylsulfonyl)-piperazin-1-yl]-propan-2-ol;

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[2-(naphth-1-yl)-ethylsulfonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-[2-(naphth-1-yl)-ethylsulfonyl]-piperazin-1-yl]-propan-2-ol.

Analog erhält man aus 4-{2-Oxo-5-[4-(6-methoxy-2-naphthylsulfonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin die Verbindung

4-{2-Hydroxy-3-[4-(6-methoxy-naphthalin-2-sulfonyl)-piperazin-1-yl]-propylamino}-benzamidin, Diacetat, FAB 498 und

aus 4-{2-Oxo-5-[4-(2-fluorbenzyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin die Verbindung

4-{2-Hydroxy-3-[4-(2-fluorbenzyl)-piperazin-1-yl]-propylamino}-benzamidin, Acetat, FAB 386.

#### Beispiel 4

Eine Lösung von 60 mg 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(2,6-dichlor-4-methoxyphenylsulfonyl)-piperazin-1-yl]-propan-2-ol in 5 ml Methanol wird mit 50 mg Raney-Nickel und einem Tropfen Essigsäure versetzt und 8 Stunden bei Raumtemperatur hydriert. Der

Katalysator wird abfiltriert und das Lösungsmittel entfernt. Man erhält 4-{3-[4-(2,6-Dichlor-4-methoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 516/518.

5 Analog erhält man durch Hydrierung aus den unter Beispiel 3 aufgeführten Propan-2-ol-derivaten die nachstehenden Verbindungen

4-{3-[4-(3-fluor-4-methoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 466;

10

4-{3-[4-(1-naphthylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 468;

15

4-{3-[4-(4-trifluormethylphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 486;

4-{3-[4-(4-biphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 494;

20

4-{3-[4-(3-trifluormethylphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 486;

4-{3-[4-(4-trifluormethoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 502;

25

4-{3-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 460;

30

4-{3-[4-(4-butylphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 474;

4-{3-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 448;

35

4-{3-[4-(4-tolylsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 432;

4-{3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 460;

5 4-{3-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 502;

4-{3-[4-(2-phenylvinylsulfonyl)-piperazin-1-yl]-2-hydroxy-propyl-amino}-benzamidin, Acetat, FAB 446;

10

4-{3-[4-[2-(naphth-1-yl)-ethylsulfonyl]-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 496.

#### Beispiel 5

15

Eine Lösung von 10,0 g {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester, 6,73 g 4-BOC-amino-piperidin und 8,5 g Natriumhydrogencarbonat in 200 ml Acetonitril wird 40 Stunden unter Rückfluß erhitzt. Man arbeitet wie üblich auf und erhält 5-(4-BOC-amino-piperidin-1-ylmethyl)-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-oxazolidin-2-on.

20

Die Abspaltung der BOC-Gruppe erfolgt mit TFA in Dichlormethan und man erhält 5-(4-Amino-piperidin-1-ylmethyl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on ("B").

25

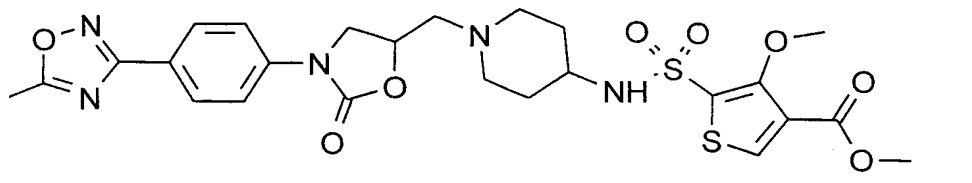
Analog Beispiel 1 erhält man durch Umsetzung von "B"

mit (3-Methoxy-4-methoxycarbonyl-thiophen-2-yl)-sulfonylchlorid

30

(3-Methoxy-4-methoxycarbonyl-thiophen-2-yl)-sulfonsäure-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-amid

35



5

mit Benzolsulfonylchlorid

N-(1-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-benzolsulfonamid;

10

mit 3,4-Dimethoxybenzolsulfonylchlorid

3,4-Dimethoxy-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-benzolsulfonamid;

15

mit Butylsulfonylchlorid

N-(1-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-butylsulfonamid;

20

mit 2,4,6-Trimethyl-benzolsulfonylchlorid

2,4,6-Trimethyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-benzolsulfonamid;

25

mit Phenylvinylsulfonylchlorid

Phenylvinyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-sulfonamid;

30

mit 2-Methylsulfonyl-benzolsulfonylchlorid

2-Methylsulfonyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-benzolsulfonamid;

35

mit 5-Dimethylamino-1-naphthylsulfonylchlorid

5-Dimethylamino-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-1-naphthylsulfonamid;

mit 1-Naphthylsulfonylchlorid

N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-piperidin-4-yl)-1-naphthylsulfonamid.

5

Durch Hydrierung analog Beispiel 2 erhält man daraus die nachstehenden Verbindungen

10

4-{5-[4-((3-Methoxy-4-methoxycarbonyl-thiophen-2-yl)-sulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 552;

15

4-{5-[4-(Benzolsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 458;

4-{5-[4-(3,4-Dimethoxy-benzolsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 518;

20

4-{5-[4-(Butylsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 438;

4-{5-[4-(2,4,6-Trimethyl-benzolsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 500;

25

4-{5-[4-(Phenylethylsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 486;

4-{5-[4-(2-Methylsulfonyl-benzolsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 536;

30

4-{5-[4-(4-Biphenylsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 533;

35

4-{5-[4-(5-Dimethylamino-1-naphthylsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 551;

4-{5-[4-(1-Naphthylsulfonylamino)-piperidin-1-ylmethyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 458.

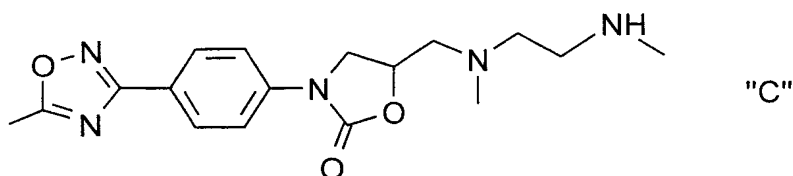
### Beispiel 6

5

Eine Lösung von 10,0 g {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester, 7,4 g N,N'-Dimethylethylendiamin und 8,5 g Natriumhydrogencarbonat in 400 ml Acetonitril wird 40 Stunden unter Rückfluß erhitzt. Man arbeitet wie üblich auf und erhält 5-[[Methyl-(2-methylamino-ethyl)-amino]-methyl]-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-oxazolidin-2-on ("C").

10

15



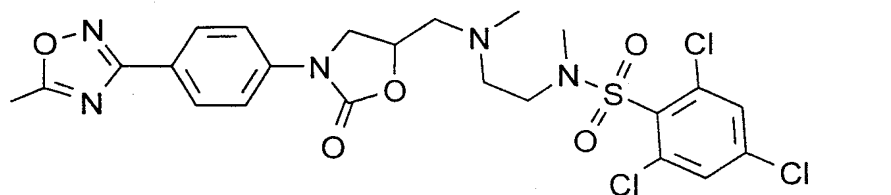
Analog Beispiel 1 erhält man durch Umsetzung von "C"

20

mit 2,4,6-Trichlorphenylsulfonylchlorid

2,4,6-Trichlor-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid

25



30

mit 2-Trifluormethoxyphenylsulfonylchlorid

2-Trifluormethoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

35

mit 2,4,6-Trichlorphenylsulfonylchlorid



2,4,6-Trichlor-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

5 mit 4-Trifluormethylphenylsulfonylchlorid

4-Trifluormethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

10 mit 4-Isopropylphenylsulfonylchlorid

4-Isopropyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Propylphenylsulfonylchlorid

15 4-Propyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Acetamidophenylsulfonylchlorid

20 4-Acetamido-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 2-Naphthylsulfonylchlorid

25 N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-2-naphthylsulfonamid;

mit 3-Trifluormethylphenylsulfonylchlorid

30 3-Trifluormethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Chlor-3-nitro-phenylsulfonylchlorid

35 4-Chlor-3-nitro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit Phenylvinylsulfonylchlorid

N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-phenylvinylsulfonamid;

mit Benzylsulfonylchlorid

5 4-Trifluormethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzylsulfonamid;

mit Tolylsulfonylchlorid

10 4-Methyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Methoxyphenylsulfonylchlorid

15 4-Methoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 1-Naphthylsulfonylchlorid

20 N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-1-naphthylsulfonamid;

mit 4-Biphenylsulfonylchlorid

N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-4-biphenylsulfonamid;

25 mit 3,4-Difluorphenylsulfonylchlorid

3,4-Difluor-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Pentylphenylsulfonylchlorid

30 4-Pentyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Butylphenylsulfonylchlorid

35 4-Butyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

mit 4-Methylsulfonylphenylsulfonylchlorid

4-Methylsulfonyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-benzolsulfonamid;

5

mit 6-Chlor-2-naphthylsulfonylchlorid

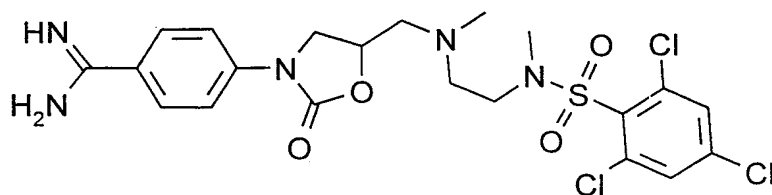
6-Chlor-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-2-naphthylsulfonamid.

10

Durch Hydrierung analog Beispiel 2 erhält man daraus die nachstehenden Verbindungen

4-{5-[(Methyl-{2-[methyl-(2,4,6-trichlor-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 548/550

15



20

4-{5-[(Methyl-{2-[methyl-(2-trifluormethoxy-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 530;

25

4-{5-[(Methyl-{2-[methyl-(4-trifluormethyl-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 514;

30

4-{5-[(Methyl-{2-[methyl-(4-isopropyl-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 488;

4-{5-[(Methyl-{2-[methyl-(4-propyl-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 488;

35

4-{5-[(Methyl-{2-[methyl-(4-acetamido-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 503;

4-{5-[(Methyl-{2-[methyl-(2-naphthylsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 496;

5 4-{5-[(Methyl-{2-[methyl-(3-trifluormethyl-benzolsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 514;

10 4-{5-[(Methyl-{2-[methyl-(3-amino-4-chlor-benzolsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 495;

4-{5-[(Methyl-{2-[methyl-(phenylethylsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 474;

15 4-{5-[(Methyl-{2-[methyl-(benzylsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 460;

4-{5-[(Methyl-{2-[methyl-(4-tolylsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 460;

20 4-{5-[(Methyl-{2-[methyl-(4-methoxy-benzolsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 476;

25 4-{5-[(Methyl-{2-[methyl-(1-naphthylsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 496;

4-{5-[(Methyl-{2-[methyl-(4-biphenylsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 522;

30 4-{5-[(Methyl-{2-[methyl-(3,4-difluor-benzolsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 516;

4-{5-[(Methyl-{2-[methyl-(4-pentyl-benzolsulfonyl)-amino]-ethyl)-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 516;

35

4-{5-[(Methyl-{2-[methyl-(4-butyl-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 502;

5 4-{5-[(Methyl-{2-[methyl-(4-methylsulfonyl-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 502;

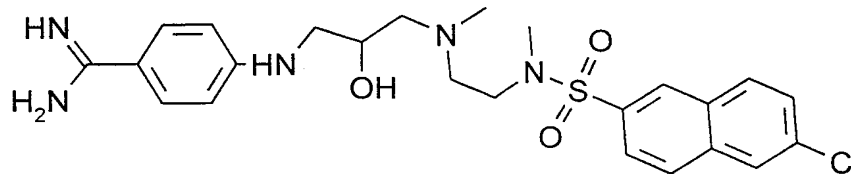
10 4-{5-[(Methyl-{2-[methyl-(6-chlor-2-naphthylsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Trifluoracetat, FAB 530.

Analog Beispiel 3 und 4 erhält man aus 6-Chlor-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-2-naphthylsulfonamid die Verbindung

15

4-[3-({2-[(6-Chlor-2-naphthylsulfonyl)-methyl-amino]-ethyl}-methylamino)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 504

20



25

und aus 7-Methoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-ethyl]-2-naphthylsulfonamid die Verbindung

30

4-[3-({2-[(7-Methoxy-2-naphthylsulfonyl)-methyl-amino]-ethyl}-methylamino)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 500.

Analog Beispiel 3 erhält man durch Spaltung des Oxazolidinonrings aus

35

4-{5-[(Methyl-{2-[methyl-(4-biphenylsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin,

4-{5-[(Methyl-{2-[methyl-(4-isopropyl-benzolsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin,

5 4-{5-[(Methyl-{2-[methyl-(1-naphthylsulfonyl)-amino]-ethyl}-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin,

die nachstehenden Verbindungen

10 4-[3-({2-[(4-Biphenylsulfonyl)-methyl-amino]-ethyl}-methylamino)-2-hydroxy-propylamino]-benzamidin, Diacetat, EI 460 ( $M^+ - NH_2$ );

4-[3-({2-[(4-Isopropylbenzolsulfonyl)-methyl-amino]-ethyl}-methylamino)-2-hydroxy-propylamino]-benzamidin, Diacetat, EI 461;

15 4-[3-({2-[(1-Naphthylsulfonyl)-methyl-amino]-ethyl}-methylamino)-2-hydroxy-propylamino]-benzamidin, Diacetat, EI 469.

#### Beispiel 7

20 Eine Lösung von 10,6 g {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester und 3,17 g Natriumazid in 50 ml Acetonitril wird 40 Stunden unter Rückfluß erhitzt. Man arbeitet wie üblich auf und erhält 5-Azidomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on.

25 7,7 g Azidoverbindung wird in Ethylenglycoldimethylether suspendiert, dann 3,6 ml Trimethylphosphit zugegeben und 1,5 Stunden unter Rückfluß gerührt. Man gibt 4,9 ml halbkonzentrierte HCl zu und kocht weitere 3 Stunden.

30 Nach üblicher Aufarbeitung erhält man 5-Aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on, Hydrochlorid.

Die Verbindung wird in Dichlormethan suspendiert, mit basischem Ionenaustauscher versetzt und 2 Stunden gerührt. Nach Entfernen des Ionenaustauschers und des Lösungsmittels erhält man 5-Aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on ("D").

35

Analog Beispiel 1 erhält man durch Umsetzung von "D"

mit 3,4-Difluor-benzolsulfonylchlorid

3,4-Difluor-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

5

mit 4-Methoxy-benzolsulfonylchlorid

4-Methoxy-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

10

mit 4-Chlor-3-nitro-benzolsulfonylchlorid

4-Chlor-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit Butylsulfonylchlorid

15

N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-butylsulfonamid;

mit 3-Trifluormethyl-benzolsulfonylchlorid

3-Trifluormethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

20

mit 2-Naphthylsulfonylchlorid

N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthylsulfonamid.

25

Analog Beispiel 2 erhält man durch Hydrierung der Sulfonamide die nachstehenden Verbindungen

30

4-{5-[(3,4-Difluor-benzolsulfonylamino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 411;

4-{5-[4-Methoxy-benzolsulfonylamino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 405;

35

4-{5-[(3-Amino-4-chlor-benzolsulfonylamino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 424;

4-{5-[(Butylsulfonylamino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin,  
Acetat, FAB 355;

5 4-{5-[(3-Trifluormethylbenzolsulfonylamino)-methyl]-2-oxo-oxazolidin-  
3-yl}-benzamidin, Acetat, FAB 443;

4-{5-[(2-Naphthylsulfonylamino)-methyl]-2-oxo-oxazolidin-3-yl}-  
benzamidin, Acetat, FAB 425.

10

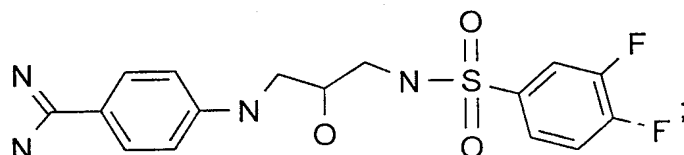
### Beispiel 8

Analog Beispiel 3 und 4 erhält man

15 aus 3,4-Difluor-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-  
oxazolidin-5-ylmethyl}-benzolsulfonamid

4-[3-(3,4-Difluor-benzolsulfonylamino)-2-hydroxy-propylamino]-  
benzamidin, Acetat, FAB 385

20



25 aus 4-Methoxy-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-  
oxazolidin-5-ylmethyl}-benzolsulfonamid

4-[3-(4-Methoxy-benzolsulfonylamino)-2-hydroxy-propylamino]-  
benzamidin;

30 aus 4-Chlor-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-  
oxazolidin-5-ylmethyl}-benzolsulfonamid

4-[3-(3-Amino-4-chlor-benzolsulfonylamino)-2-hydroxy-propylamino]-  
benzamidin;

35 aus N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-  
ylmethyl}-butylsulfonamid



4-[3-(Butylsulfonylamino)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 329;

aus 3-Trifluormethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

5

4-[3-(3-Trifluormethyl-benzolsulfonylamino)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 417;

aus N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-propylsulfonamid

10

4-[3-(Propylsulfonylamino)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 391.

#### Beispiel 9

15

Eine Lösung von 30,0 g {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester und 300 ml wässrige Methylaminlösung in 300 ml THF wird 18 Stunden unter Druck bei 80° erhitzt. Man arbeitet wie üblich auf und erhält 5-Methylaminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on ("E").

20

Analog Beispiel 1 erhält man durch Umsetzung von "E"

mit Butylsulfonylchlorid

25

N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-butylsulfonamid;

mit 4-Isopropyl-benzolsulfonylchlorid

30

4-Isopropyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 3-Trifluormethyl-benzolsulfonylchlorid

35

3-Trifluormethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit Phenylvinylsulfonylchlorid

N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-phenylvinylsulfonamid;

mit 2-Naphthylsulfonylchlorid

5 N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthylsulfonamid;

mit 4-Propyl-benzolsulfonylchlorid

10 4-Propyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 4-Methoxy-benzolsulfonylchlorid

15 4-Methoxy-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 2,4,6-Trimethyl-benzolsulfonylchlorid

20 2,4,6-Trimethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit Benzoylchlorid

N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzamid;

mit 2-Naphthylcarbonsäurechlorid

25 N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthyl-carbonsäureamid;

mit Cyclohexylcarbonsäurechlorid

30 N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-cyclohexylcarbansäureamid;

mit 4-Biphenylcarbonsäurechlorid

35 N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-biphenyl-carbonsäureamid;

mit 4-Chlorbenzoylchlorid

4-Chlor-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzamid;

mit 4-(1,1-Dimethylpropyl)-benzolsulfonylchlorid

5 4-(1,1-Dimethylpropyl)-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 3,4-Difluor-benzolsulfonylchlorid

10 3,4-Difluor-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 4-tert.-Butyl-benzolsulfonylchlorid

15 4-tert.-Butyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 4-Trifluormethyl-benzolsulfonylchlorid

20 4-Trifluormethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 4-Pentyl-benzolsulfonylchlorid

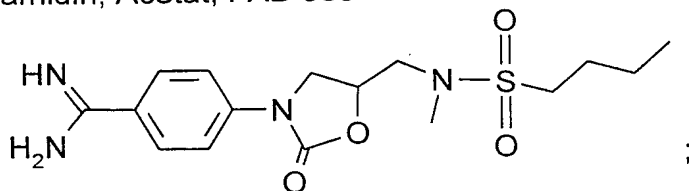
25 4-Pentyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid;

mit 1-Naphthylsulfonylchlorid

30 N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-1-naphthylsulfonamid.

Analog Beispiel 2 erhält man die nachstehenden Verbindungen

35 5-{5-[[((Butylsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl]-benzamidin, Acetat, FAB 369



5-{5-[(4-Isopropyl-benzolsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 431;

5 5-{5-[(3-Trifluormethyl-benzolsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 457;

5-{5-[(Phenylethylsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin, Acetat, FAB 417;

10 5-{5-[(2-Naphthylsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

5-{5-[(4-Propyl-benzolsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

15 5-{5-[(4-Methoxy-benzolsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

5-{5-[(2,4,6-Trimethyl-benzolsulfonyl)-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

20 5-{5-[(Benzoyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

5-{5-[(2-Naphthylcarbonyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

25 5-{5-[(Cyclohexylcarbonyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

30 5-{5-[(4-Biphenylcarbonyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin;

5-{5-[(4-Chlorbenzoyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin.

35 Analog erhält man aus {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester und Butylamin die Verbin-

dung 5-Butylaminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on ("E-1")

Man erhält durch Umsetzung von "E-1"

5

mit 6-Chlor-2-naphthylsulfonylchlorid

6-Chlor-N-Butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthyl-sulfonamid;

10

mit 4-Biphenylsulfonylchlorid

N-Butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-biphenyl-sulfonamid

mit 2-Naphthylsulfonylchlorid

15

N-Butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthyl-sulfonamid.

#### Beispiel 10

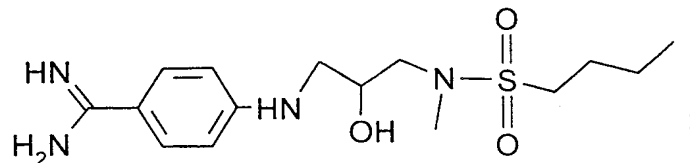
20

Analog Beispiel 3 und 4 erhält man

aus N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-butylsulfonamid

4-{3-[(Butan-1-sulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin

25



30

aus 4-Isopropyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(4-Isopropyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 405;

35

aus 3-Trifluormethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(3-Trifluormethyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 431;

5

aus N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-phenylvinylsulfonamid

4-{3-[(Phenylethylsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin;

10

aus N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthylsulfonamid

4-{3-[(2-Naphthylsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 413;

15

aus 6-Chlor-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthylsulfonamid

4-{3-[(6-Chlor-2-naphthylsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 447;

20

aus 4-Propyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(4-propyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 405;

25

aus 4-Methoxy-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(4-Methoxy-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 393;

30

aus 2,4,6-Trimethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(2,4,6-Trimethyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 405;

35

- aus 5-{5-[(Benzoyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin  
4-{3-[(Benzoyl-methyl-amino)-2-hydroxy-propylamino]-benzamidin;
- 5 aus 5-{5-[(2-Naphthylcarbonyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin  
4-{3-[(2-Naphthylcarbonyl-methyl-amino)-2-hydroxy-propylamino]-benzamidin;
- 10 aus 5-{5-[(Cyclohexylcarbonyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin  
4-{3-[(Cyclohexylcarbonyl-methyl-amino)-2-hydroxy-propylamino]-benzamidin;
- 15 aus 5-{5-[(4-Biphenylcarbonyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin  
4-{3-[(4-Biphenylcarbonyl-methyl-amino)-2-hydroxy-propylamino]-benzamidin;
- 20 aus 5-{5-[(4-Chlorbenzoyl-methyl-amino)-methyl]-2-oxo-oxazolidin-3-yl}-benzamidin  
4-{3-[(4-Chlorbenzoyl-methyl-amino)-2-hydroxy-propylamino]-benzamidin;
- 25 aus 4-(1,1-Dimethylpropyl)-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid  
4-{3-[(4-(1,1-Dimethylpropyl)-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 433;
- 30 aus 3,4-Difluor-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid  
4-{3-[(3-Fluor-4-methoxy-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 411;
- 35 aus 4-tert.-Butyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(4-tert.-Butyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 419;

5 aus 4-Trifluormethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(4-Trifluormethyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 431;

10 aus 4-Pentyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzolsulfonamid

4-{3-[(4-Pentyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 433;

15 aus N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-1-naphthylsulfonamid

4-{3-[(1-Naphthylsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 413;

20 aus 6-Chlor-N-Butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthyl-sulfonamid

4-{3-[(6-Chlor-2-naphthyl-sulfonyl)-butyl-amino]-2-hydroxy-propylamino}-benzamidin;

25 aus N-Butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-biphenyl-yl-sulfonamid

4-{3-[(4-Biphenylylsulfonyl)-butyl-amino]-2-hydroxy-propylamino}-benzamidin;

30 aus N-Butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-naphthyl-sulfonamid

4-{3-[(2-Naphthylsulfonyl)-butyl-amino]-2-hydroxy-propylamino}-benzamidin;

35 aus N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-(7-methoxy-2-naphthyl)-sulfonamid



4-{3-[(7-Methoxy-2-naphthylsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 443;

aus N-Methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-(6-methoxy-2-naphthyl)-sulfonamid

4-{3-[(6-Methoxy-2-naphthylsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 443;

### Beispiel 11

Eine Lösung von 10,9 g 3-(4-Cyanphenyl)-5-hydroxymethyl-oxazolidin-2-on ("F"), 5,9 g 3-Cyanphenol, 26,2 g Triphenylphosphin und 13,1 g Diethylazodicarboxylat in 250 ml THF wird 4 Stunden unter Schutzgasatmosphäre gerührt. Man arbeitet wie üblich auf und erhält 3-(4-Cyanphenyl)-5-[(3-cyanphenoxy)-methyl]-oxazolidin-2-on.

Eine Lösung von 8,5 g der Dicyanverbindung, 5,5 g Hydroxylammoniumchlorid und 11,2 g Natriumcarbonat in 130 ml DMF wird 3 Stunden bei 60° gerührt. Man arbeitet wie üblich auf und erhält 3-(4-N-Hydroxyamidino-phenyl)-5-[(3-N-hydroxyamidino-phenoxy)-methyl]-oxazolidin-2-on.

Analog Beispiel 2 erhält man daraus durch Hydrierung die Verbindung 3-(4-Amidino-phenyl)-5-[(3-amidino-phenoxy)-methyl]-oxazolidin-2-on, Diacetat, F. 159-160°, FAB 354.

Analog erhält man durch Umsetzung von "F"

mit 4'-Hydroxy-biphenyl-4-carbonitril, Reaktion mit Hydroxylammoniumchlorid und Reduktion die Verbindung

3-(4-Amidino-phenyl)-5-[(4'-amidino-4-biphenyl-yl-oxy)-methyl]-oxazolidin-2-on, Diacetat, F. 214-224°;

mit 4-Cyanphenol, Reaktion mit Hydroxylammoniumchlorid und Reduktion die Verbindung

3-(4-Amidino-phenyl)-5-[(4-amidino-phenoxy)-methyl]-oxazolidin-2-on, Diacetat, F. 164° (Zersetzung);

mit 4-Cyan-N-(ethoxycarbonyl)-benzolsulfonamid die Verbindung  
N-[3-(4-Cyanphenyl)-2-oxo-oxazolidon-5-ylmethyl]-N-ethoxycarbonyl-  
4-cyan-benzolsulfonamid, Diacetat, FAB 489.

5

### Beispiel 12

Eine Lösung von 400 mg {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-  
oxo-oxazolidin-5-yl}-methansulfonsäuremethylester, 240 mg Phenylpiper-  
azin und 120 mg Natriumhydrogencarbonat in 10 ml Acetonitril wird 18  
Stunden bei 80° erhitzt. Man arbeitet wie üblich auf und erhält 3-[4-(5-  
Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-phenyl-piperazin-1-ylmethyl)-  
oxazolidin-2-on.

10

15

Durch Hydrierung analog Beispiel 2 erhält man daraus  
4-[2-Oxo-5-(4-phenyl-piperazin-1-ylmethyl)-oxazolidin-3-yl]-  
benzamidin, Acetat, FAB 380.

20

Analog erhält man durch Umsetzung von "A" mit 5-Brommethyl-  
benzo[2,1,3]-thiadiazol die Verbindung  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(benzo[2,1,3]-  
thiadiazol-5-ylmethyl)-piperazin-1-ylmethyl]-oxazolidin-2-on.

25

Durch Hydrierung analog Beispiel 2 erhält man daraus  
4-[2-Oxo-5-[4-(benzo[2,1,3]-thiadiazol-5-ylmethyl)-piperazin-1-  
ylmethyl]-oxazolidin-3-yl]-benzamidin, Acetat, FAB 512.

30

Analog erhält man durch Umsetzung von {3-[4-(5-Methyl-[1,2,4]oxadiazol-  
3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester  
mit 2-Piperazin-1-yl-pyrimidin  
3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(pyrimidin-2-yl)-  
piperazin-1-ylmethyl]-oxazolidin-2-on,

35

mit Benzylpiperazin

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-benzyl-piperazin-1-ylmethyl]-oxazolidin-2-on,

mit (Benzo[2,1,3]-thiadiazol-5-yl)-piperazin

5 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(benzo[2,1,3]-thiadiazol-5-yl)-piperazin-1-ylmethyl]-oxazolidin-2-on.

Analog Beispiel 3 und 4 erhält man durch Spaltung des Oxazolidinon- und des Oxadiazolrings

10

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(pyrimidin-2-yl)-piperazin-1-ylmethyl]-oxazolidin-2-on

4-[2-Hydroxy-3-(4-pyrimidin-2-yl-piperazin-1-yl)-propylamino]-benzamidin, Acetat, FAB 356;

15

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-benzyl-piperazin-1-ylmethyl]-oxazolidin-2-on

4-[2-Hydroxy-3-(4-benzyl-piperazin-1-yl)-propylamino]-benzamidin, Acetat, FAB 368;

20

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(benzo[2,1,3]-thiadiazol-5-yl)-piperazin-1-ylmethyl]-oxazolidin-2-on

4-[2-Hydroxy-3-(4-(benzo[2,1,3]-thiadiazol-5-yl)-piperazin-1-yl)-propylamino]-benzamidin, Trifluoracetat, FAB 412.

25

aus 4-[3-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(3,5-dimethoxybenzyl)-piperazin-1-ylmethyl]-oxazolidin-2-on

4-{2-Hydroxy-3-[4-(3,5-dimethoxybenzyl)-piperazin-1-yl]-propylamino}-benzamidin, FAB 428.

30

Analog erhält man durch Umsetzung von {3-[3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester mit 4-Piperazin-1-yl-pyridin

35 3-[3-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(pyridin-4-yl)-piperazin-1-ylmethyl]-oxazolidin-2-on, das durch Hydrierung in

3-{2-Oxo-5-[4-(pyridin-4-yl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 381, F. 152-165 (Zers.), überführt wird.

### Beispiel 13

5

Eine Lösung von 200 mg "A" und 66 mg Butylisocyanat in 10 ml Dichlormethan wird 4 Stunden gerührt. Man gibt 400 mg Aminomethylpolystyrol dazu und rührt weitere 12 Stunden. Man entfernt das Polystyrol und das Lösungsmittel und erhält nach üblicher Aufarbeitung 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-butylaminocarbonyl-piperazin-1-ylmethyl)-oxazolidin-2-on.

10

Analog erhält man durch Umsetzung von "A"

15

mit Cyclohexylisocyanat

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(cyclohexylaminocarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on;

mit 4-Methoxyphenylisocyanat

20

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-{4-[N-(4-methoxyphenyl)-aminocarbonyl]-piperazin-1-ylmethyl}-oxazolidin-2-on;

mit 4-Trifluormethylphenylisocyanat

25

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-{4-[N-(4-trifluormethylphenyl)-aminocarbonyl]-piperazin-1-ylmethyl}-oxazolidin-2-on;

mit 4-Chlorphenylisocyanat

30

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-{4-[N-(4-chlorphenyl)-aminocarbonyl]-piperazin-1-ylmethyl}-oxazolidin-2-on;

mit 3-Ethoxycarbonylphenylisocyanat

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-{4-[N-(3-ethoxycarbonylphenyl)-aminocarbonyl]-piperazin-1-ylmethyl}-oxazolidin-2-on;

35

mit 1-Naphthylisocyanat

3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(naphth-1-yl-aminocarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on.

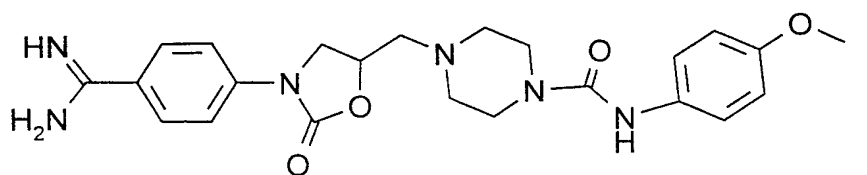
Durch Hydrierung analog Beispiel 2 erhält man

5

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[N-(4-methoxyphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on

4-{2-Oxo-5-[4-[N-(4-methoxyphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 453

10



15

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[N-(4-trifluormethylphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on

4-{2-Oxo-5-[4-[N-(4-trifluormethylphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 473;

20

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[N-(4-chlorphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on

4-{2-Oxo-5-[4-[N-(4-chlorphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 457;

25

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-butylaminocarbonyl)-piperazin-1-ylmethyl)-oxazolidin-2-on

4-[2-Oxo-5-(4-butylaminocarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl]-benzamidin, Acetat, FAB 403;

30

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-[N-(3-ethoxycarbonylphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-2-on

4-{2-Oxo-5-[4-[N-(3-ethoxycarbonylphenyl)-aminocarbonyl]-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 495;

35

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(naphth-1-yl-aminocarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on  
 4-{2-Oxo-5-[4-(naphth-1-yl-aminocarbonyl)-piperazin-1-ylmethyl]-oxazolidin-3-yl}-benzamidin, Acetat, FAB 403.

5

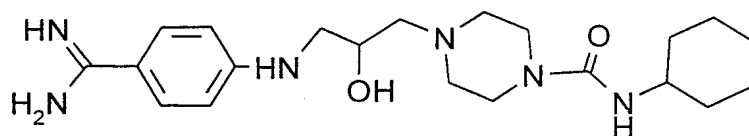
Analog Beispiel 3 und 4 erhält man

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-(4-butylaminocarbonyl-piperazin-1-ylmethyl)-oxazolidin-2-on  
 4-[3-(4-Butylaminocarbonyl-piperazin-1-yl)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 377;

10

aus 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-5-[4-(cyclohexylaminocarbonyl)-piperazin-1-ylmethyl]-oxazolidin-2-on  
 4-[3-(4-Cyclohexylaminocarbonyl-piperazin-1-yl)-2-hydroxy-propylamino]-benzamidin, Acetat, FAB 403

15



20

#### Beispiel 14

Eine Lösung von 1 Äquivalent {3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-yl}-methansulfonsäuremethylester, 3 Äquivalenten Glycinbenzylester, Methansulfonat und 3 Äquivalenten Natriumhydrogencarbonat in Acetonitril wird 18 Stunden unter Rückfluß erhitzt. Man arbeitet wie üblich auf und erhält {{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino}-essigsäurebenzylester ("G").

30

Analog Beispiel 1 erhält man durch Umsetzung von "G" mit 6-Chlor-naphth-2-yl-sulfonylchlorid

{N-[6-Chlor-naphth-2-yl-sulfonyl],N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino}-essigsäurebenzylester.

35

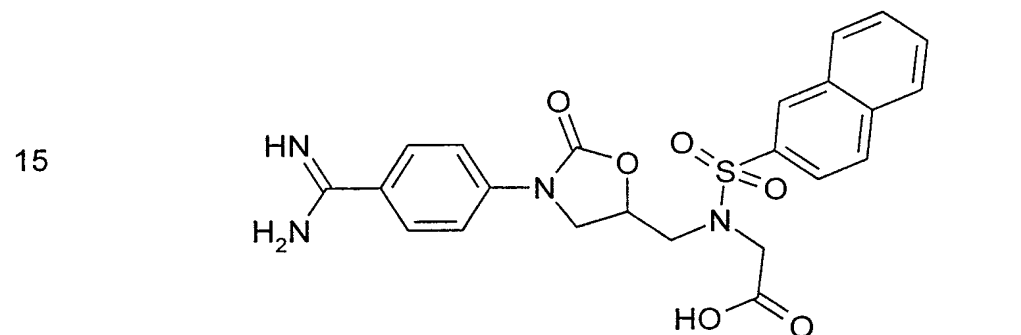
Durch Hydrierung analog Beispiel 2 erhält man daraus

{N-[6-Chlor-naphth-2-yl-sulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäure, Acetat, FAB 517,  
sowie

5 {N-[6-Chlor-naphth-2-yl-sulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäurebenzylester.

Analog erhält man durch Umsetzung von "G"  
mit Naphth-2-ylsulfonylchlorid und anschließender Hydrierung

10 {N-[Naphth-2-yl-sulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäure, Acetat, FAB 483



mit 4-Methoxy-benzolsulfonylchlorid und anschließender Hydrierung  
{N-[4-Methoxy-benzolsulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäure, Acetat, FAB 453;

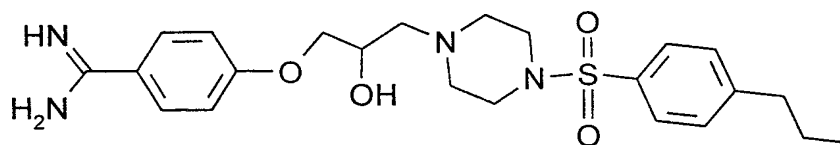
mit Phenylvinylsulfonylchlorid und anschließender Hydrierung  
25 {N-[Phenylvinylsulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäurebenzylester, Acetat, FAB 549;

mit 4-Biphenylsulfonylchlorid und anschließender Hydrierung  
30 {N-[4-Biphenylsulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäure, Acetat, FAB 509;

mit 4-Propyl-benzolsulfonylchlorid und anschließender Hydrierung  
35 {N-[4-Propyl-benzolsulfonyl],N-[3-(4-amidino-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amino}-essigsäurebenzylester, Acetat, FAB 565.

Beispiel 15

Eine Lösung von 4-Oxiranylmethoxy-benzonitril und BOC-Piperazin in Methanol wird 4 Stunden unter Rückfluß gerührt. Nach üblicher Aufarbeitung erhält man 4-[2-Hydroxy-3-(4-BOC-piperazin-1-yl)-propoxy]-benzonitril. Die anschließende Umsetzung mit Hydroxylaminhydrochlorid ergibt N-Hydroxy-4-[2-hydroxy-3-(4-BOC-piperazin-1-yl)-propoxy]-benzamidin. Durch anschließende Acylierung mit Acetanhydrid erhält man 2-Acetoxy-1-(4-BOC-piperazin-1-yl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy]-propan. Nach Abspaltung der BOC-Gruppe mit HCl in Dioxan ergibt die Umsetzung mit 4-Propylphenylsulfonylchlorid die Verbindung 2-Acetoxy-1-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy]-propan. Durch Umsetzung analog Beispiel 3 und 4 erhält man die Verbindung 4-{2-Hydroxy-3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin



Analog werden die nachstehenden Verbindungen erhalten

3-{2-Hydroxy-3-[4-(4-biphenylcarbonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 459;

3-{2-Hydroxy-3-[4-(6-chlor-2-naphthylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 503;

3-{2-Hydroxy-3-[4-(2-naphthylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 469;

3-{2-Hydroxy-3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 461;



3-{2-Hydroxy-3-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 461;

5 3-{2-Hydroxy-3-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 449;

3-{2-Hydroxy-3-[4-(4-butylphenylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 399;

10 3-{2-Hydroxy-3-[4-benzoyl-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 383;

15 3-{2-Hydroxy-3-[4-(7-methoxy-2-naphthylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 499;

3-{2-Hydroxy-3-[4-(3,5-dimethoxybenzyl)-piperazin-1-yl]-propoxy}-benzamidin, Acetat, FAB 429;

20 3-{2-Hydroxy-3-[4-(4-biphenylsulfonyl)-piperazin-1-yl]-propoxy}-benzamidin, Diacetat, FAB 495;

3-{2-Hydroxy-3-[4-(naphth-2-ylmethyl)-piperazin-1-yl]-propoxy}-benzamidin, Diacetat, FAB 419;

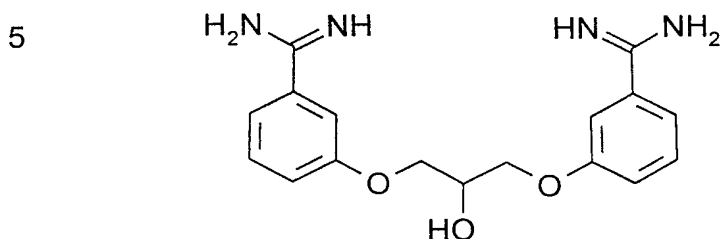
25 3-{2-Hydroxy-3-[4-(2-naphthylcarbonyl)-piperazin-1-yl]-propoxy}-benzamidin, Diacetat, FAB 433;

30 3-{2-Hydroxy-3-[4-(biphenyl-4-ylmethyl)-piperazin-1-yl]-propoxy}-benzamidin, Diacetat, FAB 445;

#### Beispiel 16

35 10,0 g 3-Oxiranylmethoxy-benzonitril ("H") und 7,1 g 3-Cyanphenol werden zusammen mit 173 mg Cäsiumfluorid bei 130° geschmolzen. Nach üblicher Aufarbeitung erhält man 11,8 g 1,3-Bis-(3-Cyan-phenoxy)-2-hydroxypropan. Die anschließende Umsetzung mit Hydroxylammoniumchlorid er-

gibt 1,3-Bis-[3-(N-hydroxyamidino)-phenoxy]-2-hydroxypropan. Durch Hydrierung analog Beispiel 2 erhält man 1,3-Bis-(3-amidino-phenoxy)-2-hydroxypropan, Diacetat, FAB 329



Analog erhält man die Verbindungen

1,3-Bis-(4-amidino-phenoxy)-2-hydroxypropan, Diacetat, FAB 329  
 und  
 1-(3-amidino-phenoxy)-3-(4-amidino-phenoxy)-2-hydroxypropan,  
 Diacetat, FAB 329.

Analog erhält man durch Umsetzung von "H" mit den nachstehenden Phenolen

4-Chlorphenol,  
 4-Methylphenol,  
 Phenol,  
 4-Methoxyphenol,  
 4-Cyclohexylphenol

und anschließender Reaktion mit Hydroxylammoniumchlorid sowie Hydrierung

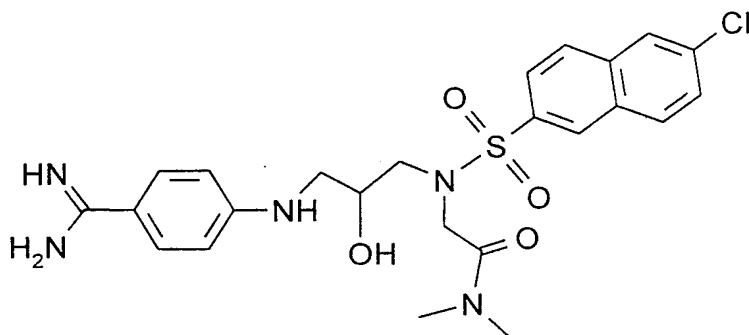
die nachstehenden Verbindungen

1-(3-Amidinophenoxy)-2-hydroxy-3-(4-chlorphenoxy)-propan,  
 1-(3-Amidinophenoxy)-2-hydroxy-3-(4-methylphenoxy)-propan,  
 1-(3-Amidinophenoxy)-2-hydroxy-3-phenoxy-propan,  
 1-(3-Amidinophenoxy)-2-hydroxy-3-(4-methoxyphenoxy)-propan,  
 1-(3-Amidinophenoxy)-2-hydroxy-3-(4-cyclohexylphenoxy)-propan.

Beispiel 17

5 Eine Lösung von 1 Äquivalent N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-(6-chlor-2-naphthyl)-sulfonamid ("I") [erhältlich durch Umsetzung von 5-Aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-oxazolidin-2-on mit 6-Chlor-2-naphthylsulfonylchlorid], je 1,1 Äquivalent N,N'-Dimethyl-chloracetamid und Cäsiumcarbonat in DMF wird 12 Stunden bei Raumtemperatur gerührt. Man arbeitet wie  
10 üblich auf und erhält 2-((6-Chlor-2-naphthylsulfonyl)-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amino)-N,N'-dimethylacetamid.

Analog Beispiel 3 und 4 erhält man daraus die Verbindung 2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(6-chlor-2-naphthylsulfonyl)-amino]-N,N'-dimethylacetamid  
15



25 Analog erhält man durch Umsetzung von "I" mit

N,N'-Diethyl-chloracetamid,  
N,N'-Dipropyl-chloracetamid,  
N-Phenyl-chloracetamid,  
30 N,N'-Diphenyl-chloracetamid und  
Chloressigsäureethylester

und anschließender Spaltung des Oxazolidinon- und des Oxadiazolrings analog Beispiel 3 und 4 die Verbindungen

35

2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(6-chlor-2-naphthylsulfonyl)-amino]-N,N'-diethyl-acetamid,

5 2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(6-chlor-2-naphthylsulfonyl)-amino]-N,N'-dipropyl-acetamid,

2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(6-chlor-2-naphthylsulfonyl)-amino]-N-phenyl-acetamid,

10 2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(6-chlor-2-naphthylsulfonyl)-amino]-N,N'-diphenyl-acetamid und

2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(6-chlor-2-naphthylsulfonyl)-amino]-essigsäure, Acetat, FAB 491.

15

Analog erhält man durch Umsetzung von N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-(4-isopropylphenyl)-sulfonamid mit

20

N,N'-Dimethyl-chloracetamid,

N,N'-Diethyl-chloracetamid,

N,N'-Dipropyl-chloracetamid,

N-Phenyl-chloracetamid,

N,N'-Diphenyl-chloracetamid,

25

Benzylbromid,

Iodbutan,

4-Chlormethyl-2-methylthiazol,

4-Methoxybenzylbromid,

Chloressigsäureethylester,

30

4-Chlorbuttersäureethylester,

3-Chlormethylbenzoesäureethylester,

4-Chlormethylbenzoesäureethylester,

3,5-Dimethoxybenzylbromid,

4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-benzylbromid,

35

3-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-benzylbromid und

2-Fluorbenzylbromid

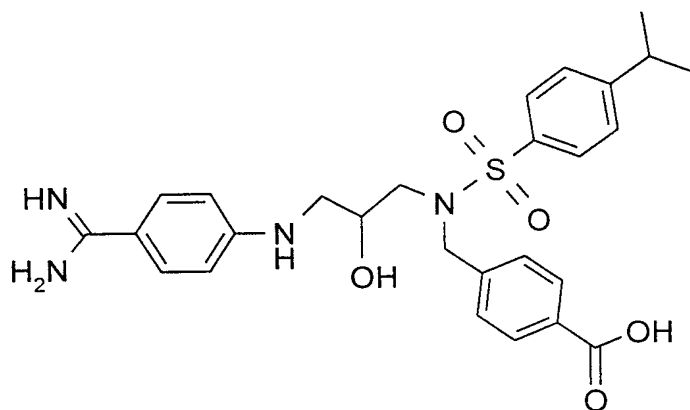
und anschließender Spaltung des Oxazolidinon- und des Oxadiazolrings analog Beispiel 3 und 4 die Verbindungen

- 5           2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylsulfonyl)-amino]-N,N'-dimethyl-acetamid,
- 2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylsulfonyl)-amino]-N,N'-diethyl-acetamid,
- 10           2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylsulfonyl)-amino]-N,N'-dipropyl-acetamid,
- 2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylsulfonyl)-amino]-N-phenyl-acetamid,
- 15           2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylsulfonyl)-amino]-N,N'-diphenyl-acetamid,
- 4-{{(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-benzyl-amino]-propylamino}-benzamidin, Acetat, FAB 481,
- 20           4-{{(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-butyl-amino]-propylamino}-benzamidin, Acetat, FAB 447,
- 25           4-{{(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-(2-methylthiazol-4-ylmethyl)-amino]-propylamino}-benzamidin, Acetat, FAB 502,
- 4-{{(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-(4-methoxybenzyl)-amino]-propylamino}-benzamidin, Acetat, FAB 511,
- 30           2-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylbenzolsulfonyl)-amino]-essigsäure, Acetat, FAB 449,
- 35           4-[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylbenzolsulfonyl)-amino]-buttersäure, Diacetat, FAB 477,

3-[[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylbenzol-sulfonyl)-amino]-methyl]-benzoesäure, Diacetat, FAB 525,

5 4-[[[3-(4-Amidino-phenylamino)-2-hydroxy-propyl]-(4-isopropylbenzol-sulfonyl)-amino]-methyl]-benzoesäure, Diacetat, FAB 525

10



15

4-[(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-(3,5-dimethoxybenzyl)-amino]-propylamino]-benzamidin, Diacetat, FAB 541,

20

4-[(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-(4-amidinobenzyl)-amino]-propylamino]-benzamidin, Triacetat, FAB 523,

25

4-[(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-(3-amidinobenzyl)-amino]-propylamino]-benzamidin, Triacetat, FAB 523 und

4-[(2-Hydroxy)-3-[(4-isopropyl-benzolsulfonyl)-(2-fluorbenzyl)-amino]-propylamino]-benzamidin, Diacetat, FAB 499.

30

Analog erhält man durch Umsetzung von "I" mit

Iodethan,

Benzylbromid,

4-Methoxybenzylbromid,

35

2-Brommethyl-naphthalin,

4-Chlormethyl-2-methylthiazol und

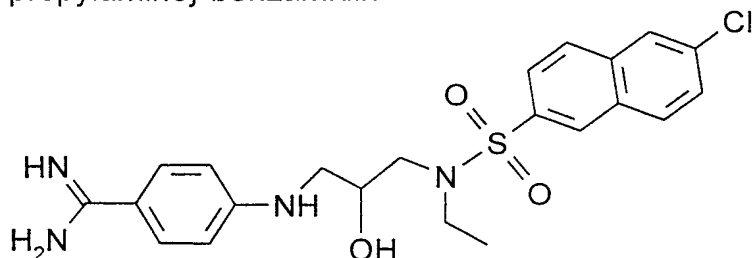
## 4-Methoxybenzylchlorid

und anschließender Spaltung des Oxazolidinon- und des Oxadiazolrings analog Beispiel 3 und 4 die Verbindungen

5

4-{3-[(6-Chlor-2-naphthylsulfonyl)-ethyl-amino]-2-hydroxy-propylamino}-benzamidin

10



15

4-{3-[(6-Chlor-2-naphthylsulfonyl)-benzyl-amino]-2-hydroxy-propylamino}-benzamidin,

4-{3-[(6-Chlor-2-naphthylsulfonyl)-(4-methoxybenzyl)-amino]-2-hydroxy-propylamino}-benzamidin,

20

4-{3-[(6-Chlor-2-naphthylsulfonyl)-(naphth-2-ylmethyl)-amino]-2-hydroxy-propylamino}-benzamidin,

4-{3-[(6-Chlor-2-naphthylsulfonyl)-(2-methylthiazol-4-ylmethyl)-amino]-2-hydroxy-propylamino}-benzamidin, Diacetat, FAB 544 und

4-{3-[(6-Chlor-2-naphthylsulfonyl)-(4-methoxybenzyl)-amino]-2-hydroxy-propylamino}-benzamidin, Diacetat, FAB 553.

25

Analog erhält man durch Umsetzung von N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl)-(4-methoxyphenyl)-sulfonamid mit Iodbutan und anschließender Spaltung des Oxazolidinon- und des Oxadiazolrings analog Beispiel 3 und 4 die Verbindung

30

4-{3-[(4-Methoxyphenylsulfonyl)-butyl-amino]-2-hydroxy-propylamino}-benzamidin, Acetat, FAB 435.

35

Analog erhält man durch Umsetzung von N-{3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl)-(2-naphthyl)-sulfonamid mit

Iodbutan und  
Iodethan

5 und anschließender Spaltung des Oxazolidinon- und des Oxadiazolrings  
analog Beispiel 3 und 4 die Verbindungen

4-{3-[(2-Naphthylsulfonyl)-butyl-amino]-2-hydroxy-propylamino}-  
benzamidin, Acetat, FAB 455 und

10

4-{3-[(2-Naphthylsulfonyl)-ethyl-amino]-2-hydroxy-propylamino}-  
benzamidin, Acetat, FAB 427.

Beispiel 18

15

Analog zu Beispiel 11 erhält man aus den entsprechenden Cyanderivaten  
durch Umsetzung mit Hydroxylammoniumchlorid nachstehende Verbin-  
dungen

20

3-(3-N-Hydroxyamidino-phenyl)-5-[(4-N-hydroxyamidino-phenoxy)-  
methyl]-oxazolidin-2-on, F. 201-205°,

3-(3-N-Hydroxyamidino-phenyl)-5-[(3-N-hydroxyamidino-phenoxy)-  
methyl]-oxazolidin-2-on,

25

3-(4-N-Hydroxyamidino-phenyl)-5-[(3-N-hydroxyamidino-benzyloxy)-  
methyl]-oxazolidin-2-on,

3-(3-N-Hydroxyamidino-phenyl)-5-[(3-N-hydroxyamidino-benzyloxy)-  
methyl]-oxazolidin-2-on.

30

Analog Beispiel 2 erhält man daraus durch Hydrierung die Verbindungen

3-(3-Amidino-phenyl)-5-[(4-amidino-phenoxy)-methyl]-oxazolidin-2-  
on, Diacetat, F. 150-166° (Zersetzung), FAB 354;

35



3-(3-Amidino-phenyl)-5-[(3-amidino-phenoxy)-methyl]-oxazolidin-2-on, Diacetat, F. 312-318°;

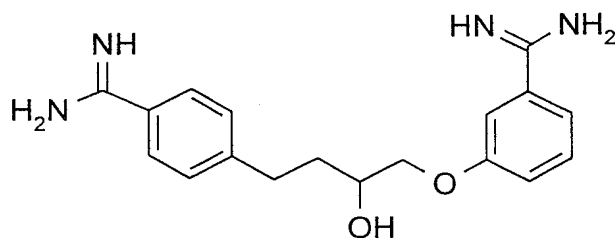
5 3-(4-Amidino-phenyl)-5-[(3-amidino-benzyloxy)-methyl]-oxazolidin-2-on, Triacetat, F. 189-205° (Zers.), FAB 368;

3-(3-Amidino-phenyl)-5-[(3-amidino-benzyloxy)-methyl]-oxazolidin-2-on, Triacetat, F. 204-222° (Zers.), FAB 368.

### 10 Beispiel 19

Analog Beispiel 16 erhält man durch Umsetzung von 4-Oxiranylethylbenzonitril und 3-Cyanphenol, anschließender Umsetzung mit Hydroxylammoniumchlorid und Hydrierung die Verbindung 4-[3-Hydroxy-4-(3-amidino-phenoxy)-butyl]-benzamidin, Diacetat, FAB 327

15



20

### 25 Beispiel 20

Unter Stickstoff wird 10,0 g 3-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenol in 50 ml DMF gegeben und anschließend bei 0° 2,6 g Natriumhydrid zugegeben. Man fügt 5,1 ml Epibromhydrin hinzu und rührt 24 Stunden bei Raumtemperatur nach. Man arbeitet wie üblich auf und erhält 5-Methyl-3-(3-oxiranylmethoxy-phenyl)-[1,2,4]oxadiazol.

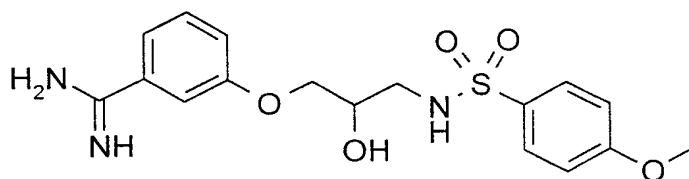
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8,0 g der Oxiranylverbindung wird in 400 ml Methanol gelöst und 6 Stunden NH<sub>3</sub>-Gas eingeleitet. Man rührt 16 Stunden nach und erhält nach Entfernen des Lösungsmittels 1-Amino-3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy]-propan-2-ol ("AB").

35

500 mg "AB" und 434 mg 4-Methoxyphenylsulfonylchlorid werden zusammen mit 2,0 g polymerem DMAP (1,6 mmol Dimethylaminopyridin /g Harz) in 5 ml Pyridin 24 Stunden bei Raumtemperatur gerührt. Das Harz wird abfiltriert und das Filtrat wie üblich aufgearbeitet und man erhält N-{2-Hydroxy-3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propyl}-4-methoxybenzolsulfonamid.

Durch Hydrierung analog Beispiel 2 erhält man daraus die Verbindung  
3-[2-Hydroxy-3-(4-methoxy-benzolsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 380



Analog erhält man durch Umsetzung von "AB" mit  
4-Isopropylphenylsulfonylchlorid,  
2-Naphthylsulfonylchlorid,  
6-Chlor-2-naphthylsulfonylchlorid,  
7-Methoxy-2-naphthylsulfonylchlorid  
und anschließender Hydrierung  
die nachstehenden Verbindungen

3-[2-Hydroxy-3-(4-isopropyl-benzolsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 392;  
3-[2-Hydroxy-3-(2-naphthylsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 400;  
3-[2-Hydroxy-3-(6-chlor-2-naphthylsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 434;  
3-[2-Hydroxy-3-(7-methoxy-2-naphthylsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 430.

Analog erhält durch Umsetzung von 1-Amino-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy]-propan-2-ol

5 mit 4-Methoxyphenylsulfonylchlorid,  
4-Isopropylphenylsulfonylchlorid,  
2-Naphthylsulfonylchlorid,  
6-Chlor-2-naphthylsulfonylchlorid,  
7-Methoxy-2-naphthylsulfonylchlorid

10

und anschließender Hydrierung

die nachstehenden Verbindungen

15

4-[2-Hydroxy-3-(4-methoxy-benzolsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 380;

4-[2-Hydroxy-3-(4-isopropyl-benzolsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 392;

20

4-[2-Hydroxy-3-(2-naphthylsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 400;

4-[2-Hydroxy-3-(6-chlor-2-naphthylsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 434;

4-[2-Hydroxy-3-(7-methoxy-2-naphthylsulfonylamino)-propoxy]-benzamidin, Acetat, FAB 430.

25

#### Beispiel 21

Man gibt 10,7 ml Natriummethylat (30 %ig in Methanol) zu 30 ml Methanol, fügt 4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-anilin unter Stickstoff dazu und rührt 10 Minuten bei 45° nach. Das Gemisch anschließend in eine Suspension aus 480 mg Paraformaldehyd und 20 ml Methanol gegeben und 2 Stunden bei 60° nachgerührt. Danach versetzt man mit 440 mg Natriumborhydrid und rührt 1 Stunde bei 60° nach. Das Gemisch wird anschließend noch zweimal mit je 1,44 g Paraformaldehyd, 3,1 g Natriummethylat und 220 mg Natriumborhydrid versetzt.

30

35

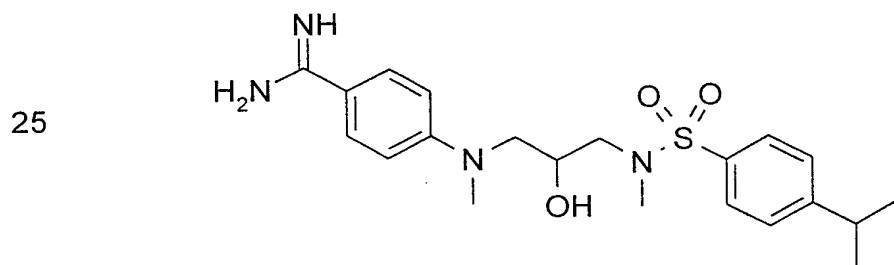
Nach Stunden wird mit 1N NaOH hydrolisiert und wie üblich aufgearbeitet. Man erhält als Rohprodukt 1,93 g N-Methyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-anilin.

5 Eine Lösung von 1,35 g g 4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-N-methyl-anilin und 1,0 ml Epichlorhydrin in 5 ml Ethanol und 3,5 ml Wasser wird 12 Stunden unter Rückfluß gekocht. Nach üblicher Aufarbeitung erhält man 0,4 g N-Methyl-N-oxiranylmethyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-anilin. Eine Lösung von 0,39 g N-Methyl-N-oxiranylmethyl-4-(5-methyl-[1,2,4]oxa-

10 diazol-3-yl)-anilin und 30 ml Methylamin (33 %ig in Ethanol) in 10 ml Ethanol wird 15 Stunden bei 65° gerührt. Nach üblicher Aufarbeitung erhält man 0,44 g 1-Methylamino-3-{methyl-[4-[5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-amino}-propan-2-ol ("BC").

15 100 mg "BC" und 87 mg 4-Isopropylphenylsulfonylchlorid werden zusammen mit 300 mg polymerem DMAP (1,6 mmol Dimethylaminopyridin /g Harz) in 5 ml Dichlormethan 16 Stunden bei Raumtemperatur gerührt. Das Harz wird abfiltriert und das Filtrat wie üblich aufgearbeitet. Man erhält 109 mg N-(2-Hydroxy-3-{methyl-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-amino}-propyl)-4-isopropyl-N-methyl-benzolsulfonamid.

20 Durch Hydrierung analog Beispiel 2 erhält man daraus die Verbindung  
4-({2-Hydroxy-3-[(4-isopropyl-benzolsulfonyl)-N-methyl-amino]-propyl}-N-methyl-amino)-benzamidin, Acetat, FAB 419



30 Analog erhält man durch Umsetzung von "BC" mit 2-Naphthylsulfonylchlorid und anschließender Hydrierung die Verbindung

4-({2-Hydroxy-3-[(naphth-2-ylsulfonyl)-N-methyl-amino]-propyl}-N-methyl-amino)-benzamidin, Diacetat, FAB 427.

35

Die nachfolgenden Beispiele betreffen pharmazeutische Zubereitungen:

**Beispiel A: Injektionsgläser**

5 Eine Lösung von 100 g eines Wirkstoffes der Formel I und 5 g Dinatriumhydrogenphosphat wird in 3 l zweifach destilliertem Wasser mit 2 n Salzsäure auf pH 6,5 eingestellt, steril filtriert, in Injektionsgläser abgefüllt, unter sterilen Bedingungen lyophilisiert und steril verschlossen. Jedes Injektionsglas enthält 5 mg Wirkstoff.

10

**Beispiel B: Suppositorien**

Man schmilzt ein Gemisch von 20 g eines Wirkstoffes der Formel I mit 100 g Sojalecithin und 1400 g Kakaobutter, gießt in Formen und läßt erkalten. Jedes Suppositorium enthält 20 mg Wirkstoff.

15

**Beispiel C: Lösung**

Man bereitet eine Lösung aus 1 g eines Wirkstoffes der Formel I, 9,38 g  $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$ , 28,48 g  $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$  und 0,1 g Benzalkoniumchlorid in 940 ml zweifach destilliertem Wasser. Man stellt auf pH 6,8 ein, füllt auf 1 l auf und sterilisiert durch Bestrahlung. Diese Lösung kann in Form von Augentropfen verwendet werden.

20

25 **Beispiel D: Salbe**

Man mischt 500 mg eines Wirkstoffes der Formel I mit 99,5 g Vaseline unter aseptischen Bedingungen.

30 **Beispiel E: Tabletten**

Ein Gemisch von 1 kg Wirkstoff der Formel I, 4 kg Lactose, 1,2 kg Kartoffelstärke, 0,2 kg Talk und 0,1 kg Magnesiumstearat wird in üblicher Weise zu Tabletten verpreßt, derart, daß jede Tablette 10 mg Wirkstoff enthält.

35

**Beispiel F: Dragees**

5 Analog Beispiel E werden Tabletten gepreßt, die anschließend in üblicher Weise mit einem Überzug aus Saccharose, Kartoffelstärke, Talk, Tragant und Farbstoff überzogen werden.

**Beispiel G: Kapseln**

10 2 kg Wirkstoff der Formel I werden in üblicher Weise in Hartgelatine-kapseln gefüllt, so daß jede Kapsel 20 mg des Wirkstoffs enthält.

**Beispiel H: Ampullen**

15 Eine Lösung von 1 kg Wirkstoff der Formel I in 60 l zweifach destilliertem Wasser wird steril filtriert, in Ampullen abgefüllt, unter sterilen Bedingungen lyophilisiert und steril verschlossen. Jede Ampulle enthält 10 mg Wirkstoff.

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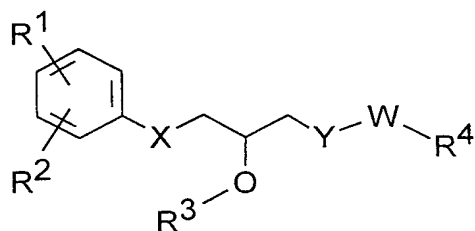
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### Patentansprüche

#### 1. Verbindungen der Formel I

5



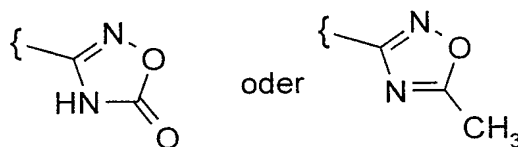
I

10

worin

R<sup>1</sup> -C(=NH)-NH<sub>2</sub>, das auch einfach durch -COA,  
-CO-[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-Ar, -COOA, -OH oder durch eine konven-  
tionelle Aminoschutzgruppe substituiert sein kann,

15



20

R<sup>2</sup> H, A, OR<sup>5</sup>, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, Hal, NR<sup>5</sup>COA, NHCOAr,  
NHSO<sub>2</sub>A, NHSO<sub>2</sub>Ar, COOR<sup>5</sup>, CON(R<sup>5</sup>)<sub>2</sub>,  
CONHAr, COR<sup>5</sup>, COAr, S(O)<sub>n</sub>A oder S(O)<sub>n</sub>Ar,

25

R<sup>3</sup> R<sup>5</sup> oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>-COOR<sup>5</sup>,

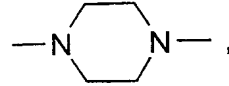
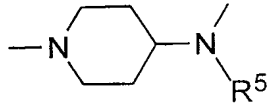
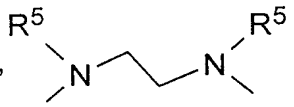
R<sup>3</sup> und X zusammen auch -CO-N- unter Ausbildung eines 5-  
Rings, wobei R<sup>3</sup> -C=O und X N bedeutet,

30

R<sup>4</sup> A, Cycloalkyl, -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar, -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het oder  
-CR<sup>5</sup>=CR<sup>5</sup>-Ar,

35

R<sup>5</sup> H, A oder Benzyl,

	X	O, NR <sup>5</sup> oder CH <sub>2</sub> ,
5	Y	O, NR <sup>5</sup> , N[C(R <sup>5</sup> ) <sub>2</sub> ] <sub>m</sub> -Ar, N[C(R <sup>5</sup> ) <sub>2</sub> ] <sub>m</sub> -Het, N[C(R <sup>5</sup> ) <sub>2</sub> ] <sub>m</sub> -COOR <sup>5</sup> ,  ,
10		 ,  ,
		N[C(R <sup>5</sup> ) <sub>2</sub> ] <sub>m</sub> -CON(R <sup>5</sup> ) <sub>2</sub> , N[C(R <sup>5</sup> ) <sub>2</sub> ] <sub>m</sub> -CONR <sup>5</sup> Ar oder N[C(R <sup>5</sup> ) <sub>2</sub> ] <sub>m</sub> -CONAr <sub>2</sub> ,
15	W	eine Bindung, -SO <sub>2</sub> -, -CO-, -COO- oder -CONR <sup>5</sup> -,
20	A	Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH <sub>2</sub> - Gruppen durch O- oder S-Atome oder durch -CR <sup>5</sup> =CR <sup>5</sup> - Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
25	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch R <sup>1</sup> , A, Ar', OR <sup>5</sup> , N(R <sup>5</sup> ) <sub>2</sub> , NO <sub>2</sub> , CN, Hal, NHCOA, NHCOAr', NHCO <sub>2</sub> A, NHCO <sub>2</sub> Ar', COOR <sup>5</sup> , CON(R <sup>5</sup> ) <sub>2</sub> , CONHAr', COR <sup>5</sup> , COAr', S(O) <sub>n</sub> A oder S(O) <sub>n</sub> Ar substituiertes Phenyl oder Naphthyl,
30	Ar'	unsubstituiertes oder ein-, zwei- oder dreifach durch R <sup>1</sup> , A, OR <sup>5</sup> , N(R <sup>5</sup> ) <sub>2</sub> , NO <sub>2</sub> , CN, Hal, NHCOA, COOR <sup>5</sup> , CON(R <sup>5</sup> ) <sub>2</sub> , COR <sup>5</sup> , oder S(O) <sub>n</sub> A substituiertes Phenyl oder Naphthyl,
35		



Het ein- oder zweikerniges unsubstituiertes oder ein- oder mehrfach durch Hal, A, Ar', OR<sup>5</sup>, COOR<sup>5</sup>, CN, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, NHCOA, NHCOAr' und/oder Carbonylsauerstoff substituiertes gesättigtes oder ungesättigtes heterocyclisches Ringsystem, welches eines, zwei, drei oder vier gleiche oder verschiedene Heteroatome wie Stickstoff, Sauerstoff und Schwefel enthält,

5

Hal F, Cl, Br oder I,  
 m 0, 1, 2, 3 oder 4,  
 n 0, 1 oder 2 bedeutet,

10

sowie deren Salze.

15

## 2. Verbindungen gemäß Anspruch 1

- a) 4-{3-[4-(2,6-Dichlor-4-methoxy-benzolsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin;  
 b) 4-{3-[(4-Isopropyl-benzolsulfonyl)-methyl-amino]-2-hydroxy-propylamino}-benzamidin  
 c) 4-{3-[4-(1-Naphthyl-benzolsulfonyl)-piperazin-1-yl]-2-hydroxy-propylamino}-benzamidin;  
 d) 3-(4-Amidino-phenyl)-5-[(3-amidino-phenoxy)-methyl]-oxazolidin-2-on.

20

25

sowie deren Salze.

30

## 3. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1 sowie ihrer Salze, dadurch gekennzeichnet, daß man

- a) sie aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt, indem man

35

i) eine Amidinogruppe aus ihrem Oxadiazolderivat durch Hydrogenolyse freisetzt,

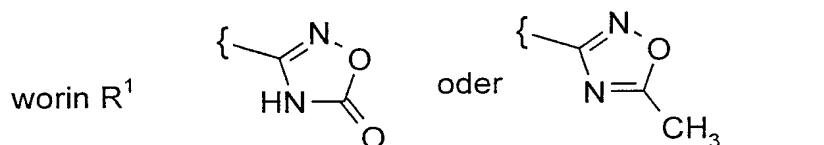
5 ii) eine konventionelle Aminoschutzgruppe durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel durch Wasserstoff ersetzt oder eine durch eine konventionelle Schutzgruppe geschützte Aminogruppe in Freiheit setzt,

10

oder

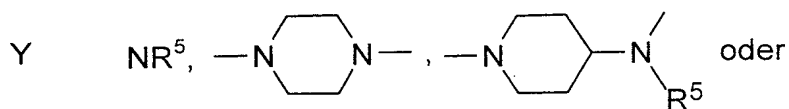
b) zur Herstellung von Verbindungen der Formel I,

15

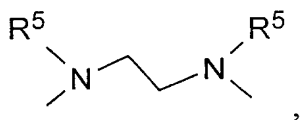


20

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



25



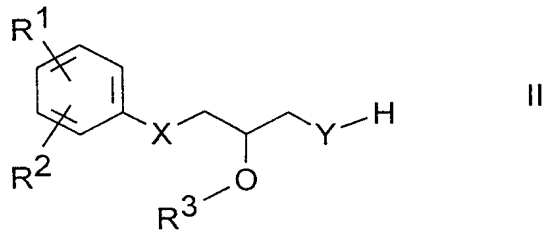
W -SO<sub>2</sub>- oder -CO- bedeuten,

30

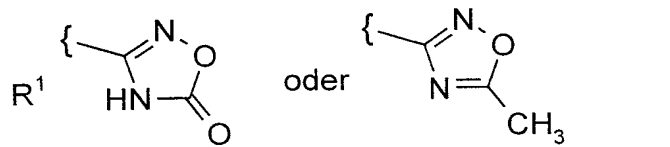
und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

eine Verbindung der Formel II

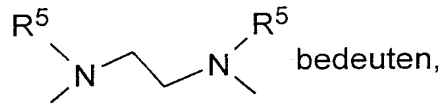
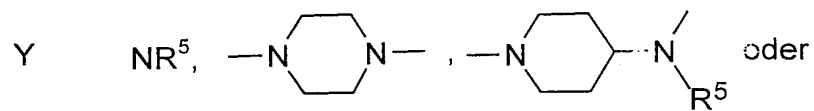
35



worin



$R^3$  und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



20 und  $R^2$  und  $R^5$  die in Anspruch 1 angegebenen Bedeutungen haben,

mit einer Verbindung der Formel III



worin

W -SO<sub>2</sub>- oder -CO- bedeutet,

30  $R^4$  die in Anspruch 1 angegebene Bedeutung hat,

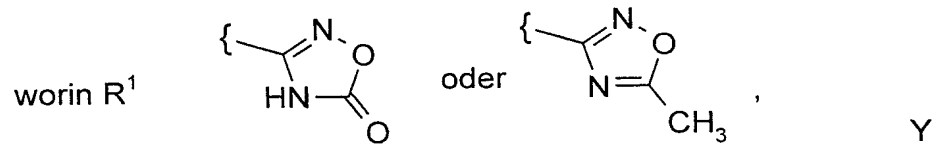
und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell abgewandelte OH-Gruppe bedeutet,

35 umsetzt,

oder

c) zur Herstellung von Verbindungen der Formel I,

5



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

Y O,

10

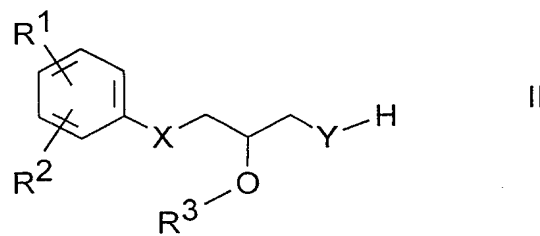
W eine Bindung bedeuten,

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

15

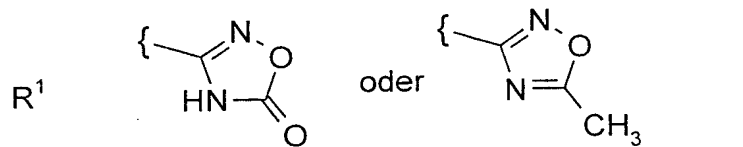
eine Verbindung der Formel II

20



worin

25



R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

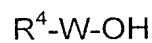
30

Y O bedeuten,

und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat,

mit einer Verbindung der Formel IV

35



IV

worin

W eine Bindung bedeutet,

und R<sup>4</sup> die in Anspruch 1 angegebene Bedeutung hat,

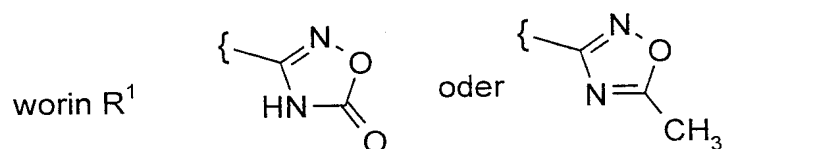
5

umsetzt,

oder

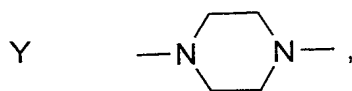
10

d) zur Herstellung von Verbindungen der Formel I,



15

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



20

W eine Bindung,

R<sup>4</sup> -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het,

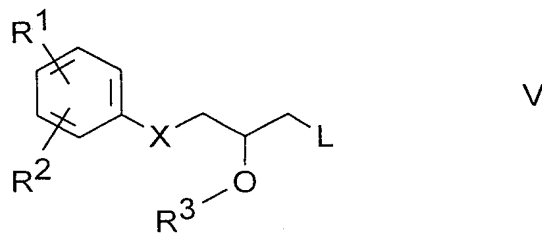
m 0 bedeuten,

25

und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat,

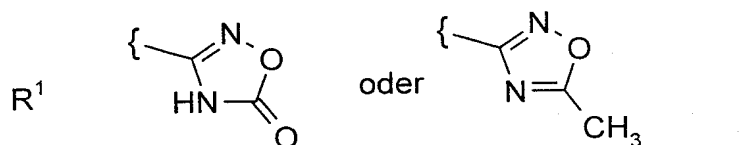
eine Verbindung der Formel V

30



35

worin



5

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

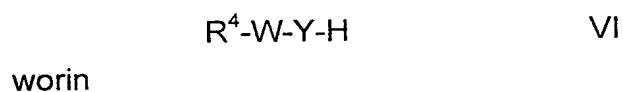
und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell  
abgewandelte OH-Gruppe bedeutet,

10

und R<sup>2</sup> die in Anspruch 1 angegebene Bedeutung hat,

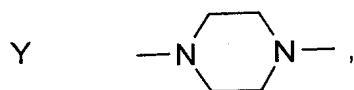
mit einer Verbindung der Formel VI

15



W eine Bindung,

20



R<sup>4</sup> -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Ar oder -[C(R<sup>5</sup>)<sub>2</sub>]<sub>m</sub>Het und

25

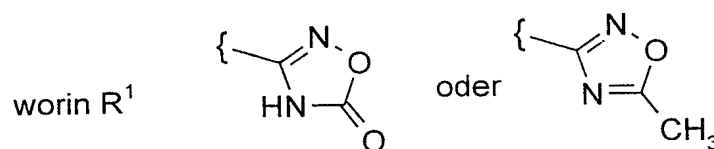
m 0 bedeuten,

umsetzt,

oder

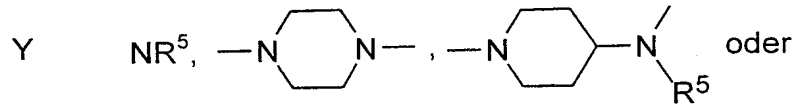
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e) zur Herstellung von Verbindungen der Formel I,

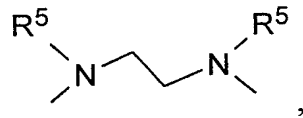


35

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



5



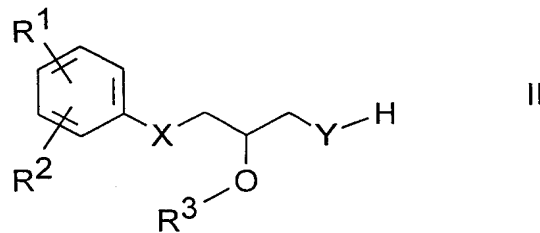
W -CONH- bedeuten,

10

und R<sup>2</sup> und R<sup>4</sup> die in Anspruch 1 angegebenen Bedeutungen haben,

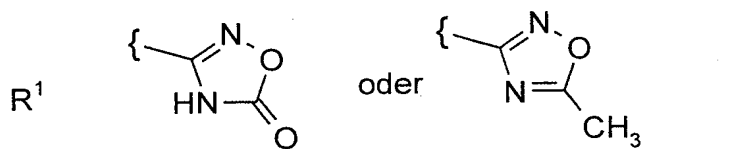
eine Verbindung der Formel II

15



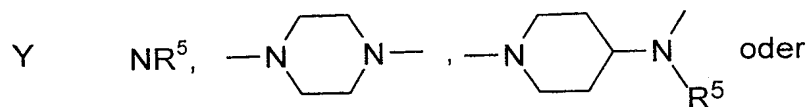
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worin

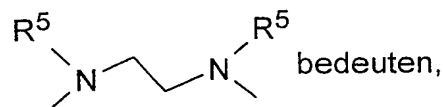


25

R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,



30



35

und R<sup>2</sup> und R<sup>5</sup> die in Anspruch 1 angegebene Bedeutung haben,

mit einer Verbindung der Formel VII



5 worin

$R^4$  die in Anspruch 1 angegebene Bedeutung hat,

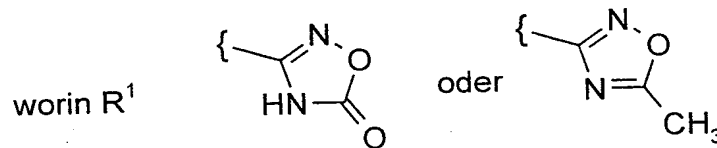
umsetzt,

10

oder

f) zur Herstellung von Verbindungen der Formel I,

15



20

$R^3$  und X zusammen -CO-N- unter Ausbildung eines 5-Rings,

Y  $N[C(R^5)_2]_m-COOR^5$ ,

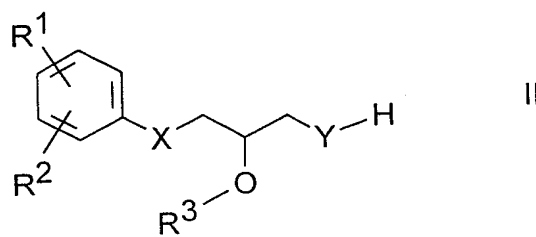
W  $SO_2$  bedeuten,

25

und  $R^2$  und  $R^4$  die in Anspruch 1 angegebenen Bedeutungen haben,

eine Verbindung der Formel II

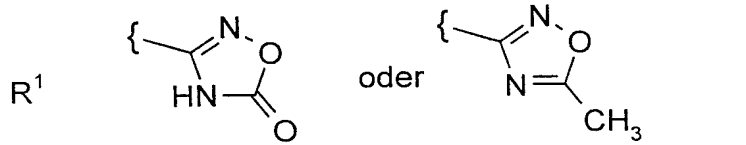
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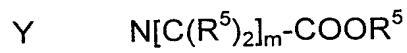
worin





5

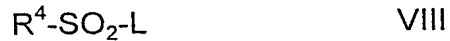
R<sup>3</sup> und X zusammen -CO-N- unter Ausbildung eines 5-Rings,  
bedeuten,



und R<sup>2</sup> und R<sup>5</sup> die in Anspruch 1 angegebene Bedeutung  
haben,

10

mit einer Verbindung der Formel VIII



worin

15

L Cl, Br, I oder eine freie oder reaktionsfähig funktionell  
abgewandelte OH-Gruppe bedeutet,

und R<sup>4</sup> die in Anspruch 1 angegebene Bedeutung hat,

20

umsetzt,

oder

25

g) zur Herstellung von Verbindungen der Formel I,

worin

30

X NH und  
R<sup>3</sup> H bedeutet,

und R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, Y und W die in Anspruch 1 angegebenen Be-  
deutungen haben,

35

sie aus ihren Oxazolidinonderivaten durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt,

5

oder

h) zur Herstellung von Verbindungen der Formel I,

worin  $R^1$   $-C(=NH)-NH_2$  bedeutet,

10

eine Cyangruppe in eine Amidinogruppe umwandelt,

oder

15

i) in einer Verbindung der Formel I einen oder mehrere Rest(e) Y,  $R^1$ ,  $R^2$ ,  $R^3$  und/oder  $R^4$  in einen oder mehrere Rest(e)  $R^1$ ,  $R^2$ ,  $R^3$  und/oder  $R^4$  umwandelt,

indem man beispielsweise

20

i) eine Estergruppe zu einer Carboxygruppe hydrolysiert,

ii) eine Nitrogruppe reduziert,

25

iii) eine Aminogruppe acyliert,

und/oder

30

k) eine Base oder Säure der Formel I in eines ihrer Salze umwandelt.

35

4. Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Anspruch 1 und/oder eines ihrer physiologischen unbedenklichen Salze zusammen mit mindestens einem festen, flüssigen oder halbflüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform bringt.

5. Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt an mindestens einer Verbindung der Formel I nach Anspruch 1 und/oder einem ihrer physiologisch unbedenklichen Salze.
- 5
6. Verbindungen der Formel I nach Anspruch 1 und ihre physiologisch unbedenklichen Salze zur Bekämpfung von Thrombosen, myocardiallem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens.
- 10
7. Arzneimittel der Formel I nach Anspruch 1 und ihre physiologisch unbedenklichen Salze als Inhibitoren des Koagulationsfaktors Xa.
8. Verwendung von Verbindungen der Formel I nach Anspruch 1 und/oder ihre physiologisch unbedenklichen Salze zur Herstellung eines Arzneimittels.
- 15
9. Verwendung von Verbindungen der Formel I nach Anspruch 1 und/oder ihrer physiologisch unbedenklichen Salze bei der Bekämpfung von Thrombosen, myocardiallem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens.
- 20
- 25
- 30
- 35

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 98/07673

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07D413/14 C07D413/12 C07D295/26 C07C257/18 A61K31/41  
A61K31/495 A61K31/155

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 C07C A61K

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	EP 0 710 657 A (MERCK PATENT GMBH) 8 May 1996 see claims 1-8 ---	1-9
X	DE 42 03 201 A (BOEHRINGER INGELHEIM KG) 12 August 1993 see example 2 ---	1
X	DE 28 35 369 A (PFIZER INC.) 22 February 1979 * compound of the formula IV * see claims 1,8; examples 46,47 ---	1
X	EP 0 623 615 A (MERCK PATENT GMBH) 9 November 1994 see claims 1,3-7; examples 10,14,16 --- -/--	1,3-9

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

Date of the actual completion of the international search

27 May 1999

Date of mailing of the international search report

10/06/1999

Name and mailing address of the ISA

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International Application No

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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 741 133 A (MERCK PATENT GMBH) 6 November 1996 * Example * see claims 1-8 ---	1,3-9
Y	EP 0 727 425 A (MERCK PATENT GMBH) 21 August 1996 see claim 1 ---	1-9
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Internationales Aktenzeichen

PCT/EP 98/07673

**A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES**

IPK 6 C07D413/14 C07D413/12 C07D295/26 C07C257/18 A61K31/41  
 A61K31/495 A61K31/155

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

**B. RECHERCHIERTE GEBIETE**

Recherchiertes Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 6 C07D C07C A61K

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.
Y	EP 0 710 657 A (MERCK PATENT GMBH) 8. Mai 1996 siehe Ansprüche 1-8 ---	1-9
X	DE 42 03 201 A (BOEHRINGER INGELHEIM KG) 12. August 1993 siehe Beispiel 2 ---	1
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Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :

- "A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
- "E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
- "L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
- "O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
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"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderscher Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderscher Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

27. Mai 1999

Absenddatum des internationalen Recherchenberichts

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Name und Postanschrift der Internationalen Recherchenbehörde  
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Bevollmächtigter Bediensteter

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2

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
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X	EP 0 741 133 A (MERCK PATENT GMBH) 6. November 1996 * Beispiele * siehe Ansprüche 1-8 ---	1,3-9
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E	WO 99 02525 A (PHARMACIA & UPJOHN CO.) 21. Januar 1999 siehe Beispiel 35 ---	1
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Y	P. BARRACLOUGH ET AL.: "Mono-arylation of 2,3- and 3,4-diaminopyridine and 4,5-diaminopyrimidine, and syntheses of putative inotrope/beta-adrenoceptor antagonists" J. CHEM. RES., SYNOP., Nr. 9, 1996, Seiten 406-407, XP002103810 * Verbindungen der Formel 1-3 * ---	1-9
P,Y	J. GANTE ET AL.: "A new class of peptidomimetic adhesion receptor antagonists" PEPTIDES 1996, PROC. EUR. PEPT. SYMP., 24TH, 1998, Seiten 401-402, XP002103811 siehe Tabelle 1 ---	1-9
X	V. BRIZZI ET AL.: "New 1,2,4-oxadiazole derivatives: synthesis and adrenergic receptor binding studies" FARMACO, Bd. 47, Nr. 6, 1992, Seiten 953-966, XP002103812 * Verbindungen der Formel V * siehe Abbildung I; Tabelle II ---	1-9
X	J. GANTE ET AL.: "New peptidomimetics in the chemistry of fibrinogen receptor antagonists" LETT. PEPT. SCI., Bd. 2, Nr. 3/4, 1995, Seiten 135-140, XP002103813 siehe Tabellen 1-4 --- -/--	1-9

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Kategorie <sup>2</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	<p>J. GANTE ET AL.: "New antithrombotic RGD-mimetics with high bioavailability" BIOORG. MED. CHEM. LETT., Bd. 6, Nr. 20, 1996, Seiten 2425-2430, XP002103814</p> <p>* Verbindungen der Formel 2 * siehe Tabellen 1,2</p>	1-9
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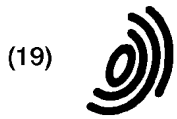
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(12)

**EUROPEAN PATENT APPLICATION**

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Toyko 140 (JP)**

• **MAEDA, Naoyuki,  
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(54) **MEDICINAL COMPOSITIONS**

(57) A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents exhibits excellent arteriosclerotic progress inhibitory effects, and is useful as a drug, particularly as a drug for the prevention or treatment of arteriosclerosis.

**EP 0 930 076 A1**



## Description

## [Technical Field of the Invention]

5 [0001] The present invention relates to a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arterio-

10 sclerotic), and a method which comprises administering in combination effective amounts of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for preventing or treating diseases (particularly arteriosclerosis).

15 [Background of the Invention]

[0002] The occurrence of atherosclerosis is increasing with the adoption of Western-style diet and the growth of the aged population. This disease is the main cause of such disorders as myocardial infarction, cerebral infarction and cerebral apoplexy, and there is a need for its effective prevention and treatment. Examples of risk factors which cause atherosclerosis include hyperlipemia (particularly hypercholesterolemia), hypertension and saccharometabolism disorders based on insulin resistance. In addition, there are many cases in which these risk factors occur in the form of complications (Syndrome X), and are considered to be mutually interrelated [Diabetes, 37, 1595-1607 (1988)].

[0003] Efforts have been made for the purpose of preventing and treating atherosclerosis by suppression of various risk factors such as hyperlipemia, hypertension and insulin resistance. Although HMG-CoA reductase inhibitors like pravastatin improve hyperlipemia, their inhibitory activity on arteriosclerosis in a case of administration alone is not enough [Biochim. Biophys. Acta, 960, 294-302 (1988)]. In addition, even insulin resistance improving agents like troglitazone do not exhibit sufficient atherosclerosis inhibitory activity in a case of administration alone (Japanese Patent Application (Kokai) No. Hei 7-41423).

[0004] On the other hand, among drugs for the treatment of hypertension, it has been reported that atherosclerotic lesions are suppressed when angiotensin converting enzyme (ACE) inhibitors that inhibit the renin-angiotensin system [Hypertension, 15, 327-331 (1990)] or angiotensin II receptor antagonists [Jpn. Circ. J., 60 (Suppl. I), 332 (1996)] are administered to animals having normal blood pressure and hypercholesterolemia. Angiotensin II not only exhibits vasoconstrictive activity, but also activity that stimulates the production of growth factors such as PDGF [Hypertension, 13, 706-711 (1989)] and activity that stimulates migration of neutrophils and macrophages [Eur. Heart J., 11, 100-107 (1990)]. Although the mechanism in which renin-angiotensin system inhibitors suppress atherosclerosis is not clear at the present time, there is a possibility that the mechanism for suppressing atherosclerosis may be a function at the site of the lesion which is different from their blood pressure lowering action. However, since inhibitors of renin-angiotensin system are unable to lower serum lipids [J. Cardiovasc. Pharmacol., 15, S65-S72 (1990)], their administration alone has limitations on the treatment of arteriosclerosis.

[0005] In addition, although troglitazone, glibenclamide and captopril are administered concomitantly to diabetes patients, there is no suggestion indicated whatsoever relating to the prevention and treatment of arteriosclerosis [J. Clinical Therapeutic & Medicines, 9 (Supp. 3), 39-60 (1993)].

45 [Disclosure of the Invention]

[0006] As a result of earnestly conducting various research in consideration of the importance of the prevention and treatment of arteriosclerosis, the inventors of the present invention found a method to solve the above-mentioned problems involved in the prior art and to obtain a preventive and/or therapeutic effect on arteriosclerosis by using the combination of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of one or more of insulin resistance improving agents.

[0007] The present invention provides a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arterio-

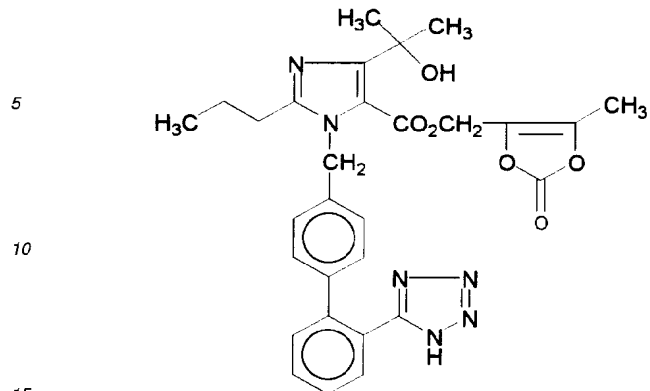
55 sclerotic), a method which comprises administering in combination effective amounts of one or more drugs selected

from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for prevention or treatment of diseases (particularly arteriosclerosis), or a pharmaceutical composition for administering at the same time or at the different time one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis).

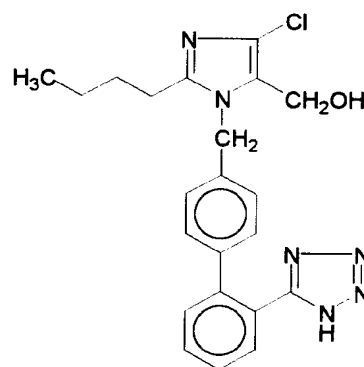
**[0008]** The active ingredients of the pharmaceutical composition of the present invention (particularly a pharmaceutical composition for the prevention or treatment of arteriosclerosis), or the active ingredients of a method for preventing or treating diseases (particularly arteriosclerosis) include one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.

**[0009]** Representative examples of angiotensin II receptor antagonists as an active ingredient of the present invention include biphenyltetrazole compounds and biphenylcarboxylic acid compounds described in Japanese Patent Application (Kokai) No. Hei 5-78328, Japanese Patent Application (Kokai) No. Sho 63-23868, Japanese Patent Application (Kokai) No. Hei 4-364171, Japanese Patent Application (Kokai) No. Hei 4-159718 or Japanese PCT Application (Kokai) No. Hei 4-506222, preferably biphenyltetrazole compounds, more preferably CS-866, losartan, candesartan, valsartan or irbesartan, still more preferably CS-866, losartan or candesartan, and most preferably CS-866.

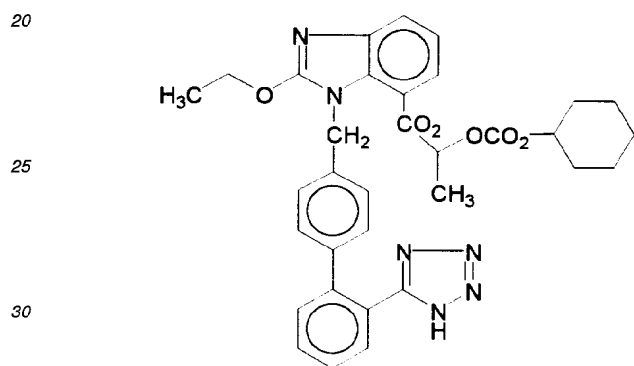
**[0010]** The following indicates the chemical planar structural formulae of some typical examples of angiotensin II receptor antagonists.



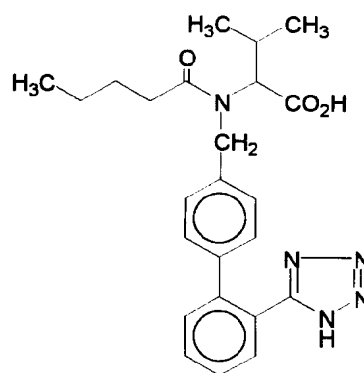
CS-866



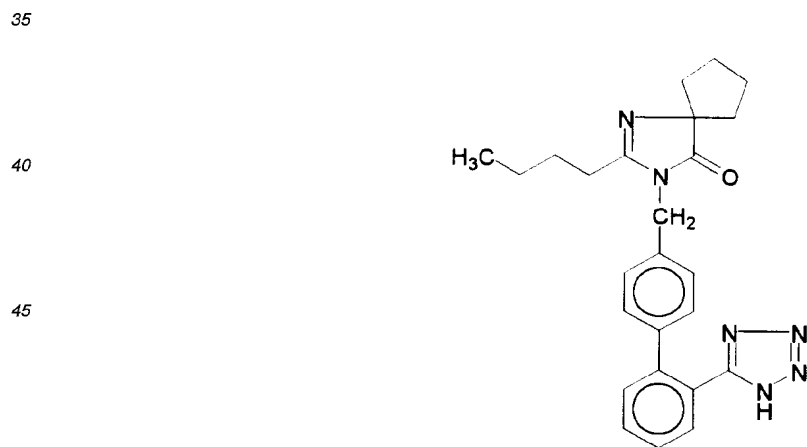
Losartan



Candesartan



Valsartan



Irbesartan

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[0011] CS-866 is described in Japanese Patent Application No. (Kokai) No. Hei 5-78328 and the like, and its chemical name is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate. The CS-866 of the present application includes its carboxylic acid derivative, phar-

macologically acceptable esters of its carboxylic acid derivative (such as CS-866) and their pharmacologically acceptable salts.

5 **[0012]** Losartan (DUP-753) is described in Japanese Patent Application (Kokai) No. Sho 63-23868, U.S. Patent No. 5,138,069 and the like, and its chemical name is 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-imidazole-5-methanol. The losartan of the present application includes its pharmacologically acceptable salts (such as losartan potassium salt).

10 **[0013]** Candesartan (TCV-116) is described in Japanese Patent Application (Kokai) No. Hei 4-364171, EP-459136, U.S. Patent No. 5,354,766 and the like, and its chemical name is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-benzimidazole-7-carboxylate. The candesartan of the present application includes its carboxylic acid derivative, pharmacologically acceptable esters of its carboxylic acid derivative (such as TCV-116) and their pharmacologically acceptable salts.

**[0014]** Valsartan (CGP-48933) is described in Japanese Patent Application (Kokai) No. Hei 4-159718, EP-433983 and the like, and its chemical name is (S)-N-valeryl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]valine. The valsartan of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

15 **[0015]** Irbesartan (SR-47436) is described in Japanese PCT Application (Kokai) No. Hei 4-506222, WO91-14679 and the like, and its chemical name is 2-N-butyl-4-spirocyclopentane-1-[2'-(tetrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazol-5-one. The irbesartan of the present application includes its pharmacologically acceptable salts.

20 **[0016]** In addition, where the above-mentioned compounds have asymmetric carbons, the angiotensin II receptor antagonists of the present invention also include optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included.

**[0017]** Representative examples of the angiotensin converting enzyme inhibitors as an active ingredient of the present invention include tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds described in Japanese Patent Application (Kokai) No. Sho 61-267579, Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,374,829, Japanese Patent Application (Kokai) No. Sho 58-126851, Japanese Patent Application (Kokai) No. Sho 58-206591, Japanese Patent Application (Kokai) No. Sho 57-77651, Japanese Patent Application (Kokai) No. Sho 55-9058, Japanese Patent Application (Kokai) No. Sho 58-203971 and Japanese Patent Application (Kokai) No. Sho 63-258459, preferably temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril or quinapril, more preferably temocapril, captopril or enalapril, and most preferably temocapril.

30 **[0018]** The following indicates the chemical planar structural formulae of some typical examples of angiotensin converting enzyme inhibitors.

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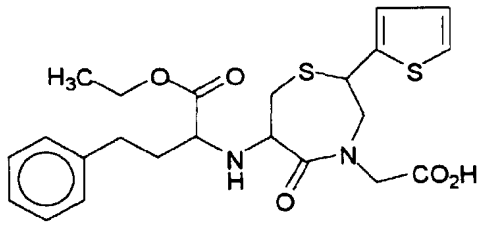
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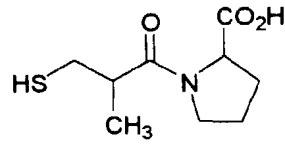
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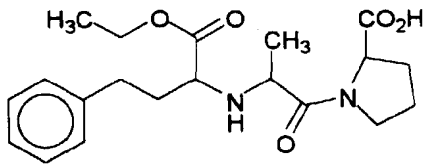
Temocapril

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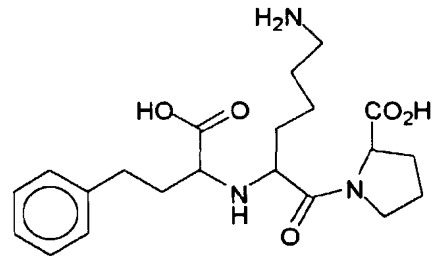
Captopril

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Enalapril

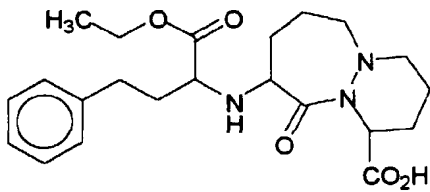
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Lisinopril

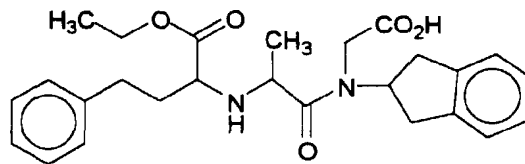
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Cilazapril

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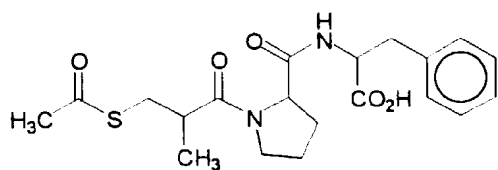
Delapril

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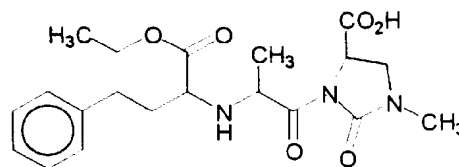
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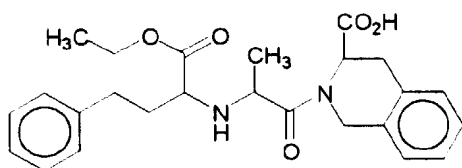
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Alacepril



Imidapril



Quinapril

**[0019]** Temocapril is described in Japanese Patent Application (Kokai) No. Sho 61-267579, U.S. Patent No. 4,699,905 and the like, and its chemical name is (+)-(2S,6R)-[6-(1S)-1-ethoxycarbonyl-3-phenylpropylamino]-5-oxo-2-(2-thienyl)perhydro-1,4-thiazepin-4-yl acetic acid. The temocapril of the present application includes its dicarboxylic acid derivatives, its pharmacologically acceptable salts, its pharmacologically acceptable monoesters and its pharmacologically acceptable salts (such as temocapril hydrochloride).

**[0020]** Captopril is described in Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,046,889 and the like, and its chemical name is 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. The captopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

**[0021]** Enalapril is described in U.S. Patent No. 4,374,829 and the like, and its chemical name is N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline. The enalapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts (such as enalapril maleate).

**[0022]** Lisinopril is described in Japanese Patent Application (Kokai) No. Sho 58-126851, U.S. Patent No. 4,555,502 and the like, and its chemical name is (S)-1-[N<sup>2</sup>-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline. The lisinopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

**[0023]** Cilazapril is described in Japanese Patent Application (Kokai) No. Sho 58-206591, U.S. Patent No. 4,512,924 and the like, and its chemical name is (1S,9S)-9-[(S)-1-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazino[1,2- $\alpha$ ][1,2]diazepine-1-carboxylic acid. The cilazapril of the present application includes its pharmacologically acceptable esters and pharmacologically acceptable salts.

**[0024]** Delapril is described in Japanese Patent Application (Kokai) No. Sho 57-77651, U.S. Patent No. 4,385,051 and the like, and its chemical name is (S)-N-(2,3-dihydro-1H-inden-2-yl)-N-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]glycine. The delapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

**[0025]** Alacepril is described in Japanese Patent Application (Kokai) No. Sho 55-9058, U.S. Patent No. 4,248,883 and the like, and its chemical name is 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine. The alacepril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

**[0026]** Imidapril is described in Japanese Patent Application (Kokai) No. Sho 58-203971, U.S. Patent No. 4,508,727 and the like, and its chemical name is (4S)-3-[(2S)-2-[(1S)-1-ethoxycarbonyl-3-phenylpropylamino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid. The imidapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

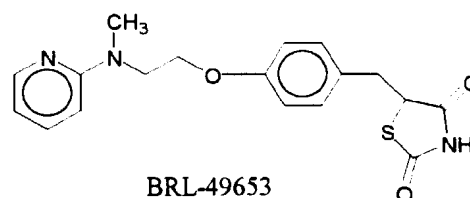
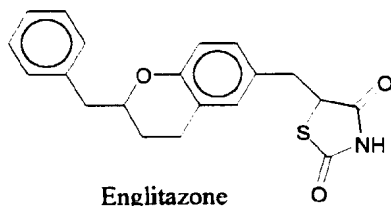
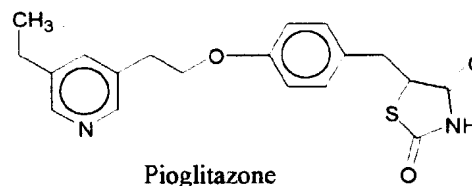
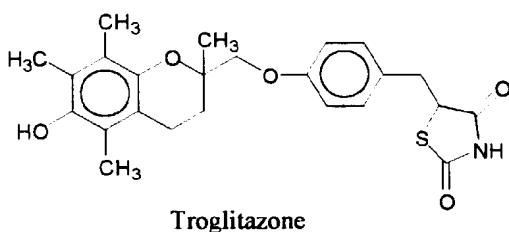
**[0027]** Quinapril is described in Japanese Patent Application (Kokai) No. Sho 63-258459, U.S. Patent No. 4,761,479 and the like, and its chemical name is (S)-2-[(2S)-2-(1S)-1-ethoxycarbonyl-3-phenylpropylamino]propionyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid. The quinapril of the present application includes its pharmacologically acceptable

ble esters and its pharmacologically acceptable salts.

[0028] Where the above-mentioned angiotensin converting enzyme inhibitors of the present invention have asymmetric carbons, said angiotensin converting enzyme inhibitors of the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0029] The insulin resistance improving agents as another active ingredient of the present invention are inherently used for the prevention and treatment of diabetes. Representative examples include thiazolidinedione compounds, oxazolidinedione compounds or oxadiazolidinedione compounds described in Japanese Patent Application (Kokai) No. Hei 4-69383, WO 89/08651, WO 91/07107, WO 92/02520, WO 94/01433, USP-4287200, USP-4340605, USP-4438141, USP-4444779, USP-4461902, USP-4572912, USP-4687777, USP-4703052, USP-4725610, USP-4873255, USP-4897393, USP-4897405, USP-4918091, USP-4948900, USP-5002953, USP-5061717, USP-5120754, USP-5132317, USP-5194443, USP-5223522, USP-5232925 and USP-5260445, preferably thiazolidinedione compounds, more preferably troglitazone, pioglitazone, englitazone or BRL-49653, still more preferably troglitazone or pioglitazone, and most preferably troglitazone.

[0030] The following indicates the chemical planar structural formulae of some typical examples of insulin resistance improving agents.



[0031] Troglitazone is described in Japanese Patent Application (Kokai) No. Sho 60-51189, U.S. Patent No. 4,572,912 and the like, and its chemical name is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione. The troglitazone of the present application includes its pharmacologically acceptable salts.

[0032] Pioglitazone is described in Japanese Patent Application (Kokai) No. Sho 55-22636, U.S. Patent No. 4,287,200 and the like, and its chemical name is 5-[4-[2-(5-ethyl-pyridin-2-yl)ethoxy]phenylmethyl]-2,4-thiazolidinedione. The pioglitazone of the present application includes its pharmacologically acceptable salts.

[0033] Englitazone is described in Japanese Patent Application (Kokai) No. Sho 61-271287, U.S. Patent No. 4,703,052 and the like, and its chemical name is 5-(3,4-dihydro-2-benzyl-2H-benzopyran-6-ylmethyl)-2,4-thiazolidinedione. The englitazone of the present application includes its pharmacologically acceptable salts.

[0034] BRL-49653 is described in Japanese Patent Application (Kokai) No. Hei 1-131169, U.S. Patent No. 5,002,953 and the like, and its chemical name is 5-[4-[2-[N-methyl-N-(pyridin-2-yl)amino]ethoxy]phenylmethyl]-2,4-thiazolidinedione. The BRL-49653 of the present application includes its pharmacologically acceptable salts.

[0035] Where the above-mentioned insulin resistance improving agents of the present invention have asymmetric carbons, said resistance improving agents the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0036] In the present invention, one or more drugs are selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors (preferably the group consisting of angiotensin II receptor antagonists), and one or more insulin resistance improving agents are selected; and preferably the one drug is selected from angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and the other drug is selected

from insulin resistance improving agents to use in combination.

**[0037]** Preferable examples of the pharmaceutical composition of the present invention are as follows:

5 (1) a pharmaceutical composition wherein as active ingredients, the angiotensin II receptor antagonists are chosen from biphenyltetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds;

(2) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril;

10 (3) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril;

(4) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril;

(5) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan;

20 (6) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866;

(7) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists;

(8) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan;

25 (9) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from angiotensin converting enzyme inhibitors;

(10) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is temocapril;

30 (11) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds;

(12) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;

35 (13) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone; and,

(14) a pharmaceutical composition wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

In addition, a pharmaceutical composition obtained by selecting as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors from the group (1) to (10), by selecting as active ingredients, insulin resistance improving agents from the group (11) to (14) and by combining these groups in an arbitrary manner is also preferable, examples of which are as follows:

40 (15) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;

45 (16) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;

50 (17) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

55 (18) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone.



zone;

(19) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

(20) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agent is troglitazone;

(21) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agent is troglitazone; and,

(22) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and as the other active ingredient, the insulin resistance improving agent is troglitazone.

[Effect of the Invention]

**[0038]** A drug comprising one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents, which are the active ingredients of the pharmaceutical composition of the present invention (particularly a composition for prevention or treatment of arteriosclerosis), has excellent inhibitory action on atherosclerosis and excellent inhibitory action against onset of xanthochromia occurring in limb joints, and low toxicity. Consequently, it is useful as a drug for the prevention and treatment (particularly for treatment) of arteriosclerosis or xanthochromia.

**[0039]** According to the present invention, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and insulin resistance improving agents exhibit excellent effects by using two of these agents in combination as compared with being used alone. In addition, these effects can be achieved without requiring that both types of agents be present in the body simultaneously.

**[0040]** Namely, such effects can be obtained even if both types of agents do not simultaneously have certain concentrations in the blood. According to hypothesis, if two types of agents used in the present invention are both incorporated *in vivo* and reach the receptors, they have the effect of turning on a switch *in vivo*. Thus, even if it appears that such effects are not demonstrated at their blood concentrations in course of time after their administration, the switch is actually still on, thereby allowing demonstration of preventive or therapeutic effects on arterial sclerosis possessed by the one type of substance. When the other type of agent is administered in this state, in addition to the preventive or therapeutic effects on arterial sclerosis possessed by that agent, the effects of the drug initially administered are combined to obtain excellent effects. Naturally, since it is convenient clinically to administer two types of agents simultaneously, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and an insulin resistance improving agent can be administered in the form of a combination drug. In cases where it is undesirable to physically mix both agents simultaneously in consideration of pharmaceutical formulation technology, each individual agent may be administered simultaneously. In addition, as was stated above, since excellent effects are demonstrated even if the two types of agents are not administered simultaneously, each individual agent can also be administered at a suitable interval in succession. The maximum administration interval of the two types of agents to demonstrate the excellent effects brought about by said two types of agents can be determined by clinical or animal studies.

[Industrial Applicability]

**[0041]** The administration route of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention is typically the oral administration route. Thus, the two types of agents can either be prepared in the form of two separate administrations or in the form of a single administration by physically mixing the two types of agents. The administration form can be, for example, a powder, granules, tablet or capsule and the like, and can be prepared by using conventional pharmaceutical formulation techniques.

**[0042]** The dose and administration ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention can be changed over a wide range according to various conditions such as the individual activity of each agent, the patient's symptoms, age and body weight, and the like. For example, in the case of insulin resistance improving agents, since the *in vivo* activities of troglitazone and BRL-49653 by using a diabetic animal model are different, the dose of these two agents may be different by a factor of ten or more. In addition, for both agents consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and insulin resistance improving agents, their doses in the case used for prevention or treatment of arteriosclerosis in the present invention can be lower than their dose for use

as hypotensive agents and diabetes therapeutic agents respectively, which are their well-known applications. In addition, their doses can be made even lower due to the excellent effects resulting from combined use of both types of agents. For example, in the case of using CS-866 and troglitazone for the object of the present invention, their doses are lower than the approximately 5 to 100 mg and approximately 10 to 2000 mg, respectively, which are the doses for adults (mg/day) for use as a hypotensive agent and diabetes therapeutic agent in their well-known applications, being able to be approximately 1 to 80 mg and approximately 1 to 1000 mg, respectively.

**[0043]** As has been described above, the doses of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of the insulin resistance improving agents can be varied over a wide range, in general, and their doses for adults (mg/day) are approximately 0.5 to 100 mg and approximately 0.05 to 1,500 mg, respectively.

**[0044]** The ratio of the doses of these two types of agents can also be varied over a wide range, in general, and the dose ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors to the insulin resistance improving agents can be, in terms of weight ratio, within the range from 1:200 to 200:1.

**[0045]** In the present invention, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and the insulin resistance improving agents are administered at the respective doses described above once a day or divided among several times per day, and may be administered simultaneously or separately at respectively different times.

[Best Mode for Carrying Out the Invention]

**[0046]** The present invention will be described more specifically by way of Examples and Preparation examples, but the scope of the present invention is not limited to them.

(Example 1)

Arterial sclerosis Progress Inhibitory Effect

**[0047]** A certain amount of an agent was administered orally for 32 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: supra (Biochimica et Biophysica Acta), etc.] in groups of 4 to 7 animals each. Incidentally, food consumption was restricted to 120 g/day per animal. Blood samples were collected immediately before administration of the agent and 4, 8, 12, 16, 20, 24, 28 and 32 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. The test animals were subjected to autopsy in the 32nd week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints (%). Those results are shown in Tables 1 and 2.

[Table 1]

Surface Area of Aortic Lesions											
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)							
				Arcuate region		Thoracic part		Abdominal region		Overall	
1	CS-866	1	5	52	10	9	3	13	2	21	4
	+	25									
	Troglitazone										
50	CS-866	1	6	68	10	26	8	19	5	34	7
	Troglitazone	25	7	80	7	57	12	32	8	54	9
	Control	-	7	83	6	59	7	39	4	56	4

[Table 2]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
1	CS-866 +	1				
	Troglitazone	25	4	75	63	69
	CS-866	1	6	100	100	100
	Troglitazone	25	7	93	86	89
	Control	-	7	100	100	100

(Example 2)

20 Arterial sclerosis Progress Inhibitory Effect

[0048] A certain amount of an agent was administered orally for 31 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: described supra (Biochimica et Biophysica Acta), etc.] in groups of 5 to 7 animals each. Incidentally, food consumption was restricted to 100 g/day per animal. Blood samples were collected immediately before administration of the agent and 8, 16, 24 and 31 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. In addition, the test animals were subjected to autopsy in the 31st week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints. Those results are shown in Tables 3 and 4.

[Table 3]

Surface Area of Aortic Lesions							
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)			
				Arcuate region	Thoracic part	Abdominal region	Overall
2	CS-866 +	0.5					
	pioglitazone	20	6	62±8	29±10	24±6	36±7
3	CS-866 +	0.5					
	BRL-49653	2.5	5	52±5	32±7	25±5	34±5
	CS-866	0.5	7	66±5	41±10	32±8	44±7
	Pioglitazone	20	7	65±6	62±12	32±6	52±8
	BRL-49653	2.5	6	83±2	54±12	29±4	52±5
	Control	-	7	84±5	59±9	32±11	54±8

[Table 4]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
4	Candesartan +	1				
	troglitazone	25	7	86	86	86
	Candesartan	1	7	100	100	100
	Troglitazone	25	7	100	86	93
	Control	-	7	100	100	100

(Formulation Example 1)

[0049]

Tablets	
CS-866	4.0 mg
Troglitazone	100.0
Lactose	244.0
Cornstarch	50.0
Magnesium stearate	2.0
	400 mg

[0050] The above-mentioned prescriptions are mixed and formed into tablets with a tablet-making machine to obtain tablets containing 400 mg per tablet.

[0051] These tablets can be provided with a sugar-coating if necessary.

#### Claims

1. A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.
2. A pharmaceutical composition according to Claim 1 wherein the angiotensin II receptor antagonists are biphenyl tetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.
3. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril.
4. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

5. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril.
- 5 6. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from chosen from CS-866, losartan and candesartan.
7. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is CS-866.
- 10 8. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists.
- 15 9. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan.
- 20 10. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin converting enzyme inhibitors.
- 25 11. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril.
12. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.
- 30 13. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
14. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone.
- 35 15. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the insulin resistance improving agent is troglitazone.
- 40 16. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
- 45 17. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
- 50 18. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.
- 55 19. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

20. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.
- 5 21. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent is troglitazone.
- 10 22. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is CS-866, and the insulin resistance improving agent is troglitazone.
- 15 23. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and the insulin resistance improving agent is troglitazone.
- 20 24. A pharmaceutical composition according to Claims 1 to 23, wherein said pharmaceutical composition is a composition for preventing or treating arteriosclerosis.
- 25 25. The use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of one or more insulin resistance improving agents for preparing a pharmaceutical composition.
- 30 26. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
- 35 27. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
- 40 28. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.
- 45 29. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.
- 50 30. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866 and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.
- 55 31. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent is troglitazone.
32. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866 and the insulin resistance improving agent is troglitazone.
33. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril and the insulin resistance improving agent is troglitazone.
34. The use according to Claims 25 to 33, wherein the pharmaceutical composition is a composition for preventing or treating arteriosclerosis.

- 5
35. A method for preventing or treating arteriosclerosis which comprises administering in combination an effective amount of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to a warm blooded animal.
- 10
36. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
- 15
37. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.
- 20
38. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.
- 25
39. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.
- 30
40. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is CS-866 and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.
- 35
41. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent administered in combination is troglitazone.
- 40
42. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is CS-866 and the insulin resistance improving agent administered in combination is troglitazone.
- 45
43. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is temocapril and the insulin resistance improving agent administered in combination is troglitazone.
- 50
- 55

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP97/02407

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl <sup>6</sup> A61K45/06, A61K31/33 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) Int. Cl <sup>6</sup> A61K45/06, A61K31/33 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 practicable, search terms used) CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Toru Murakami, Nobuhiro Yamada "Can ACE inhibitors prevent arteriosclerosis? (in Japanese)", Strides of Medicine, (1995), Vol. 174, No. 10. p. 810-813	1 - 34
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search October 1, 1997 (01. 10. 97)		Date of mailing of the international search report October 21, 1997 (21. 10. 97)
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP97/02407

**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.: 35 - 43  
because they relate to subject matter not required to be searched by this Authority, namely:  
Inventions of Claims 35 to 43 pertain to methods for treatment of the human or animal body by therapy.
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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US99/01682</p> <p>(22) International Filing Date: 27 January 1999 (27.01.99)</p> <p>(30) Priority Data: 60/072,707 27 January 1998 (27.01.98) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/072,707 (CIP) Filed on 27 January 1998 (27.01.98)</p> <p>(71) Applicant (for all designated States except US): RHONE-POULENC RORER PHARMACEUTICALS INC. [US/US]; Legal/Patents, 500 Arcola Road, Mail Stop #3C43, Collegeville, PA 19426-0997 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): EWING, William, R. [US/US]; 805 Graystone Lane, Downingtown, PA 19335 (US). BECKER, Michael, R. [US/US]; 62 Church Road, Norristown, PA 19401 (US). CHOI-SLEDESKI, Yong, Mi [US/US]; 5 Dana Drive, Collegeville, PA 19426 (US). PAULS, Heinz, W. [CA/US]; 3770 Worthington Circle, Collegeville, PA 19426 (US). HE, Wei [US/US]; 1005</p>		<p>Bayberry Lane, Collegeville, PA 19426 (US). CONDON, Stephen, M. [US/US]; 2130 Art School Road, Chester Springs, PA 19425 (US). DAVIS, Roderick, S. [US/US]; Apartment B16, 1100 West Chester Pike, West Chester, PA 19382 (US). HANNEY, Barbara, A. [US/US]; 2813 Upper Ridge Road, Pennsburg, PA 18073 (US). SPADA, Alfred, P. [US/US]; 473 Painter Way, Lansdale, PA 19446 (US). BURNS, Christopher, J. [US/US]; Unit 49, 138 Montrose Avenue, Rosemont, PA 19010 (US). JIANG, John, Z. [CN/US]; 1003 Bayberry Lane, Collegeville, PA 19426 (US). LI, Aiwen [CN/US]; Apartment F0101, 2828 Egypt Road, Audubon, PA 19403 (US). MYERS, Michael, R. [US/US]; 205 Lincoln Road, Reading, PA 19606 (US). LAU, Wan, F. [MY/US]; 64 Prospect Hill Road, Groton, CT 06340-5627 (US). POLI, Gregory, B. [US/US]; 1415 Azalea Court, Perkasia, PA 18944 (US).</p> <p>(74) Agents: NEWMAN, Irving et al.; Rhône-Poulenc Rorer Pharmaceuticals Inc., 500 Arcola Road, P.O. Box 5093, Collegeville, PA 19426-0997 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, 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, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>
<p>(54) Title: SUBSTITUTED OXOAZAHETEROCYCLYL FACTOR Xa INHIBITORS</p>		
<p>(57) Abstract</p> <p>This invention is directed to oxoazaheterocyclyl compounds which inhibit factor Xa, to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds and to a method of inhibiting factor Xa.</p>		

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<b>CM</b>	Cameroon			<b>PL</b>	Poland		
<b>CN</b>	China	<b>KR</b>	Republic of Korea	<b>PT</b>	Portugal		
<b>CU</b>	Cuba	<b>KZ</b>	Kazakstan	<b>RO</b>	Romania		
<b>CZ</b>	Czech Republic	<b>LC</b>	Saint Lucia	<b>RU</b>	Russian Federation		
<b>DE</b>	Germany	<b>LI</b>	Liechtenstein	<b>SD</b>	Sudan		
<b>DK</b>	Denmark	<b>LK</b>	Sri Lanka	<b>SE</b>	Sweden		
<b>EE</b>	Estonia	<b>LR</b>	Liberia	<b>SG</b>	Singapore		

## SUBSTITUTED OXOAZAHETEROCYCLYL FACTOR Xa INHIBITORS

## FIELD OF THE INVENTION

5 This invention is directed to oxoazaheterocycl compounds which inhibit factor Xa, to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds and to a method of inhibiting factor Xa.

## BACKGROUND OF THE INVENTION

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Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) activates prothrombin to generate thrombin. Factor Xa is strategically located at the intersection of extrinsic and intrinsic pathways of the blood coagulation system. Thus, an inhibitor of Factor Xa inhibits the formation of thrombin and therefore is useful for preventing or treating disorders related to blood coagulation in mammals.

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Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems.

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In addition to their use in anticoagulant therapy, Factor Xa inhibitors are useful in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by

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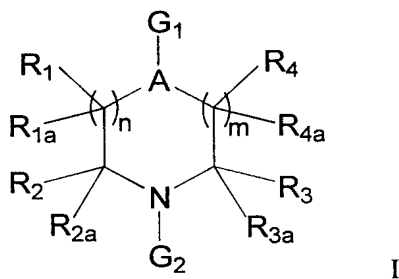
virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

The representative indications discussed above include some, but not all, of the possible clinical situations amenable to treatment with a Factor Xa inhibitor.

Oxoazaheterocyclyl Factor Xa inhibitors are disclosed in International Patent Numbers PCT/US98/07158, published Oct. 22, 1998; PCT/US98/07159, published Oct. 22, 1998; PCT/US98/07160, published Oct. 22, 1998; PCT/US98/07161, published Oct. 22, 1998; and PCT/US96/09290, published Dec. 19, 1996. Oxoazaheterocyclyl fibrinogen antagonists are disclosed in International Patent Application Number PCT/US92/09467, published May 13, 1993.

#### SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I



or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof

wherein

$G_1$  and  $G_2$  are  $L_1-Cy_1$  or  $L_2-Cy_2$ , provided that when  $R_1$  and  $R_{1a}$  or  $R_4$  and  $R_{4a}$  taken together form O or S, then  $G_1$  is  $L_2-Cy_2$  and  $G_2$  is  $L_1-Cy_1$ , or when  $R_2$  and  $R_{2a}$  or  $R_3$  and  $R_{3a}$  taken together form O or S, then  $G_1$  is  $L_1-Cy_1$  and  $G_2$  is  $L_2-Cy_2$ ;

$Cy_1$  and  $Cy_2$  are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted

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heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl,  
 optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally  
 substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcyloalkyl, optionally  
 substituted fused heteroarylcyloalkenyl, optionally substituted fused heteroarylheterocyclyl and  
 5 optionally substituted fused heteroarylheterocyclenyl;

$L_1$  is O,  $NR_5$ ,  $-S(O)_p-$ ,  $-S(O)_pNR_5-$ ,  $-C(X)Y-$  or  $-L_3-Q-L_4-Q'-L_5-$ ,

$L_3$  and  $L_5$  are independently absent, optionally substituted alkylene, optionally substituted alkenylene or  
 10 optionally substituted alkynylene;

$L_4$  is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted  
 alkynylene;

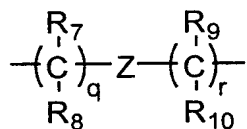
15  $Q$  and  $Q'$  are independently absent, O, S,  $NR_5$ ,  $-S(O)_p-$ ,  $-S(O)_pNR_5-$  or  $-C(X)Y-$ ;

$A$  is CH or N;

$R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_{2a}$ ,  $R_3$ ,  $R_{3a}$ ,  $R_4$  and  $R_{4a}$  are independently selected from hydrogen, carboxy, alkoxycarbonyl,  
 20  $Y^1Y^2NCO$ , optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl,  
 optionally substituted heteroaryl and optionally substituted heteroaralkyl, or  $R_1$  and  $R_{1a}$ ,  $R_2$  and  $R_{2a}$ ,  $R_3$   
 and  $R_{3a}$ , or  $R_4$  and  $R_{4a}$  taken together form O or S;

$m$  and  $n$  are independently 0, 1 or 2, provided that  $m$  and  $n$  are not both 0 and further provided that when  
 25  $R_1$  and  $R_{1a}$  taken together form O or S,  $n$  is 1 and when  $R_4$  and  $R_{4a}$  taken together form O or S,  $m$  is 1;

$L_2$  is absent or a group of formula



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R<sub>5</sub> is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, R<sub>6</sub>O(CH<sub>2</sub>)<sub>v</sub>-, R<sub>6</sub>O<sub>2</sub>C(CH<sub>2</sub>)<sub>x</sub>-, Y<sup>1</sup>Y<sup>2</sup>NC(O)(CH<sub>2</sub>)<sub>x</sub>-, or Y<sup>1</sup>Y<sup>2</sup>N(CH<sub>2</sub>)<sub>v</sub>-;

5 R<sub>6</sub> is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y<sup>1</sup> and Y<sup>2</sup> taken together with the N through which Y<sup>1</sup> and Y<sup>2</sup> are linked form a monocyclic heterocyclyl;

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R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R<sub>7</sub> and R<sub>8</sub> or one of R<sub>9</sub> and R<sub>10</sub> is hydroxy or alkoxy, and further provided when R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> is hydroxy or alkoxy, then the hydroxy or alkoxy is not α substituted to a N, O or S in Z;

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X is O or S;

Y is absent or is selected from O, S and NR<sub>5</sub>;

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Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkenylene, O, S(O)<sub>p</sub>, NR<sub>5</sub>, -NR<sub>5</sub>C(O)- and -C(O)NR<sub>5</sub>-;

x is 1, 2, 3 or 4;

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v is 2, 3 or 4;

p is 1 or 2; and

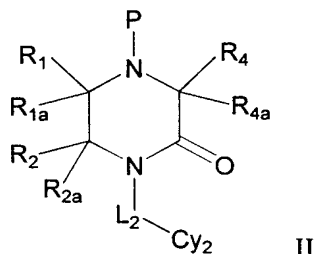
30 q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0.

In another aspect, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I and a pharmaceutically acceptable carrier.

In another aspect, this invention is directed to a method of treating a physiological disorder capable of being modulated by inhibiting Factor Xa comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I.

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In another aspect, this invention is directed to a compound of formula II



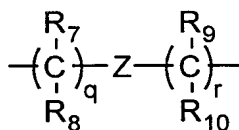
wherein

10 P is H or a nitrogen protecting group;

$R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_{2a}$ ,  $R_3$ ,  $R_{3a}$ ,  $R_4$  and  $R_{4a}$  are independently selected from hydrogen, carboxy, alkoxycarbonyl,  $Y^1Y^2NCO$ , optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

15

$L_2$  is a group of formula



20  $Cy_2$  is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroaryl cycloalkyl, optionally substituted fused heteroaryl cycloalkenyl, optionally substituted fused heteroaryl heterocyclyl and optionally substituted fused heteroaryl heterocyclenyl;

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$R_5$  is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl,  $R_6O(CH_2)_v$ -,  $R_6O_2C(CH_2)_x$ -,  $Y^1Y^2NC(O)(CH_2)_x$ -, or  $Y^1Y^2N(CH_2)_v$ -;



R<sub>6</sub> is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

- 5 Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y<sup>1</sup> and Y<sup>2</sup> taken together with the N through which Y<sup>1</sup> and Y<sup>2</sup> are linked form a monocyclic heterocyclyl;

- 10 R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R<sub>7</sub> and R<sub>8</sub> or one of R<sub>9</sub> and R<sub>10</sub> is hydroxy or alkoxy, and further provided when R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> is hydroxy or alkoxy, then the hydroxy or alkoxy is not α substituted to a N, O or S in Z;

- 15 Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkyneylene, O, S(O)<sub>p</sub>, NR<sub>5</sub>, -NR<sub>5</sub>C(O)- and -C(O)NR<sub>5</sub>-;

x is 1, 2, 3 or 4;

- 20 v is 2, 3 or 4; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0, which is an intermediate useful in the preparation of the compound of formula I.

## 25 DETAILED DESCRIPTION OF THE INVENTION

### Definitions

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

- 30 "Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be

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straight or branched. The alkyl may be substituted with one or more "alkyl group substituents" which may be the same or different, and include halo, cycloalkyl, hydroxy, alkoxy, amino, carbamoyl, acylamino, aroylamino, carboxy, alkoxy-carbonyl, aralkyloxy-carbonyl and heteroaralkyloxy-carbonyl. Representative alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl, benzyloxy-carbonylmethyl, and pyridylmethyloxy-carbonylmethyl.

"Alkenyl" means a straight or branched aliphatic hydrocarbon group containing a carbon-carbon double bond and having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more alkyl group substituents as defined herein. Representative alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, decenyl, and the like.

"Alkylene" means a straight or branched bivalent hydrocarbon chain having from 1 to about 20 carbon atoms. The preferred alkylene groups are the lower alkylene groups having from 1 to about 6 carbon atoms. Alkylene may be substituted with 1 or more alkyl group substituents as defined herein. Representative alkylene groups include methylene, ethylene, and the like.

"Alkenylene" means a bivalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. The preferred alkenylene groups are the lower alkenylene groups having from 1 to about 6 carbon atoms. Alkenylene may be substituted by one or more alkyl group substituents as defined herein. Representative alkenylene include -CH=CH-, -CH<sub>2</sub>CH=CH-, -C(CH<sub>3</sub>)=CH-, -CH<sub>2</sub>CH=CHCH<sub>2</sub>-, and the like.

"Alkynylene" means a bivalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon triple bond. Preferred alkynylene groups are the lower alkynylene groups having from 1 to about 6 carbon atoms. Alkynylene may be substituted by one or more alkyl group substituents as defined herein. Representative alkynylene include —CH≡CH—, —CH≡CH-CH<sub>2</sub>—, —CH≡CH-CH(CH<sub>3</sub>)—, and the like.

"Amidino" or "amidine" means a group of formula

$$\begin{array}{c} \text{NR}_{11} \\ | \\ \text{—C—NHR}_{12} \end{array}$$

wherein R<sub>11</sub> is selected from hydrogen, R<sub>6</sub>O<sub>2</sub>C-, R<sub>6</sub>O-, R<sub>6</sub>C(O)-, cyano, optionally substituted lower alkyl, nitro or Y<sup>1</sup>Y<sup>2</sup>N- and R<sub>12</sub> is selected from hydrogen, optionally substituted lower alkyl, optionally substituted aralkyl and optionally substituted heteroaralkyl. Preferred amidino groups are those in which R<sub>11</sub> is hydrogen, R<sub>6</sub>O, or optionally substituted lower alkyl and R<sub>12</sub> is as defined above. Most preferred amidino groups are those in which R<sub>11</sub> and R<sub>12</sub> are hydrogen.

"Basic nitrogen atom" means an  $sp^2$  or  $sp^3$  hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Examples of basic nitrogen atoms, which may be optionally substituted where possible, include those in heteroaryl, heterocyclyl, heterocyclenyl, fused arylheterocyclyl, fused arylheterocyclenyl, fused heteroaryl(cycloalkyl), fused heteroaryl(cycloalkenyl), fused heteroarylheterocyclyl, fused heterocyclylheterocyclenyl, imino, amino and amidino groups.

"Cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl rings include decalinyl, norbornyl, adamantyl, and the like. The cycloalkyl group is optionally substituted with one or more cycloalkyl group substituents which may be the same or different, where "cycloalkyl group substituent" includes oxo, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy-carbonyl, aryloxy-carbonyl, aralkoxy-carbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, amidino, amino, carbamoyl, or sulfamoyl. Preferred cycloalkyl group substituents are amino and amidino.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system containing a carbon-carbon double bond and having about 3 to about 10 carbon atoms. The cycloalkenyl group is optionally substituted by one or more cycloalkyl group substituents as defined herein. Representative monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl, and the like. A representative multicyclic cycloalkenyl ring is norbornenyl. Preferred cycloalkenyl group substituents are amino and amidino.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 ring atoms wherein the ring system contains one or more element(s) other than carbon.

"Azaheterocyclyl" means heterocyclyl wherein one or more of the atoms in the ring system is/are nitrogen. Preferred heterocyclyl comprise about 5 to about 6 ring atoms wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen or sulfur. "Aza", "oxo" or "thia", when used as a prefix before heterocyclyl means that the ring system contains at least one nitrogen, oxygen or sulfur atom. The heterocyclyl is optionally substituted with one or more heterocyclyl group substituents which may be the same or different, where "heterocyclyl group substituent" includes oxo, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, carboxyalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, aryloxy-carbonyl, aralkoxy-carbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, amino, carbamoyl, or sulfamoyl. Preferred heterocyclyl group substituents include amino, amidino, halogen, hydroxy, alkoxy-carbonylalkyl and carboxyalkyl. Representative heterocyclyl include piperidyl,

pyrrolidinyl, piperazinyl, pyrazolidinyl, imidazolanyl, tetrahydrofuryl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, 1,4-dithianyl, 1,3,5-triathianyl, tetrahydrothienyl, tetrahydrothiopyranyl, quinuclidinyl, and the like. The thio or nitrogen moiety of the heterocyclyl may also be optionally oxidized to the corresponding S-oxide, S,S-dioxide or N-oxide.

5 "Heterocyclenyl" means a heterocyclyl as defined herein which contains at least one carbon-carbon or carbon-nitrogen double bond. "Aza", "oxo" or "thia", when used as a prefix before heterocyclenyl means that the ring system contains at least one nitrogen, oxygen or sulfur atom. The heterocyclenyl is optionally substituted with one or more heterocyclyl group substituents as defined herein. Representative heterocyclenyl include 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolanyl, 10 2-pyrazolinyl, 2H-pyranyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,4-tetrahydropyridyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. Preferred heterocyclyl group substituents include amino, amidino, halogen, hydroxy, alkoxy carbonylalkyl and carboxyalkyl. The thio or nitrogen moiety of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

15 "Aryl" means a 6 to 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system. The aryl is optionally substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aryldiazo, heteroaryldiazo, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryloxy carbonyl, aralkoxy carbonyl, acylamino, aroylamino, 20 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, arylazo, heteroarylazo, amino, alkylamino, carbamyl and sulfamyl. Preferred aryl groups are optionally substituted phenyl or optionally substituted naphthyl. Preferred aryl group substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, 25 thiocarbamyl and amidino.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is/are element(s) other than carbon. Preferred heteroaryl contain one to about 4 heteroatoms selected from oxygen, nitrogen and sulfur. "Aza", "oxo" or "thia", when used as a prefix before heteroaryl means that the ring system contains at 30 least one nitrogen, oxygen or sulfur atom. The heteroaryl is optionally substituted with one or more aryl group substituents as defined herein. Representative heteroaryl groups include pyrrolyl, pyrazinyl, furyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thienopyridyl, pyrrolopyridyl, furanopyridyl, furazanyl, quinoxalanyl, quinazolinyl, quinoliziny, imidazo[1,2-a]pyridyl, phthalazinyl, imidazo[2,1-b]thiazolyl, benzofuranyl, 35 indolyl, isoindolyl, indoliziny, indazolyl, azaindolyl, benzimidazolyl, benzothienyl, benzisoxazolyl,

benzothiazolyl, purinyl, benzotriazolyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, imidazolyl, isoquinolinyl, cinnolinyl, triazinyl, benzotriazinyl, and the like. Preferred heteroaryl group substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy, carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. When heteroaryl  
5 contains a nitrogen atom, the nitrogen atom may be oxidized to the N-oxide.

“Fused arylcycloalkyl” means a fused aryl and cycloalkyl as defined herein. Preferred fused arylcycloalkyls are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 carbon atoms. Representative fused phenylcycloalkyl groups include 1,2,3,4-tetrahydronaphthyl, indanyl, and the like. The fused arylcycloalkyl is optionally substituted with one or more fused  
10 arylcycloalkyl group substituents selected from, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aryldiazo, heteroaryldiazo, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy, carbonyl, aryloxy, carbonyl, aralkoxy, carbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, arylazo, heteroarylazo, amino, alkylamino, carbamyl and  
15 sulfamyl. The cycloalkyl moiety is further optionally substituted with oxo. Preferred fused phenylcycloalkyl group substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy, carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino.

“Fused arylcycloalkenyl” means a fused aryl and cycloalkenyl as defined herein. Preferred fused  
20 arylcycloalkenyl are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 carbon atoms. The fused arylcycloalkenyl is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. Representative fused phenylcycloalkenyls include 1,2-dihydronaphthyl, indenyl, and the like. The cycloalkyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo,  
25 nitro, cyano, alkoxy, carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino.

“Fused arylheterocyclyl” means a fused aryl and heterocyclyl as defined herein. Preferred fused arylheterocyclyl are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms wherein one or two of the ring atoms is/are independently selected from oxygen,  
30 nitrogen and sulfur. “Aza”, “oxo” or “thia”, when used as a prefix before the heterocyclyl portion of the fused arylheterocyclyl means that the heterocyclyl contains at least one nitrogen, oxygen or sulfur atom. Representative preferred fused phenylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 1H-2,3-dihydroisoindolyl, 2,3-dihydrobenz[f]isoindolyl, 1,2,3,4-tetrahydrobenz[g]isoquinolinyl, and the like. The fused  
35 phenylheterocyclyl is optionally substituted with one or more fused phenylcycloalkyl group substituents

as defined herein. The heterocyclyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding

5 N-oxide, S-oxide or S,S-dioxide.

“Fused arylheterocyclenyl” means a fused aryl and heterocyclenyl as defined herein. “Aza”, “oxo” or “thia”, when used as a prefix before the heterocyclenyl portion of the fused arylheterocyclenyl means that the heterocyclenyl contains at least one nitrogen, oxygen or sulfur atom. Preferred fused arylheterocyclenyl are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to

10 about 6 ring atoms wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen and sulfur. Representative preferred fused arylheterocycloalkenyl ring systems include 3H-indolynyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, and the like. The fused arylheterocyclenyl is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen,

15 alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

“Fused heteroarylcyaloalkyl” means a fused heteroaryl and cycloalkyl as defined herein. “Aza”, “oxo” or “thia”, when used as a prefix before the heteroaryl portion of the fused heteroarylcyaloalkyl

20 means that the heteroaryl contains at least one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylcyaloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the cycloalkyl consists of about 5 to about 6 ring atoms. Representative preferred fused heteroarylcyaloalkyl include 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalynyl,

25 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidazole-[4,5]-pyridin-2-onyl, and the like. The fused heteroarylcyaloalkyl is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The cycloalkyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano,

30 alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. The nitrogen atom of the heteroaryl portion of the fused heteroarylcyaloalkyl is optionally oxidized to the N-oxide.

“Fused heteroarylcyaloalkenyl” means a 5- or 6-membered heteroaryl fused with a cycloalkenyl ring. “Aza”, “oxo” or “thia”, when used as a prefix before the heteroaryl portion of the fused

35 heteroarylcyaloalkenyl means that the cycloalkenyl contains at least one nitrogen, oxygen or sulfur

atom. Preferred fused heteroarylcyloalkenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the cycloalkenyl consists of about 5 to about 6 ring atoms. Representative preferred fused heteroarylcyloalkenyl include 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalyl, 5,6-dihydroquinazolyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, and the like. The fused heteroarylcyloalkenyl is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The cycloalkenyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. The nitrogen atom of the heteroaryl portion of the fused heteroarylcyloalkyl is optionally oxidized to the N-oxide.

“Fused heteroarylheterocyclyl” means a fused heteroaryl and heterocyclyl as defined herein. “Aza”, “oxo” or “thia”, when used as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl means that the heteroaryl or heterocyclyl contains at least one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylheterocyclyls are ring systems wherein one or two of the ring atoms of the heteroaryl are independently selected from oxygen, nitrogen and sulfur and the heterocyclyl portion consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur. Representative fused heteroarylheterocyclyl include 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2-yl, 2,3-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2-yl, 5,6,7,8-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa-4,6-diazanaphthalenyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro-5,8-diazanaphthalenyl, and the like. The fused heteroarylheterocyclyl is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. The nitrogen atom of the heteroaryl portion is optionally oxidized to the N-oxide. The nitrogen or sulphur atom of the heterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

“Fused heteroarylheterocyclenyl” means a fused heteroaryl and heterocyclenyl as defined herein. “Aza”, “oxo” or “thia”, when used as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl means that the heteroaryl or heterocyclenyl contains at least one nitrogen,

oxygen or sulfur atom. Preferred fused heteroaryl-cycloalkenyls are ring systems wherein the heteroaryl portion thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the heterocyclenyl portion consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen,  
5 nitrogen and sulfur. Representative fused heteroaryl-heterocyclenyl include 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, and the like. The fused heteroaryl-heterocyclenyl is optionally substituted with one or more fused aryl-cycloalkyl group substituents as defined herein. The heterocyclenyl moiety is further optionally substituted with oxo. Preferred substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl,  
10 aroyl, halo, nitro, cyano, alkoxy-carbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. The nitrogen atom of the heteroaryl portion is optionally oxidized to the N-oxide. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as defined herein. Preferred  
15 aralkyls contain a lower alkyl moiety. Representative aralkyl groups include benzyl, 2-phenethyl and naphthylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as defined herein. Preferred heteroaralkyls contain a lower alkyl moiety. Representative heteroaralkyl groups may contain thienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

20 "Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as defined herein. Preferred aralkenyls contain a lower alkenyl moiety. An representative aralkenyl group is 2-phenethenyl.

"Heteroaralkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as defined herein. Preferred heteroaralkenyls contain a lower alkenyl moiety. Representative  
25 heteroaralkenyl groups may contain thienylethenyl, pyridylethenyl, imidazolethenyl and pyrazinylethenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is defined herein. Preferred hydroxyalkyls contain lower alkyl. Representative hydroxyalkyl groups include hydroxymethyl and  
30 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which alkyl is defined herein. Preferred acyls contain a lower alkyl. Representative acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which aryl is defined herein. Representative aroyl groups include benzoyl and 1- and 2-naphthoyl.



"Aryldiazo" means an aryl-N=N- group in which aryl is defined herein. Representative aryldiazo groups include phenyldiazo and naphthyldiazo.

"Heteroaryl" means a heteroaryl-CO- group in which heteroaryl is defined herein. Representative heteroaryl groups include thiophenoyl and pyridinoyl.

5 "Heteroaryldiazo" means a heteroaryl-N=N- group in which heteroaryl is defined herein. Representative heteroaryldiazo groups include pyridyldiazo and thienyldiazo.

"Alkoxy" means an alkyl-O- group in which alkyl is defined herein. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

10 "Aryloxy" means an aryl-O- group in which aryl is defined herein. Representative aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in aralkyl is defined herein. Representative aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Alkylthio" means an alkyl-S- group in which alkyl is defined herein. Representative alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio.

15 "Arylthio" means an aryl-S- group in which the aryl group is defined herein. Representative arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which aralkyl is defined herein. A representative aralkylthio group is benzylthio.

20 "Amino" means a group of formula  $Y^1Y^2N-$  wherein  $Y^1$  and  $Y^2$  are defined herein. Preferred amino groups include amino ( $H_2N-$ ), methylamino, dimethylamino, diethylamino, benzylamino, or phenethylamino.

"Aminoalkyl" means a  $Y^1Y^2N$ -alkylene- group wherein  $Y^1$ ,  $Y^2$  and alkylene are defined herein.

"Alkoxy carbonyl" means an alkyl-O-CO- group wherein alkyl is defined herein. Representative alkoxy carbonyl groups include methoxycarbonyl, ethoxycarbonyl, or t-butyloxycarbonyl.

25 "Alkoxy carbonylalkyl" means an alkyl-O-CO-alkylene- group wherein alkyl and alkylene are defined herein.

"Aryloxy carbonyl" means an aryl-O-CO- group wherein aryl is defined herein. Representative aryloxy carbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

30 "Aralkoxy carbonyl" means an aralkyl-O-CO- group wherein aralkyl is defined herein. A representative aralkoxy carbonyl group is benzyloxycarbonyl.

"Carbamyl" means a group of formula  $Y^1Y^2NCO-$  wherein  $Y^1$  and  $Y^2$  are defined herein. Representative carbamyl groups are carbamyl ( $H_2NCO-$ ) and dimethylaminocarbamyl ( $Me_2NCO-$ ).

15

"Sulfamyl" means a group of formula  $Y^1Y^2NSO_2$ - wherein  $Y^1$  and  $Y^2$  are defined herein.

Representative sulfamyl groups are aminosulfamoyl ( $H_2NSO_2$ -) and dimethylaminosulfamoyl ( $Me_2NSO_2$ -).

"Acylamino" means an acyl-NH- group wherein acyl is defined herein.

5 "Aroylamino" means an aroyl-NH- group wherein aroyl is defined herein.

"Alkylsulfonyl" means an alkyl-SO<sub>2</sub>- group wherein alkyl is defined herein. Preferred alkylsulfonyl groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group wherein alkyl is defined herein. Preferred alkylsulfinyl groups are those in which the alkyl group is lower alkyl.

10 "Arylsulfonyl" means an aryl-SO<sub>2</sub>- group wherein aryl is defined herein.

"Arylsulfinyl" means an aryl-SO- group wherein aryl is defined herein.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Nitrogen protecting group" means an easily removable group which is known in the art to  
15 protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of N-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, CF, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred N-protecting groups are  
20 acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilyloxyethyl, vinyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl (BOC), 1,1-dimethylpropyloxycarbonyl,  
25 benzyloxycarbonyl (CBZ), p-nitrophenylsulfinyl, p-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, allyloxycarbonyl (Alloc), and the like.

"Oxo" means a carbonyl (>C=O) group.

"Compounds of the invention", and equivalent expressions, are meant to embrace compounds of  
30 general formula (I) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. It is understood that the activity of individual compounds of formula (I) will vary depending on the individual compound and assay employed. Compounds of the invention as used herein includes all compounds of formula (I) having an in-vitro activity of greater than 10% at 3.9  $\mu$ M in the Factor Xa in vitro enzyme assay described herein. Similarly, reference to intermediates, whether or not they themselves are

claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

5           “Prodrug” means a form of the compound of formula I which may or may not itself be biologically active but which may be converted, for example by metabolic, solvolytic, or other physiological means, to a biologically active chemical entity, and is suitable for administration to a patient without undue toxicity, irritation, allergic response, and the like, and effective for their intended use, including ketal, ester and zwitterionic forms. A prodrug is transformed in vivo to yield the parent  
10           compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

          “Solvate” means a physical association of a compound of this invention with one or more solvent  
15           molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Representative solvates include ethanolates, methanolates, and the like. “Hydrate” is a solvate wherein the solvent molecule(s) is/are H<sub>2</sub>O.

20           Where the compound of this invention is substituted with a basic moiety, acid addition salts may be formed. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically  
25           acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.

          Pharmaceutically acceptable salts within the scope of the invention are those derived from the following  
30           acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate,  
35           malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate,

methylene-bis- $\beta$ -hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

Acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial effects inherent in the free acid are not vitiated by side effects ascribable to the cations.

Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylenediamine, n-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, n-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as

tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

Compounds of this invention may exhibit stereoisomerism by virtue of the presence of one or more asymmetric or chiral centers in the compounds. The present invention contemplates the various stereoisomers and mixtures thereof. Desired enantiomers are obtained by chiral synthesis from commercially available chiral starting materials by methods well known in the art, or may be obtained from mixtures of the enantiomers by resolution using known techniques.

Compounds of this invention may also exhibit geometrical isomerism. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl or alkenylenyl moieties. The present invention comprises the individual geometrical isomers and stereoisomers and mixtures thereof.

#### 20 Preferred Embodiments

Compounds contemplated as falling within the scope of this invention, include, but are not limited to

- 4-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxo-piperazine-1-ylmethyl]benzamide,
- 4-[4-(4-Methoxy-benzenesulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 25 4-[4-(5-Chloro-thieno[3,2-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 4-[2-Oxo-4-(thieno[2,3-c]pyridine-2-sulfonyl)-piperazin-1-ylmethyl]-benzamide,
- 4-[4-(7-Chloro-thieno[2,3-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 4-[4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 30 4-[4-(4-Chloro-thieno[3,2-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 4-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamide,
- 4-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 4-Amino-3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,
- 3-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamide,
- 35 3-[4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamide,

- 3-[4-(4-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
3-[4-(5-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
3-[4-(6-Methoxy-naphthalene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
3-{4-[5-(5-Nitro-pyridine-2-sulfonyl)-thiophene-2-sulfonyl]-2-oxo-piperazin-1-ylmethyl}-benzamidine,  
5 3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]- benzamidine,  
3-{4-[2-(3-Chloro-phenyl)-ethenesulfonyl]-2-oxo-piperazin-1-ylmethyl}- benzamidine,  
3-[2-Oxo-4-(4-phenylazo-benzenesulfonyl)-piperazin-1-ylmethyl]-benzamidine,  
3-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]- benzamidine,  
4-[4-(6-Chloro-1H-benzimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
10 4-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl} benzamidine,  
3-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl} benzamidine,  
3-[4-(6-Chloro-1H-benzimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)piperazin-2-one,  
6-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]-1H-quinolin-2-one,  
15 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-3-ylmethyl-piperazin-2-one,  
1-(2-Amino-quinoxalin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-one,  
1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,  
20 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-hydroxy-isoquinolin-6-ylmethyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-6-ylmethyl)-piperazin-2-one,  
7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-7-ylmethyl)-piperazin-2-one,  
1-(7-Amino-thieno[2,3-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-  
25 one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-quinolin-6-ylmethyl-piperazin-2-one,  
7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-1H-quinolin-2-one,  
1-(2-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
30 1-(4-Amino-thieno[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-  
one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1,2,3,4-tetrahydro-isoquinolin-6-ylmethyl)-piperazin-2-  
one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-isoquinolin-6-ylmethyl-piperazin-2-one,  
35 1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-6-ylmethyl)-piperazin-2-one,  
 1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-7-ylmethyl)-piperazin-2-one,  
 1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
 5 1-(4-Amino-thieno[3,2-c]pyridin-3-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
 (+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid,  
 (+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid,  
 10 1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,  
 1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,  
 15 (3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-piperazin-2-one,  
 (3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-piperazin-2-one,  
 (S)-4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one,  
 20 1-(2-Amino-quinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,  
 1-(2-Aminoquinolin-6-ylmethyl)-4-(4-methoxybenzyl)piperazin-2-one,  
 1-(2-Aminoquinolin-6-ylmethyl)-4-6-chlorobenzo[b]thiophen-2-ylmethyl)piperazin-2-one,  
 1-(2-Aminoquinolin-6-ylmethyl)-4-(5-methoxy-1H-benzoimidazol-2-ylmethyl)piperazin-2-one,  
 25 1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)piperazin-2-one,  
 1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,  
 1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]piperazin-2-one,  
 3-[4-(2-Aminoquinolin-6-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one,  
 30 1-(2-Aminoquinolin-6-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one,  
 3-(4-Biphenyl-3-ylmethyl-3-oxo-piperazin-1-ylmethyl)-benzamidine,  
 4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-piperazin-2-one,  
 1,4-Bis-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,  
 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one,

- 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,
- 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,
- 5 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-,
- 4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
- 4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-benzamidine,
- 4-(4-Cyclohexylmethyl-2-oxo-piperazin-1-ylmethyl)-benzamidine,
- 10 1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one,
- 15 4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,
- (S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one,
- (S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one,
- 20 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one,
- 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 3-chloro-benzylamide,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one,
- 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 4-chloro-benzylamide,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-isoxazol-3-yl-thiophene-2-sulfonyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one,
- 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(3-chloro-phenyl)-ethyl]-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(4-chloro-phenyl)-ethyl]-amide,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,
- 4-(3-Amino-benzenesulfonyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-ethyl-piperazin-2-
- 35 one,



- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methyl-piperazin-2-one,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,
- (+/-)-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-piperazin-10 2-yl]-acetic acid,
- 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,
- 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 15 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-6-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-thieno[3,2-d]pyrimidin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-7-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one,
- 1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-25 one,
- 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(5-oxy-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 30 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-(3-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-(6-Bromobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,

- 2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]-benzo[b]thiophene-6-carbonitrile,
- 4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-[2-(4-Chlorophenyl)ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 5 {2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid,
- 4-(5-Pyridin-4-ylthiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- {2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid ethyl ester,
- 10 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-methoxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one,
- 4-(6-Chlorothiemo[3,2-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[2,3-c]pyridin-1-yl} acetic acid methyl ester,
- 15 2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]benzo[b]thiophene-5-carbonitrile,
- 4-(5-Aminomethylbenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 2-{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetamide,
- 20 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one,
- 4-(6-Chloro-1H-benzimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(1H-Benzimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 25 4-(6-Aminomethyl-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,
- 1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one,
- 4-[2-(5-Chloro-thiophen-2-yl)-ethanesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 30 4-(2-Benzo[b]thiophen-2-yl-ethanesulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[2-(5-Chloro-4-methoxy-thiophen-2-yl)-ethanesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one,
- 4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one,
- 35 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one,

- 4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one,  
{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[2,3-c]pyridin-1-yl}-acetic acid methyl ester,
- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one,  
5 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)piperazin-2-one,
- 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
(±)-1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-  
10 piperazine-2-carboxylic acid methyl ester,  
(±)-1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,  
(±)-1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid,  
15 (±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
(-)-1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,  
(+)-1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-  
20 piperazine-2-carboxylic acid methyl ester,  
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
25 (±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,  
(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,  
(±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-  
30 piperazine-2-carboxylic acid,  
(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid,  
(±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

- (±)-4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- (±)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid amide,
- 5 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 10 4-[2-(4-Chloro-phenyl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-ylmethyl)piperazin-2-one,
- 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzimidazol-2-ylmethyl)piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzothiazol-2-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzothiazol-2-ylmethyl)-piperazin-2-one,
- 3-[4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-(E)-enyl]-piperazin-2-one
- ditrifluoroacetate,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-2-methyl-(E)-allyl]-piperazin-2-one
- ditrifluoroacetate,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-furan-2-yl)-(E)-allyl]-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-methoxy-pyridin-3-yl)-(E)-allyl]-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-4-oxy-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-prop-2-ynyl]-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-2-yl-prop-2-ynyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-indol-2-ylmethyl)-piperazin-2-one,
- 35 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-4-methyl-thiophen-2-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-5-ylmethyl)-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,7-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-p-tolyl-prop-2-ynyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-m-tolyl-prop-2-ynyl)-piperazin-2-one,  
10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-4-yl-prop-2-ynyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4,5-dibromo-thiophen-2-yl)-allyl]-piperazin-2-one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-3-yl-prop-2-ynyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-thiophen-3-yl)-prop-2-ynyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-propyl]-piperazin-2-one,  
1,4-Bis-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one,  
20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-nitro-thiophen-2-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-pyridin-3-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-allyl]-piperazin-2-one,  
25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-methyl-thiophen-2-yl)-penta-2,4-dienyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-5-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methyl-thiophen-2-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methoxy-thiophen-2-yl)-allyl]-piperazin-2-one,  
4-(1-Amino-7-chloro-isoquinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,  
30 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-acetamide,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenyl)-2-(S)-hydroxy-ethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-methylene-1,1-dioxo-2,3-dihydro-1H-11 6-benzo[b]thiophen-3-  
35 yl)-piperazin-2-one ,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-nitro-phenyl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-6-ylmethyl)-piperazin-2-one,  
2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(4-chloro-phenyl)-acetamide,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propyl]-piperazin-2-one,  
2-[4-(4-Aminoquinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chlorophenyl)-acrylic acid,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-1-hydroxy-isoquinolin-3-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one,  
10 1-(4-Amino-quinazolin-7-ylmethyl)-4-isoquinolin-3-ylmethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(3-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(1,7-dichloro-isoquinolin-3-ylmethyl)-piperazin-2-one,  
4-(2-Amino-7-chloro-quinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,  
1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(6-chloro-benzo[b]thiophen-2-yl)-ethyl]-piperazin-2-one,  
1-(4-Aminoquinazolin-7-ylmethyl)-4-[2-(4-chloro-phenoxy)-ethyl]-piperazine-2-one,  
2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-4H-benzo[1,4]thiazin-3-  
one,  
20 1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,7-dichloro-quinolin-3-ylmethyl)-piperazin-2-one,  
2-[[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-(4-chloro-phenyl)-methyl]-acrylic acid  
ethyl ester,  
2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chloro-phenyl)-acrylic acid  
ethyl ester,  
25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-allyl]-piperazin-2-one,  
3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one,  
30 3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinoxalin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-benzimidazol-2-ylmethyl)-piperazin-2-  
one,  
2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-3H-quinazolin-4-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-thiophen-2-yl-propyl)-piperazin-2-one,  
35 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-quinolin-3-ylmethyl)-piperazin-2-one,

- 3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5,7-dichloro-1H-quinolin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6,7-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-1H-quinolin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-[2,3']bithiophenyl-5'-ylmethyl)-piperazin-2-one,  
5 4-(6-Amino-benzo[b]thiophen-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-1H-benzimidazol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-nitro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one,  
10 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-piperazin-2-  
one,  
3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinolin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-trifluoromethyl-1H-benzimidazol-2-ylmethyl)-piperazin-2-  
one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3,3'-dimethyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-  
2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-  
20 ylmethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-  
25 one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-benzimidazol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-bromo-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-oxazol-2-ylmethyl]-  
piperazin-2-one,  
30 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4,5-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-  
one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-benzooxazol-2-yl-benzyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2,2']bithiophenyl-5-ylmethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-fluoro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(1-methyl-5-trifluoro-methyl-1H-pyrazol-3-yl)-thiophen-2-ylmethyl]-piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophen-2-ylmethyl] piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-nitro-phenyl)-furan-2-ylmethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-6-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-methoxy-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-hydroxy-2-pyridin-2-yl-pyrimidin-5-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-fluoro-phenoxy)-benzyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-benzo[b]thiophen-2-ylmethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-bis-trifluoromethyl-benzyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-biphenyl-4-ylmethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-naphthalen-2-ylmethyl-piperazin-2-one,
- 35 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-3-ylmethyl)-piperazin-2-one,



- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-piperazin-2-one,  
1-(4-Aminoquinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-thiophene-2-carbonyl)-piperazin-2-one,  
4-[3-(3-Amino-4-chloro-phenyl)-(E)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,  
5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-amide,  
10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one,  
15 5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-methyl-2-oxo-ethyl}-amide,  
5-Chloro-thiophene-2-carboxylic acid {3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-amide,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one,  
20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one,  
N-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-(5-chloro-thiophen-2-ylmethyl)-2-oxo-ethyl]-benzamide,  
25 N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-benzamide,  
N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-acetamide,  
30 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yl)-acetyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one,  
2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-6-chloro-4H-benzo[1,4]thiazin-3-one,  
35 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-benzo[b]thiophen-2-yl)-acetyl]-piperazin-2-one,

- 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid 4-chloro-benzylamide,  
4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-ylmethyl)amide,  
4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide,  
5 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3-amino-4-chloro-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,  
10 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester,  
15 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-carboxylic acid 6-chloro-benzooxazol-2-ylmethyl ester,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 1-(3-chloro-phenyl)-pyrrolidin-3-yl ester,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
20 4-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-methyl-piperazin-2-  
25 one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methyl-piperazin-  
30 2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-benzoimidazol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-  
10 2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-3-(S)-methyl-piperazin-2-one,  
20 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,  
25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-methyl-piperazin-2-one,  
30 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-piperazin-2-one,  
35 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-
- 15 thiophen-3-yl)-acetamide,
- (2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one,
- (2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-
- 25 one,
- (2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-(3S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-ethyl-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-
- 35 one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-1H-pyrrole-2-carbonyl]-3-(S)-ethyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-3-(S)-ethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-3-(S)-ethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propionyl]-3-(S)-ethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethyl-4-[3-(4-methoxy-phenyl)-propionyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-ethyl-piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,
- 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,
- 25 one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one,
- 30 one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(R)-methoxymethyl-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-3H-imidazol-4-yl-acryloyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- (1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-fluoro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenoxy)-propionyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-[(4-trifluoromethylsulfanyl-phenoxy)-acetyl]-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- (2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-ylsulfanyl)-acetyl]-3-(S)-methoxymethyl-
- 10 piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-
- 20 piperazin-2-one,
- (2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester,
- (2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,3-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-
- 30 one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,4-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,



- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,  
(1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(R)-methoxymethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-  
10 piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethoxymethyl-4-[(3-fluoro-phenoxy)-acetyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethoxymethyl-piperazin-2-one,  
20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-  
25 piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one,  
30 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one,  
35 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-isopropyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,3-dimethyl-piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,3-dimethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,3-dimethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3,3-dimethyl-piperazin-2-one,
- 20 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one,
- 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-(2-methoxy-ethyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(S)-methyl-piperazin-2-one,
- 30 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-6-methyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(R)-methyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-6-
- 35 methyl-piperazin-2-one,

- (1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-6-dimethyl-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-  
10 methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-4-fluoro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-phenyl)-acryloyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-2-methyl-phenoxy)-acetyl]-3(S)-methoxymethyl-6-  
20 methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,  
25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3(S)-ethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-ethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-  
30 piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one,  
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one,

- (S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3(S)-6-dimethyl-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-6-methyl-piperazin-2-one,  
10 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-  
15 thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,  
20 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-3-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-  
25 thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-bromo-phenyl)-amide,  
30 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-2-methoxy-phenyl)-amide,  
4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-  
35 bromo-2-chloro-phenyl)-amide,

- 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-trifluoromethoxy-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide,
- 5 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-dichloro-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-difluoro-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide,
- 10 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide,
- 15 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-5-(R,S)-methyl-3-oxo-piperazine-1-
- 20 carboxylic acid (4-chloro-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
- 25 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
- 4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-4-methoxy-thiophen-2-yl)-amide,
- (3S, 5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-
- 30 piperazin-2-one,
- (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,
- (3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,

- (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,  
(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,  
5 (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-sulfonyl)-3,5-dimethyl-piperazin-2-one,  
(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-piperazin-2-one,  
(3S, 5R)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-  
10 phenyl)-amide,  
(3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide,  
(3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,  
15 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one,  
  
1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,  
(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-methyl-piperazin-2-one,  
20 (3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,  
(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,  
(S,R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-  
25 carboxylic acid,  
1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide,  
1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,  
30 1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,  
1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,  
(S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one,  
35 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

- (3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one,  
(3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one,  
5 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-methyl-piperazin-2-one,  
(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-methyl-piperazin-2-one,  
(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,  
(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-  
10 2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,  
(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-ethyl-piperazin-2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-3-((R)-1-methoxy-ethyl)-  
piperazin-2-one,  
15 1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-(S)-3-((R)-1-methoxy-ethyl)-  
piperazin-2-one,  
(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-  
one,  
(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methyl-piperazin-2-one,  
20 4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(2-hydroxy-ethylamino)-quinolin-7-ylmethyl]-piperazin-2-one,  
(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one,  
(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methoxymethyl-  
piperazin-2-one,  
(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-  
25 one,  
(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-  
piperazin-2-one,  
(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-4-oxy-piperazin-2-  
one,  
30 (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-  
piperazin-2-one,  
4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-(S)-3-ethyl-1-(4-hydroxyamino-quinolin-7-ylmethyl)-piperazin-  
2-one,  
35 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one,

- (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one,  
 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,  
 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one,  
 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-  
 5 piperazin-2-one,  
 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one,  
 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one,  
 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-6-  
 methyl-piperazin-2-one,  
 10 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-3-(1-(R)-methoxy-ethyl)-  
 piperazin-2-one,  
 1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)-acryl-oyl]-3-(S)-(1-(R)-methoxyethyl)-  
 piperazin-2-one trifluoroacetate,  
 1-(4-Aminoquinolin-7-ylmethyl)-4-[(5-chlorothiophen-2-yloxy-acetyl]-3-(S)-(1-(R)-methoxyethyl)-  
 15 piperazin-2-one trifluoroacetate,  
 (S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one,  
 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,  
 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(methyl-pyridin-4-yl-amino)-ethyl]-piperazin-2-one,  
 20 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-  
 one,  
 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,  
 4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 25 1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one,  
 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(methylpyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
 30 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-yl-ethyl)-piperazin-2-one,  
 1-[2-(2-Amino-3-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-  
 piperazin-2-one,  
 1-[2-(2-Amino-5-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-  
 piperazin-2-one,



- 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(2,3,5,6-tetrachloro-pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
1-[2-(2-Amino-3,5,6-trichloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,
- 5 4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridazin-4-yl-amino)-ethyl]-piperazin-2-one,  
1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,  
1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 10 1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,  
1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,  
4-[2-(5-Chlorothiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,  
4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.
- 15 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(6-Chloro-1H-benzimidazol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(5-Chloro-1H-indol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 20 4-(6-Chloro-naphthalen-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(7-Chloro-isoquinolin-3-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester,  
1-(5-Chloro-1H-indol-2-ylmethyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester,
- 25 1-[(5-Chloro-thiophen-2-yloxy)-acetyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,  
1-(6-Chloro-benzo[b]thiophene-2-carbonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,
- 30 1-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester,  
1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(3-Phenyl-prop-2-ynyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-[3-(5-Chloro-thiophen-2-yl)-prop-2-ynyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

- 4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 5 4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 10 4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- (S)-2-Methoxymethyl-3-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
- 15 (S)-4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one,
- 4-[3-(6-Chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 20 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(5'-Chloro-[2,2']bithiophenyl-5-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(5-Chloro-1H-indole-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 25 4-[4-(6-Methoxy-pyridin-3-yl)-benzoyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-(4-Pyridin-3-yl-benzoyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[3-(4-Bromo-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[3-(5-Chloro-thiophen-2-yl)-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 30 4-[2-(4-Chloro-phenyl)-2-methyl-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[3-(3,4-Dichloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[(4-Chloro-phenyl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 35 4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

- (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,
- (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,
- 5 (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-
- 10 carboxylic acid dimethylamide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid benzylamide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide,
- 15 (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid bis-(2-hydroxy-ethyl)-amide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-
- 20 carboxylic acid methylcarbamoylmethyl-amide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-
- carboxylic acid methyl ester,
- 25 (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid amide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid ethylamide,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-(4-methyl-piperazine-1-
- 30 carbonyl)-piperazin-2-one,
- (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,
- (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

- (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide,  
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester,  
5 (+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,  
(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide,  
(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-  
10 carboxylic acid ethylamide,  
(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,  
(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,  
15 (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,  
(±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methylamide,  
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-  
20 carboxylic acid ethylamide,  
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid,  
4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.  
1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
25 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzotrile,  
4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzamidine,  
1-(4-Amino-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one,  
4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(2,4-diamino-quinazolin-7-ylmethyl)-piperidin-2-one,  
1-(4-Amino-2-methyl-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-  
30 one,  
(3S, 5R)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
(3S,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
35 4-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl}-benzamidine,

- (3R,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine,
820. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide,
- 5 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-4-yl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-3-ylmethyl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-piperidin-4-yl-acetamide,  
N-(1-Carbamimidoyl-piperidin-4-yl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,
- 10 5-(2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetylamino}-ethyl)-imidazole-1-carboxylic acid ethyl ester,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyrimidin-4-yl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-phenyl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(9H-purin-6-yl)-acetamide,
- 15 N-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-imidazol-1-yl-propyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-imidazol-4-yl)-ethyl]-acetamide,
- 20 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-4-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(3-methyl-3H-imidazol-4-yl)-ethyl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-2-yl-ethyl)-acetamide,
- 25 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-3-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-imidazol-1-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]-acetamide,
- 30 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(4-dimethylamino-[1,3,5]triazin-2-yl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-pyridin-4-yl-acetamide,

- N-[2-(2-Amino-pyridin-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(4-methyl-thiazol-5-yl)-ethyl]-acetamide,  
5 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-thiazol-4-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-guanidino-propyl)-acetamide trifluoroacetic acid salt,  
N-(3-Amino-propyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-mercapto-1H-imidazol-4-yl)-ethyl]-acetamide,  
10 N-[2-(2-Amino-thiazol-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-(2-pyridin-4-yl-ethyl)-acetamide,  
15 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-methylsulfanyl-1H-imidazol-4-yl)-ethyl]-acetamide,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one,  
4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamidine,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperazin-1-yl-propyl)-piperazin-2-one,  
20 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-pyridin-4-yl-propyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-piperidin-4-yl-butyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-piperidin-4-yl-ethyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperidin-4-yl-propyl)-piperazin-2-one,  
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-  
25 piperazin-2-one,  
4'-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-3-hydroxy-benzyl)-piperazin-2-one,  
1-Benzyl-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-benzyl)-piperazin-2-one,  
30 4-[(4-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,  
4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,  
4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-  
35 piperazin-2-one,

- 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one,
- 5 4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,
- 1-Biphenyl-4-ylmethyl-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one,
- 4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-
- 10 methoxymethyl-piperazin-2-one,
- 4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,
- 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,
- 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one,
- 15 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(S)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamide,
- 4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(R)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamide,
- 20 3-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamide and
- 4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamide.

Preferred compounds have formula I wherein  $Cy_2$  contains at least one nitrogen atom and when  $Cy_2$  is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl,

25 optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

Other preferred compounds have formula I wherein Z is absent or is selected from O,  $S(O)_p$  and  $NR_5$ ,

30

Other preferred compounds have formula I wherein Z is  $-NR_5C(O)-$  or  $-C(O)NR_5-$ .

Preferred compounds wherein Z is  $-NR_5C(O)-$  or  $-C(O)NR_5-$  are selected from

2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-

35 ethyl]acetamide,

- 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-4-yl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-3-ylmethyl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-piperidin-4-yl-acetamide,  
N-(1-Carbamimidoyl-piperidin-4-yl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,  
5 5-(2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetylamino}-ethyl)-imidazole-1-carboxylic acid ethyl ester,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyrimidin-4-yl-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-phenyl-acetamide,  
10 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(9H-purin-6-yl)-acetamide,  
N-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-imidazol-1-yl-propyl)-acetamide,  
15 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-imidazol-4-yl)-ethyl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-4-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(3-methyl-3H-imidazol-4-yl)-ethyl]-acetamide,  
20 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-2-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-3-yl-ethyl)-acetamide,  
25 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-imidazol-1-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-acetamide,  
30 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(4-dimethylamino-[1,3,5]triazin-2-yl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-pyridin-4-yl-acetamide,



N-[2-(2-Amino-pyridin-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(4-methyl-thiazol-5-yl)-ethyl]-acetamide,

- 5 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-thiazol-4-yl-ethyl)-acetamide,  
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-guanidino-propyl)-acetamide  
trifluoroacetic acid salt,

N-(3-Amino-propyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,

- 10 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-mercapto-1H-imidazol-4-yl)-ethyl]-acetamide,

N-[2-(2-Amino-thiazol-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-(2-pyridin-4-yl-ethyl)-acetamide, or

- 15 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-methylsulfanyl-1H-imidazol-4-yl)-ethyl]-acetamide,

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

- 20 Other preferred compounds have formula I wherein m is 1; and n is 1.

Other preferred compounds have formula I wherein A is N.

- 25 Other preferred compounds have formula I wherein R<sub>3</sub> and R<sub>3a</sub> taken together are O; and R<sub>1</sub>, R<sub>1a</sub>, R<sub>2</sub>, R<sub>2a</sub>, R<sub>4</sub> and R<sub>4a</sub> are hydrogen.

Other preferred compounds have formula I wherein R<sub>3</sub> and R<sub>3a</sub> taken together are O; R<sub>1</sub>, R<sub>1a</sub>, R<sub>2</sub>, R<sub>2a</sub> and R<sub>4</sub> are hydrogen; and R<sub>4a</sub> is optionally substituted alkyl.

- 30 Other preferred compounds have formula I wherein R<sub>3</sub> and R<sub>3a</sub> taken together are O; R<sub>1</sub>, R<sub>1a</sub>, R<sub>2</sub> and R<sub>4</sub> are hydrogen; and R<sub>2a</sub> and R<sub>4a</sub> are optionally substituted alkyl.

Other preferred compounds have formula I wherein R<sub>3</sub> and R<sub>3a</sub> taken together are O; R<sub>1</sub>, R<sub>2</sub>, R<sub>2a</sub> and R<sub>4</sub> are hydrogen; and R<sub>1a</sub> and R<sub>4a</sub> are optionally substituted alkyl.

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Other preferred compounds have formula I wherein  $R_3$  and  $R_{3a}$  taken together are O;  $R_1$ ,  $R_2$ ,  $R_{2a}$ ,  $R_4$  and  $R_{4a}$  are hydrogen; and  $R_{1a}$  is carboxy, alkoxy carbonyl,  $Y^1Y^2NCO$  or optionally substituted alkyl.

Other preferred compounds have formula I wherein  $R_3$  and  $R_{3a}$  taken together are O; and  $R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_4$  and  $R_{4a}$  are hydrogen; and  $R_{2a}$  is carboxy, alkoxy carbonyl,  $Y^1Y^2NCO$  or optionally substituted alkyl.

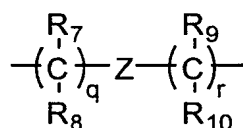
Other preferred compounds have formula I wherein  $L_1$  is  $-S(O)_p-$ ,  $-C(X)Y-$  or  $-L3-Q-L4-Q'-L5-$ .

Other preferred compounds have formula I wherein  $Cy_1$  is optionally substituted aryl or optionally substituted heteroaryl.

More preferred compounds have formula I wherein  $L_2$  is alkylene of one to three carbon atoms.

Other more preferred compounds have formula I wherein  $L_2$  is  $-CH_2-$ .

Other more preferred compounds have formula I wherein  $L_2$  is a group of formula



wherein  $Z$  is  $NR_5$ ;  $q$  is 2;  $r$  is 0;  $R_5$  is hydrogen or optionally substituted alkyl; and  $R_7$  and  $R_8$  are hydrogen.

Other more preferred compounds have formula I wherein  $R_5$  is hydrogen.

Other more preferred compounds have formula I wherein  $Cy_2$  is optionally substituted aryl or optionally substituted heteroaryl.

Other more preferred compounds have formula I wherein  $L_1$  is  $-S(O)_2-$ .

Other more preferred compounds have formula I wherein  $L_1$  is  $-C(X)Y-$ ;  $X$  is O; and  $Y$  is NH.

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Other more preferred compounds have formula I wherein  $L_1$  is -L3-Q-L4-Q'-L5-; Q is -S(O)<sub>2</sub>- or -C(O)-; and  $L_4$  is optionally substituted alkenylene.

Other more preferred compounds have formula I wherein  $L_1$  is -L3-Q-L4-Q'-L5-; and  $L_4$  is  
5 optionally substituted alkylene.

Other more preferred compounds have formula I wherein  $L_1$  is -L3-Q-L4-Q'-L5-; Q is -C(O)-; Q' is O; and  $L_4$  is optionally substituted alkylene.

10 Other more preferred compounds have formula I wherein  $L_1$  is -L3-Q-L4-Q'-L5-;  $L_3$  is optionally substituted alkylene; and  $L_4$  is optionally substituted alkenylene.

Other more preferred compounds have formula I wherein  $Cy_1$  is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl,  
15 optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

Other more preferred compounds have formula I wherein  $Cy_2$  is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl,  
20 optionally substituted isoquinolinyl, optionally substituted quinazoliny, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

Still more preferred compounds are selected from

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-  
25 piperazin-2-one,

1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-  
ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one,  
30 (S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-  
one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one,

35 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-4-oxy-piperazin-2-one,

- 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,  
4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-  
piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-  
piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-  
piperazin-2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-4-oxy-piperazin-2-  
one,  
1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-  
piperazin-2-one,
- 15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethoxymethyl-piperazin-  
2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-  
one,
- 20 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-((S)-1-(R)-methoxy-ethyl)-  
piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(R)-  
carboxylic acid ethyl ester,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one,
- 25 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one,  
3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-butyl-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-piperazin-2-one,  
4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one,
- 30 1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-  
2-carboxylic acid methyl ester,

- (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 10 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,
- 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-
- 15 piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-6-methyl-
- 20 piperazin-2-one,
- (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3,5-dimethyl-piperazin-2-one,
- (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one,
- 25 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-6-dimethyl-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one,
- 30 1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one,
- (4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,
- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-ethyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamide,
- 35 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

- 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-  
piperazin-2-one,  
4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-(S)-propyl-piperazine-1-carboxylic acid (5-chloro-  
5 thiophen-2-yl)-amide,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-  
one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-  
piperazin-2-one,  
10 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-  
thiophen-2-yl)-amide,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-6-methyl-  
piperazin-2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,  
15 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-  
piperazin-2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-  
one,  
20 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzimidazole-2-sulfonyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxy-ethyl)-1H-pyrrolo[3,2-c]pyridin-2-  
ylmethyl]-piperazin-2-one,  
4-(6-Bromo-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-  
25 piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-6-  
methyl-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-  
2-carboxylic acid,  
30 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-6-methyl-  
piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-6-methyl-  
piperazin-2-one,  
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-  
35 piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,  
5 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,  
(3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3, 5-dimethyl-piperazin-2-one,  
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-  
10 piperazine-2-carboxylic acid methyl ester,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(R)-carboxylic acid methyl ester,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid methyl ester,  
15 1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-(R)-hydroxymethyl-3-(S)-methoxymethyl-piperazin-2-one,  
1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-  
20 piperazin-2-one,  
4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,  
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-  
25 2-carboxylic acid amide  
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,  
(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,  
30 1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one,  
4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide,  
4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,  
35 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)- propyl-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one,
- 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-
- 5 thiophen-2-yl)-amide,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)- propyl-piperazin-2-one,
- (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-
- 10 2-carboxylic acid amide,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)- propyl-piperazin-2-one,
- 15 1-(4-Amino-cinnolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,
- 20 1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-
- 25 methyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid ethyl ester,
- 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
- 30 1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,
- (3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3, 5-dimethyl-piperazin-2-one,
- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one,
- 1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,