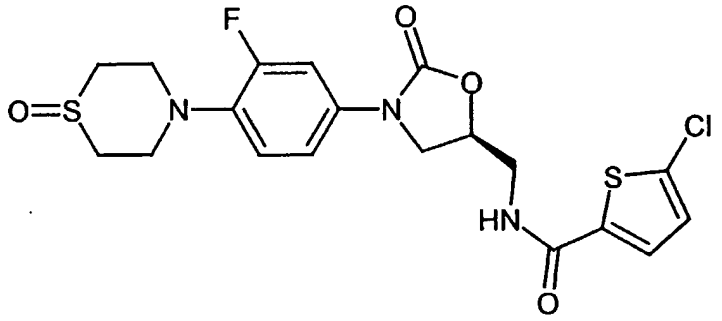
Die folgenden Beispiele 14 bis 16 sind Ausführungsbeispiele für den fakultativen, d.h. gegebenenfalls stattfindenden Oxidationsverfahrensschritt.

Beispiel 14

5-Chloro-N-({(5S)-3-[3-fluoro-4-(1-oxo-1[lambda]^4,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid



5-Chloro-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid (0.1 g, 0.22 mmol) aus Beispiel 3 in Methanol (0.77 ml) wird bei 0°C zu einer Lösung von Natriumperiodat (0.05 g, 0.23 mmol) in Wasser (0.54 ml) gegeben und 3 h bei 0°C gerührt. Anschließend gibt man 1 ml DMF hinzu und rührt 8 h bei RT. Nach Zugabe von weiteren 50 mg Natriumperiodat wird nochmals über Nacht bei RT gerührt. Man versetzt anschließend den Ansatz mit 50 ml Wasser und saugt das unlösliche Produkt ab. Man erhält nach Waschen mit Wasser und Trocknen 60 mg (58 % d. Th.) Kristalle.

Smp.: 257°C;

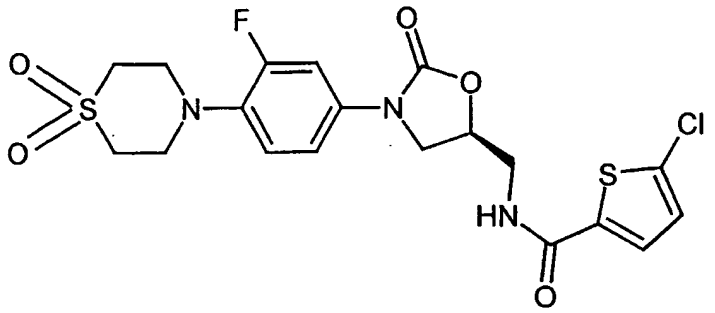
R_f (Kieselgel, Toluol/Essigester 1:1) = 0.54 (Edukt = 0.46);

IC_{50}-Wert = 1.1 µM;

MS (DCI) 489 ($M+NH_4$), Cl-Muster.

Beispiel 15

Darstellung von 5-Chloro-N-({(5S)-3-[4-(1,1-dioxo-1[lambda]^6,4-thiazinan-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid



Man versetzt 5-Chloro-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid aus Beispiel 3 (0.1 g, 0.22 mmol) in 3.32 ml einer Mischung von 1 Teil Wasser und 3 Teilen Aceton mit 80 mg (0.66 mmol) N-Methylmorpholin-N-oxid (NMO) und 0.1 ml einer 2.5 %igen Lösung von Osmiumtetroxid in 2-Methyl-2-propanol. Man rührt über Nacht bei Raumtemperatur und gibt nochmals 40 mg NMO hinzu. Nachdem eine weitere Nacht gerührt wurde, gibt man den Ansatz in 50 ml Wasser und extrahiert dreimal mit Essigester. Aus der organischen Phase erhält man nach Trocknen und Eindampfen 23 mg und aus der wässrigen Phase nach Absaugen des unlöslichen Feststoffs 19 mg (insges. 39% d. Th.) der Zielverbindung.

Smp.: 238°C;

R_f (Toluol/Essigester 1:1) = 0.14 (Edukt = 0.46);

IC_{50}-Wert = 210 nM;

MS (DCI): 505 ($M+NH_4$), Cl-Muster.

Beispiel 16

5-Chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophencarboxamid N-oxid

wird durch Behandeln von 5-Chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophencarboxamid aus Beispiel 1 mit Monoperoxyphthalsäure-Magnesiumsalz erhalten.
MS (ESI): 456 (M+H, 21%, Cl-Muster), 439 (100%).

Die folgenden Beispiele 31 bis 35 und 140 bis 147 beziehen sich auf den fakultativen, d.h. gegebenenfalls stattfindenden Amidinierungsverfahrensschritt.

Allgemeine Methode zur Darstellung von Amidinen und Amidinderivaten ausgehend von cyanomethylphenylsubstituierten 5-Chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid Derivaten

Das jeweilige cyanomethylphenylsubstituierte 5-Chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid-Derivat (1.0 eq.) wird zusammen mit Triethylamin (8.0 eq.) für ein bis zwei Tage bei RT in einer gesättigten Lösung von Schwefelwasserstoff in Pyridin gerührt (ca. 0.05 – 0.1 mol/l). Das Reaktionsgemisch wird mit Ethylacetat (EtOAc) verdünnt und mit 2 N Salzsäure gewaschen. Die organische Phase wird mit $MgSO_4$ getrocknet, filtriert und im Vakuum eingedampft.

Das Rohprodukt wird in Aceton gelöst (0.01-0.1 mol/l) und mit Methyliodid (40 eq.) versetzt. Das Reaktionsgemisch wird 2 bis 5 h bei Raumtemperatur (RT) gerührt und dann im Vakuum eingeengt.

Der Rückstand wird in Methanol gelöst (0.01-0.1 mol/l) und zur Darstellung der unsubstituierten Amidine mit Ammoniumacetat (3 eq.) und Ammoniumchlorid (2 eq.) versetzt. Zur Darstellung der substituierten Amidinderivate werden primäre oder sekundäre Amine (1.5 eq.) und Essigsäure (2 eq.) zu der methanolischen Lösung

gegeben. Nach 5-30 h wird das Lösungsmittel im Vakuum entfernt und der Rückstand durch Chromatographie an einer RP8-Kieselgel-Säule gereinigt (Wasser/Acetonitril 9/1-1/1 + 0.1% Trifluoressigsäure).

Auf analoge Weise wurden hergestellt:

Beispiel 31:

N-({3-[4-(2-Amino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophencarboxamid

MS (ESI): m/z (%) = 393 (M+H, 100);
HPLC (Methode 4): rt = 2.63 min

Beispiel 32:

5-Chloro-N-({3-[3-(4,5-dihydro-1H-imidazol-2-ylmethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid

MS (ESI): m/z (%) = 419 (M+H, 100);
HPLC (Methode 4): rt = 2.61 min

Beispiel 33:

5-Chloro-N-[(3-{3-[2-imino-2-(4-morpholinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 463 (M+H, 100);
HPLC (Methode 4): rt = 2.70 min

Beispiel 34:

5-Chloro-N-[(3-{3-[2-imino-2-(1-pyrrolidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 447 (M+H, 100);
HPLC (Methode 4): rt = 2.82 min

Beispiel 35:

N-({3-[3-(2-Amino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophencarboxamid

MS (ESI): m/z (%) = 393 (M+H, 100);
HPLC (Methode 4): rt = 2.60 min

Beispiel 140

5-Chloro-N-({3-[4-(4,5-dihydro-1H-imidazol-2-ylmethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid

MS (ESI): m/z (%) = 419 (M+H, 100);
HPLC (Methode 4): rt = 2.65 min

Beispiel 141

5-Chloro-N-[(3-{4-[2-imino-2-(4-morpholinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 463 (M+H, 100);
HPLC (Methode 4): rt = 2.65 min

Beispiel 142

5-Chloro-N-[(3-{4-[2-imino-2-(1-piperidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 461 (M+H, 100);
HPLC (Methode 4): rt = 2.83 min

Beispiel 143

5-Chloro-N-[(3-{4-[2-imino-2-(1-pyrrolidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 447 (M+H, 100);
HPLC (Methode 4): rt = 2.76 min

Beispiel 144

5-Chloro-N-[(3-{4-[2-(cyclopentylamino)-2-iminoethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 461 (M+H, 100);
HPLC (Methode 4): rt = 2.89 min

Beispiel 145

5-Chloro-N-{[3-(4-{2-imino-2-[(2,2,2-trifluoroethyl)amino]ethyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophencarboxamid

MS (ESI): m/z (%) = 475 (M+H, 100);
HPLC (Methode 4): rt = 2.79 min

Beispiel 146

N-({3-[4-(2-Anilino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophencarboxamid

MS (ESI): m/z (%) = 469 (M+H, 100);
HPLC (Methode 4): rt = 2.83 min

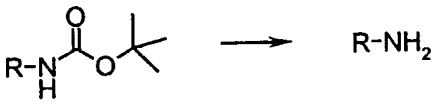
Beispiel 147

5-Chloro-N-[(3-{4-[2-imino-2-(2-pyridinylamino)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 470 (M+H, 100);
HPLC (Methode 4): rt = 2.84 min

Die folgenden Beispiele 148 bis 151 beziehen sich auf die Abspaltung von BOC-Aminoschutzgruppen:

Allgemeine Methode zur Abspaltung von Boc-Schutzgruppen (*tert*-Butyloxycarbonyl):



Zu einer eisgekühlten Lösung einer *tert.*-Butyloxycarbonyl- (Boc) geschützten Verbindung in Chloroform oder Dichlormethan (ca.0.1 bis 0.3 mol/l) wird wässrige Trifluoressigsäure (TFA, ca. 90 %) getropft. Nach ca. 15 min wird die Eiskühlung entfernt und die Mischung ca. 2-3 h bei Raumtemperatur gerührt, bevor die Lösung eingeengt und am Hochvakuum getrocknet wird. Der Rückstand wird in Dichlormethan oder Dichlormethan/Methanol aufgenommen und mit gesättigter Natriumhydrogencarbonat- oder 1N Natriumhydroxid-Lösung gewaschen. Die organische Phase wird mit gesättigter Natriumchlorid-Lösung gewaschen, über wenig Magnesiumsulfat

getrocknet und konzentriert. Gegebenenfalls erfolgt eine Reinigung durch Kristallisation aus Ether oder Ether/Dichlormethan-Gemischen.

Auf analoge Weise wurden aus den entsprechen Boc-geschützten Vorläufern hergestellt:

Beispiel 148

***N*-({3-[4-(Aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophen-carboxamid**

ausgehend von Beispiel 92:

MS (ESI): m/z (%) = 349 ($M-NH_2$, 25), 305 (100);

HPLC (Methode 1): rt (%) = 3.68 (98).

IC_{50}: 2.2 µM

Beispiel 149

***N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophen-carboxamid**

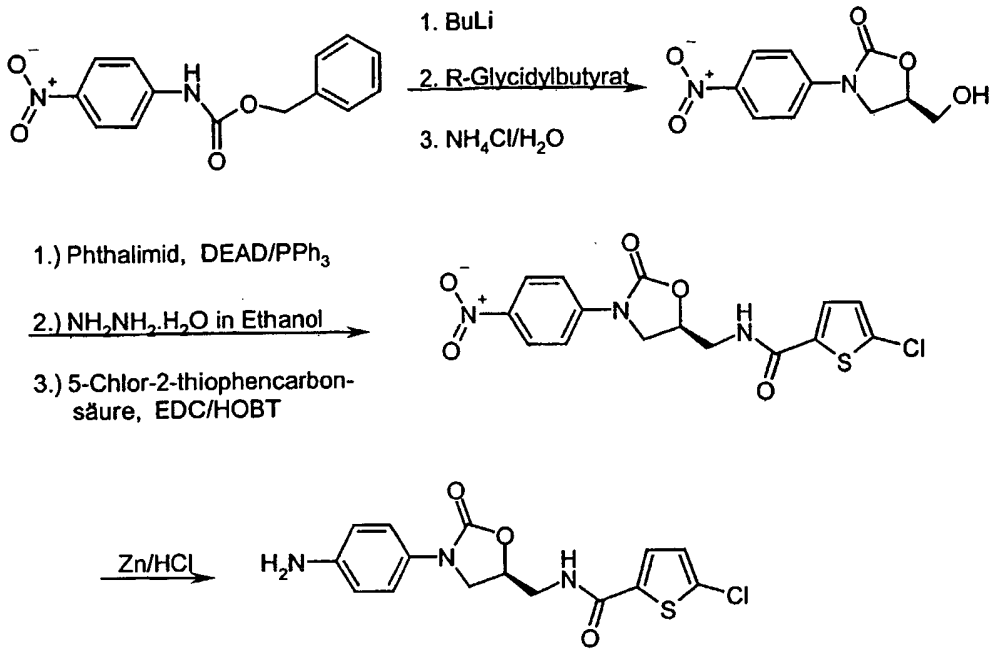
ausgehend von Beispiel 93:

MS (ESI): m/z (%) = 352 (M+H, 25);

HPLC (Methode 1): rt (%) = 3.50 (100).

IC_{50}: 2 µM

Eine enantiomerenreine Alternativsynthese dieser Verbindung ist im folgenden Schema dargestellt (vgl. auch Delalande S.A., DE 2836305,1979; Chem.Abstr. 90, 186926):



Beispiel 150

5-Chloro-*N*-({3-[4-(glycylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid

ausgehend von Beispiel 152:

MS (ES-pos): m/z (%) = 408 (100);

HPLC (Methode 3): rt (%) = 3.56 (97).

IC_{50}: 2 µM

Beispiel 151

5-(Aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-on

ausgehend von Beispiel 60:

MS (ESI): m/z (%) = 276 (M+H, 100);

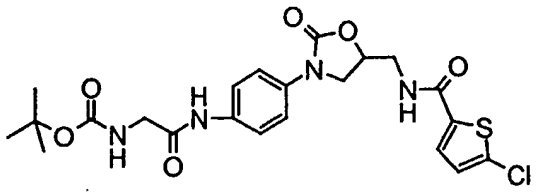
HPLC (Methode 3): rt (%) = 2.99 (100).

IC_{50}: 2 µM

Die folgenden Beispiele 152 bis 166 beziehen sich auf die Aminogruppenderivatisierung von Anilin- oder Benzylamin-substituierten Oxazolidinonen mit verschiedenen Reagenzien:

Beispiel 152

5-Chloro-*N*-({3-[4-(N-*tert.*-butyloxycarbonyl-glycylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid



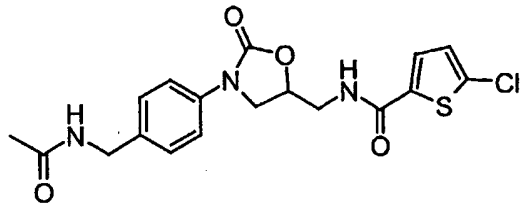
Zu einer Lösung von 751 mg (4.3 mmol) Boc-Glycin, 870 mg (6.4 mmol) HOBT (1-Hydroxy-1H-benzotriazol x H_2O), 1790 mg (4.7 mmol) HBTU [O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluroniumhexafluorophosphat] und 1.41 ml (12.9 mmol) *N*-Methylmorpholin in 15 ml DMF/CH_2Cl_2 (1:1) werden bei 0°C 754 mg (2.1 mmol) *N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophencarboxamid (aus Beispiel 149) gegeben. Die Mischung wird über Nacht bei Raumtemperatur gerührt, bevor mit Wasser verdünnt wird. Der ausgefallene Feststoff wird abfiltriert und getrocknet. Ausbeute: 894 mg (79.7 % der Theorie);

MS (DCI, NH_3): m/z (%) = 526 ($M+NH_4$, 100);

HPLC (Methode 3): rt (%) = 4.17 (97).

Beispiel 153

***N*-[(3-{4-[(Acetylamino)methyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophencarboxamid**



Eine Mischung von 30 mg (0.082 mmol) *N*-({3-[4-(Aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophen-carboxamid (aus Beispiel 148) in 1.5 ml absolutem THF und 1.0 ml absolutem Dichlormethan, 0.02 ml absolutem Pyridin wird bei 0°C mit Acetanhydrid (0.015 ml, 0.164 mmol) versetzt. Die Mischung wird über Nacht bei Raumtemperatur gerührt. Nach Zusetzen von Ether und Kristallisation wird das Produkt gewonnen. Ausbeute: 30 mg (87 % der Theorie),

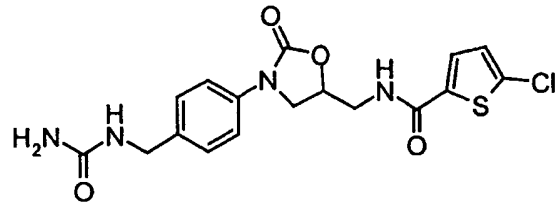
MS (ESI): m/z (%) = 408 (M+H, 18), 305 (85);

HPLC (Methode 1): rt (%) = 3.78 (97).

IC_{50}: 0.6 µM

Beispiel 154

***N*-{[3-(4-{[(Aminocarbonyl)amino]methyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophencarboxamid**



Zu einer Mischung von 30 mg (0.082 mmol) *N*-({3-[4-(Aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophen-carboxamid (aus Beispiel 148) in

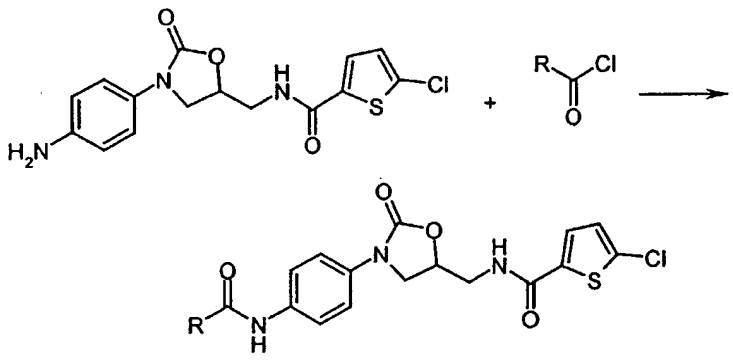
1.0 ml Dichlormethan werden bei Raumtemperatur 0.19 ml (0.82 mmol) Trimethylsilylisocyanat getropft. Es wird über Nacht gerührt, bevor nach Zusatz von Ether das Produkt durch Filtration gewonnen wird. Ausbeute: 21.1 mg (52 % der Theorie),

MS (ESI): m/z (%) = 409 (M+H, 5), 305 (72);

HPLC (Methode 1): rt (%) = 3.67 (83).

IC_{50}: 1.3 µM

Allgemeine Methode zur Acylierung von *N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophencarboxamid mit Carbonsäurechloriden:



Unter Argon wird zu entsprechendem Säurechlorid (2.5 eq.) eine ca. 0.1 molare Lösung von *N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophencarboxamid (aus Beispiel 149) (1.0 eq.) in absolutem Dichlormethan/Pyridin (19:1) getropft. Die Mischung wird über Nacht gerührt, bevor mit ca. 5 eq PS-Trisamine (Argonaut Technologies) und 2 ml absolutem Dichlormethan versetzt wird. Nach 1 h leichtem Rühren, wird abfiltriert und das Filtrat konzentriert. Gegebenenfalls erfolgt eine Reinigung der Produkte durch präparative RP-HPLC.

Auf analoge Weise wurden hergestellt:

Beispiel 155

***N*-({3-[4-(Acetylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophen-carboxamid**

LC-MS: m/z (%) = 394 (M+H, 100);
LC-MS (Methode 6): rt (%) = 3.25 (100).
IC_{50}: 1.2 µM

Beispiel 156

5-Chloro-*N*-[(2-oxo-3-{4-[(2-thienylcarbonyl)amino]phenyl}-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

LC-MS: m/z (%) = 462 (M+H, 100);
LC-MS (Methode 6): rt (%) = 3.87 (100).
IC_{50}: 1.3 µM

Beispiel 157

5-Chloro-*N*-[(3-{4-[(methoxyacetyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)-methyl]-2-thiophencarboxamid

LC-MS: m/z (%) = 424 (M+H, 100);
LC-MS (Methode 6): rt (%) = 3.39 (100).
IC_{50}: 0.73 µM

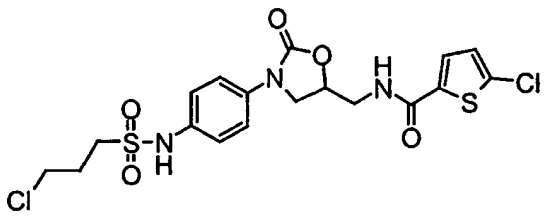
Beispiel 158

***N*-{4-[5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3,5-dimethyl-4-isoxazolcarboxamid**

LC-MS: m/z (%) = 475 (M+H, 100).
IC_{50}: 0.46 µM

Beispiel 159

5-Chloro-*N*-{[3-(4-{[(3-chloropropyl)sulfonyl]amino}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophencarboxamid



Zu einer eisgekühlten Lösung von 26.4 mg (0.15 mmol) 3-Chloro-1-propansulfonsäurechlorid und 0.03 ml (0.2 mmol) Triethylamin in 3.5 ml absolutem Dichlormethan werden 35 mg (0.1 mmol) *N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophen-carboxamid (aus Beispiel 149) gegeben. Nach 30 min wird die Eiskühlung entfernt und die Mischung über Nacht bei Raumtemperatur gerührt, bevor 150 mg (ca. 5.5 eq) PS-Trisamine (Argonaut Technologies) und 0.5 ml Dichlormethan zugesetzt werden. Die Suspension wird 2 h leicht gerührt, filtriert (das Harz wird mit Dichlormethan/Methanol nachgewaschen) und das Filtrat eingeengt. Das Produkt wird durch präparative RP-HPLC gereinigt. Ausbeute: 19.6 mg (40 % der Theorie),

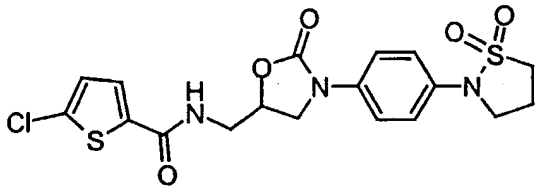
LC-MS: m/z (%) = 492 (M+H, 100);

LC-MS (Methode 5): rt (%) = 3.82 (91).

IC_{50}: 1.7 µM

Beispiel 160

5-Chloro-*N*-({3-[4-(1,1-dioxido-2-isothiazolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid



Eine Mischung aus 13.5 mg (0.027 mmol) 5-Chloro-*N*-{[3-(4-{[(3-chloropropyl)sulfonyl]amino}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophen-carboxamid (aus Beispiel 159) und 7.6 mg (0.055 mmol) Kaliumcarbonat in 0.2 ml DMF wird 2 h auf 100°C erhitzt. Nach Abkühlen wird mit Dichlormethan verdünnt und mit Wasser gewaschen. Die organische Phase wird getrocknet und eingeengt. Der Rückstand wird durch präparative Dünnschichtchromatographie (Silicagel, Dichlormethan/Methanol, 95:5) gereinigt. Ausbeute: 1.8 mg (14.4 % der Theorie),

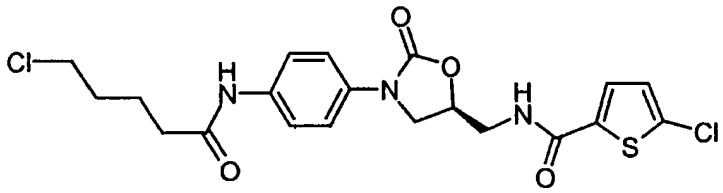
MS (ESI): m/z (%) = 456 (M+H, 15), 412 (100);

LC-MS (Methode 4): rt (%) = 3.81 (90).

IC_{50}: 0.14 µM

Beispiel 161

5-Chloro-N-[((5S)-3-{4-[(5-chloropentanoyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid



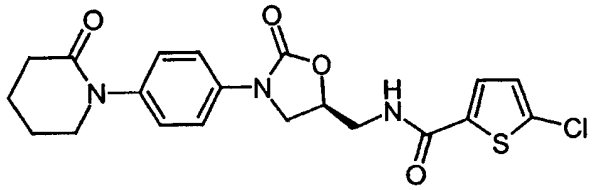
0.5 g (1.29 mmol) N-{[(5S)-3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophencarboxamid (aus Beispiel 149) werden in 27 ml Tetrahydrofuran

gelöst und mit 0.2 g (1,29 mmol) 5-Chlorvaleriansäurechlorid sowie 0.395 ml (2.83 mmol) Triethylamin versetzt. Man dampft den Ansatz im Vakuum ein und chromatographiert auf Kieselgel mit einem Toluol/Essigester=1:1 -> Essigester-Gradienten. Man erhält 315 mg (52% d.Th.) eines Feststoffs.

Smp.: 211°C.

Beispiel 162

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-piperidinyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophencarboxamid



Man gibt unter inerten Bedingungen zu 5 ml DMSO 30 mg 60-proz. NaH in Paraffinöl und erwärmt 30 min lang auf 75°C bis zur Beendigung der Gasentwicklung. Anschließend tropft man eine Lösung von 290 mg (0.617 mmol) 5-Chloro-N-[((5S)-3-{4-[(5-chloropentanoyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid (aus Beispiel 161) in 5 ml Methylenchlorid hinzu und rührt über Nacht bei Raumtemperatur. Die Reaktion wird abgebrochen und das Gemisch in 100 ml Wasser gegeben und mit Essigester extrahiert. Die eingedampfte organische Phase wird auf einer RP-8 Säule chromatographiert und mit Acetonitril/Wasser eluiert. Man erhält 20 mg (7.5% d.Th.) der Zielverbindung.

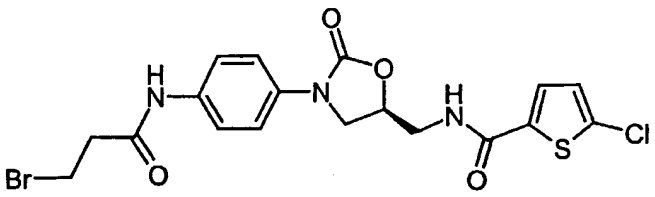
Smp.: 205°C;

NMR (300 MHz, d_6-DMSO): δ = 1.85 (m,4H), 2.35 (m,2H), 3.58 (m,4H), 3.85 (m,1H), 4.2 (t,1H), 4.82 (m,1H), 7.18 (d,1H,thiophen), 7.26 (d,2H), 7.5 (d,2H), 2.68 (d,1H,thiophen), 9.0 (t,1H,CONH).

IC_{50}: 2.8 nM

Beispiel 163

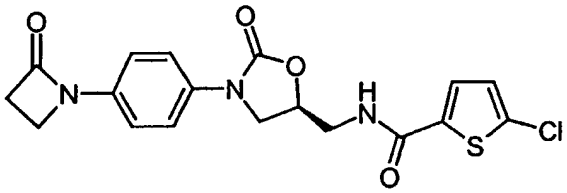
5-Chloro-N-[((5S)-3-{4-[(3-bromopropionyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid



wird in analoger Weise aus Beispiel 149 erhalten.

Beispiel 164

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-azetidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid



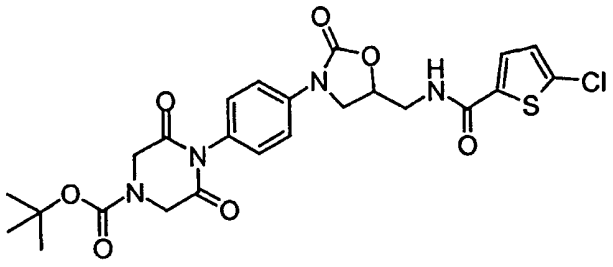
wird in analoger Weise durch Cyclisierung der offenkettigen Bromopropionylverbindung aus Beispiel 163 mittels NaH/DMSO erhalten.

MS (ESI): m/z (%) = 406 ($[M+H]^+$, 100), Cl-Muster.

IC_{50}: 380 nM

Beispiel 165

***tert*-Butyl 4-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3,5-dioxo-1-piperazincarboxylat**



Zu einer Lösung von 199 mg (0.85 mmol) Boc-Iminodiessigsäure, 300 mg (2.2 mmol) HOBT, 0.66 ml (6 mmol) *N*-Methylmorpholin und 647 mg (1.7 mmol) HBTU werden 300 mg (0.85 mmol) *N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophen-carboxamid in 6 ml einer Mischung aus DMF und Dichlormethan (1:1) gegeben. Die Mischung wird über Nacht gerührt, bevor nach Verdünnen mit Dichlormethan mit Wasser, gesättigter Ammoniumchlorid-Lösung, gesättigter Natriumhydrogencarbonat-Lösung, Wasser und gesättigter Natriumchlorid-Lösung gewaschen wird. Die organische Phase wird über Magnesiumsulfat getrocknet und eingeengt. Das Rohprodukt wird durch Chromatographie an Silicagel (Dichlormethan/Methanol 98:2) gereinigt. Ausbeute: 134 mg (29 % der Theorie);

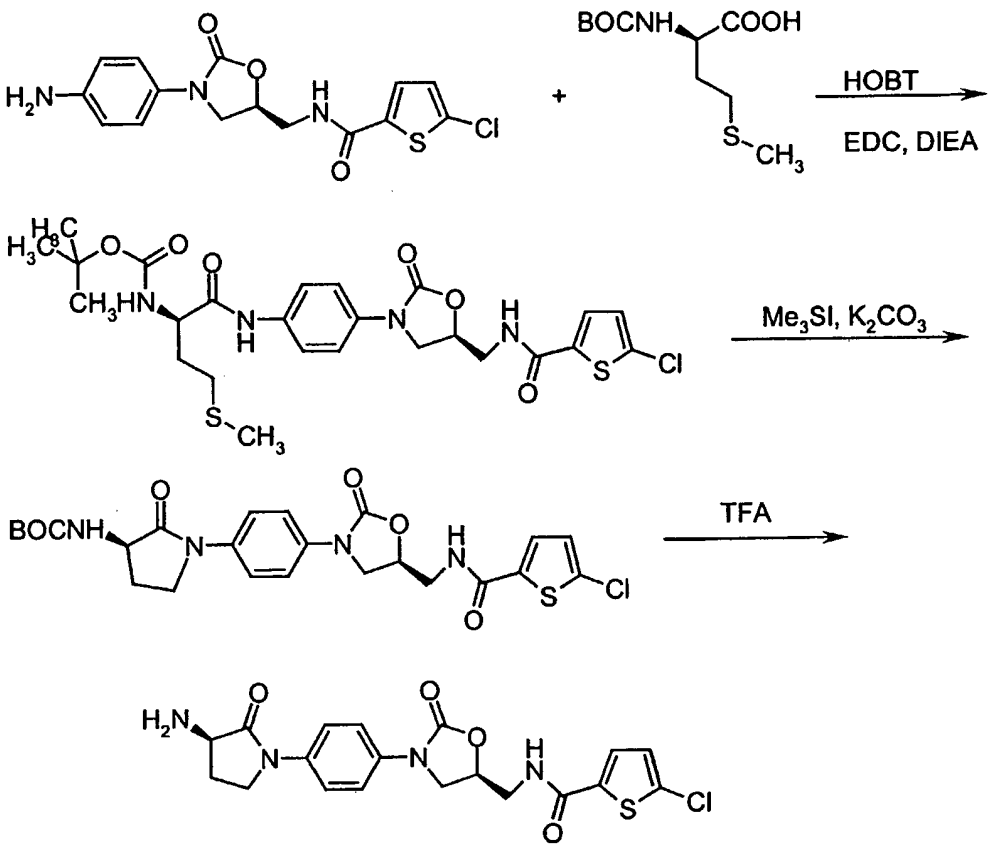
MS (ESI): m/z (%) = 571 (M+Na, 82), 493 (100);

HPLC (Methode 3): rt (%) = 4.39 (90).

IC_{50}: 2 µM

Beispiel 166

N-[((5S)-3-{4-[(3R)-3-Amino-2-oxo-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophencarboxamid Trifluoracetat



N2-(tert-Butoxycarbonyl)-N1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-D-methioninamid

429 mg (1.72 mmol) N-BOC-D-Methionin, 605 mg (1.72 mmol) N-{[(5S)-3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophencarboxamid, und 527 mg (3.44 mmol) HOBT-Hydrat werden in 35 ml DMF gelöst, mit 660 mg (3.441 mmol) EDCI Hydrochlorid und anschließend tropfenweise mit 689 mg (5.334 mmol) N-Ethyl-diisopropylamin versetzt. Man rührt bei Raumtemperatur zwei Tage lang. Die erhaltene Suspension wird abgesaugt und der Rückstand mit

DMF gewaschen. Die vereinigten Filtrate werden mit etwas Kieselgel versetzt, im Vakuum eingedampft und auf Kieselgel mit einem Toluol -> T10EE7 – Gradienten chromatographiert. Man erhält 170 mg (17% d.Th.) der Zielverbindung mit einem Schmelzpunkt von 183°C.

R_f (SiO_2, Toluol/Essigester=1:1):0.2.

^{1}H-NMR (300 MHz, d_6-DMSO): δ=1.4 (s,1H,BOC), 1.88-1.95 (m,2H), 2.08 (s,3H,SMe), 2.4-2.5 (m,2H, teilweise verdeckt durch DMSO), 3.6 (m,2H), 3.8 (m,1H), 4.15 (m,2H), 4.8 (m,1H), 7.2 (1H, thiophen), 7.42 (d, Teil eines AB-Systems, 2H), 7.6 (d, Teil eines AB-Systems, 2H), 7.7 (d, 1H, thiophen), 8.95 (t,1H, CH_2NHCO), 9.93 (bs,1H,NH).

tert-Butyl (3R)-1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-oxo-3-pyrrolidinylcarbamat

170 mg (0.292 mmol) N2-(tert-butoxycarbonyl)-N1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-D-methioninamid werden in 2 ml DMSO gelöst und mit 178.5 mg (0.875 mmol) Trimethylsulfoniumiodid sowie 60.4 mg (0.437 mmol) Kaliumcarbonat versetzt und 3.5 Stunden bei 80°C gerührt. Anschließend wird im Hochvakuum eingedampft und der Rückstand mit Ethanol gewaschen. Es verbleiben 99 mg der Zielverbindung.

^{1}H-NMR (300 MHz, d_6-DMSO): δ =1.4 (s,1H,BOC), 1.88-2.05 (m,1H), 2.3-2.4 (m,1H), 3.7-3.8 (m,3H), 3.8-3.9 (m,1H), 4.1-4.25 (m,1H), 4.25-4.45 (m,1H), 4.75-4.95 (m,1H), 7.15 (1H, thiophen), 7.25 (d,1H), 7.52 (d, Teil eines AB-Systems, 2H), 7.65 (d, Teil eines AB-Systems, 2H), 7.65 (d, 1H, thiophen), 9.0 (breites s,1H).

N-[((5S)-3-{4-[(3R)-3-Amino-2-oxo-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophencarboxamid Trifluoracetat

Man suspendiert 97 mg (0.181 mmol) tert-butyl (3R)-1-{4-[(5S)-5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-oxo-3-pyrrolidinylcarbamat in 4 ml Methylenchlorid, gibt 1.5 ml Trifluoressigsäure hinzu und

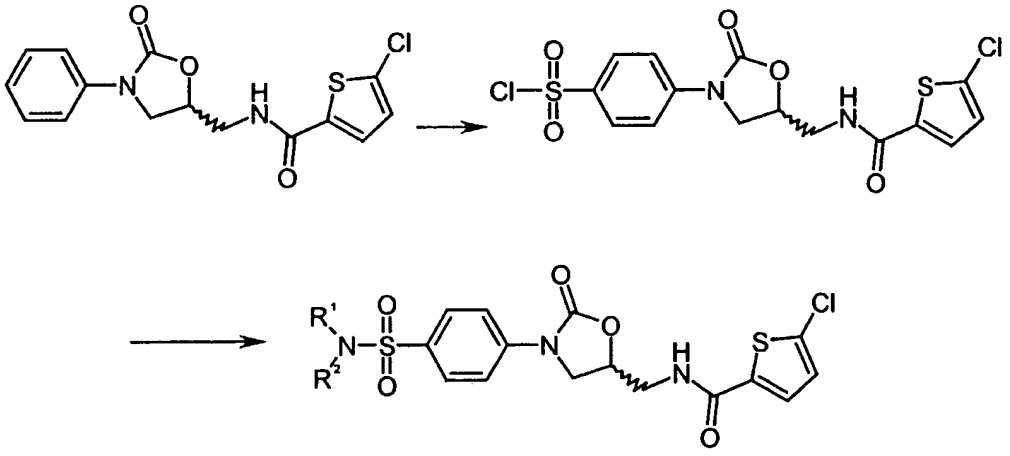
rührt 1 Stunde bei Raumtemperatur. Anschließend wird im Vakuum eingedampft und auf einer RP-HPLC gereinigt (Acetonitril/Wasser/0.1%TFA-Gradient). Man erhält nach Eindampfen der betreffenden Fraktion 29 mg (37% d.Th.) der Zielverbindung mit einem Schmelzpunkt von 241°C (Zers.).

R_f (SiO_2,EtOH/TEA=17:1) 0.19.

^{1}H-NMR (300 MHz, d_6-DMSO): δ =1.92-2.2 (m,1H), 2.4-2.55 (m,1H, teilweise verdeckt durch DMSO-peak), 3.55-3.65 (m,2H), 3.75-3.95 (m,3H), 4.1-4.3 (m,2H), 4.75-4.9 (m,1H), 7.2 (1H, thiophen), 7.58 (d, Teil eines AB-Systems, 2H), 7.7 (d, Teil eines AB-Systems, 2H), 7.68 (d, 1H, thiophen), 8.4 (breites s,3H, NH3), 8.9 (t,1H,NHCO).

Die folgenden Beispiele 167 bis 170 beziehen sich auf die Einführung von Sulfonamidgruppen in Phenyl-substituierten Oxazolidinonen:

Allgemeine Methode zur Darstellung von substituierten Sulfonamiden ausgehend von 5-Chloro-*N*-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid



Zu Chlorsulfonsäure (12 eq.) wird unter Argon bei 5°C 5-Chloro-*N*-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid (aus Beispiel 96) gegeben. Das Reaktionsgemisch wird bei Raumtemperatur für 2 h gerührt und anschlie-

ßend auf Eiswasser gegeben. Der ausfallende Niederschlag wird filtriert, mit Wasser gewaschen und getrocknet.

Anschließend wird unter Argon bei Raumtemperatur in Tetrahydrofuran (0.1 mol/l) gelöst und mit dem entsprechenden Amin (3 eq.), Triethylamin (1.1 eq.) und Dimethylaminopyridin (0.1 eq.) versetzt. Das Reaktionsgemisch wird 1-2 h gerührt und anschließend im Vakuum eingeengt. Das gewünschte Produkt wird mittels Flash-Chromatographie (Dichlormethan-Methanol-Gemische) gereinigt.

Auf analoge Weise wurden hergestellt:

Beispiel 167

5-Chloro-*N*-({2-oxo-3-[4-(1-pyrrolidinylsulfonyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophencarboxamid

MS (ESI): m/z (%) = 492 ($[M+Na]^+$, 100), 470 ($[M+H]^+$, 68), Cl-Muster;
HPLC (Methode 3): rt (%) = 4.34 (100).
IC_{50}: 0.5 µM

Beispiel 168

5-Chloro-*N*-[(3-{4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 499 ($[M+H]^+$, 100), Cl-Muster;
HPLC (Methode 2): rt (%) = 3.3 (100).

Beispiel 169

5-Chloro-*N*-({2-oxo-3-[4-(1-piperidinylsulfonyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophencarboxamid

MS (ESI): m/z (%) = 484 ($[M+H]^+$, 100), Cl-Muster;
HPLC (Methode 2): rt (%) = 4.4 (100).

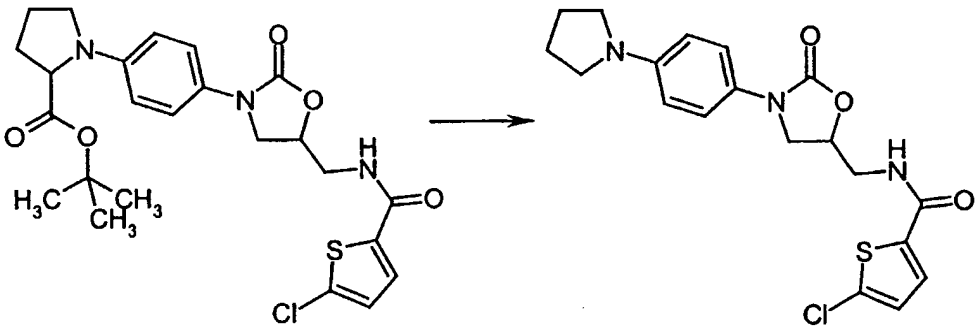
Beispiel 170

5-Chloro-*N*-[(3-{4-[(4-hydroxy-1-piperidinyl)sulfonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamid

MS (ESI): m/z (%) = 500 ($[M+H]^+$, 100), Cl-Muster;
HPLC (Methode 3): rt (%) = 3.9 (100).

Beispiel 171

5-Chloro-N-({2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid



780 mg (1.54 mmol) tert.-Butyl-1-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}-methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}prolinat werden in 6 ml Dichlormethan und 9 ml Trifluoressigsäure gelöst und das Gemisch wird zwei Tage lang bei 40°C gerührt. Dann wird das Reaktionsgemisch eingeengt und mit Ether und 2 N Natronlauge verrührt. Die wässrige Phase wird eingeengt und mit Ether und 2 N Salzsäure

verrührt. Die organische Phase dieser Extraktion wird über $MgSO_4$ getrocknet, filtriert und eingeengt. Das Rohprodukt wird an Kieselgel chromatographiert (CH_2Cl_2/EtOH/konz. wässr. NH_3-Lsg. = 100/1/0.1 bis 20/1/0.1).

Es werden 280 mg (40 % d. Th.) des Produkts erhalten.

MS (ESI): m/z (%) = 406 (M+H, 100);

HPLC (Methode 4): rt = 3.81 min.

HPLC-Parameter und LC-MS Parameter der in den vorrangegangenen Beispielen angegebenen HPLC- und LC-MS-Daten (die Einheit der Retentionszeit (rt) ist Minuten):

[1] Säule: Kromasil C18, L-R Temperatur: 30°C, Fluss = 0.75 $mlmin^{-1}$, Eluent: A = 0.01 M $HClO_4$, B = CH_3CN, Gradient: -> 0.5 min 98%A -> 4.5 min 10%A ->6.5 min 10%A

[2] Säule: Kromasil C18 60*2, L-R Temperatur: 30°C, Fluss = 0.75 $mlmin^{-1}$, Eluent: A = 0.01 M H_3PO_4, B = CH_3CN, Gradient: -> 0.5 min 90%A -> 4.5 min 10%A ->6.5 min 10%A

[3] Säule: Kromasil C18 60*2, L-R Temperatur: 30°C, Fluss = 0.75 $mlmin^{-1}$, Eluent: A = 0.005 M $HClO_4$, B = CH_3CN, Gradient: -> 0.5 min 98%A -> 4.5 min 10%A ->6.5 min 10%A

[4] Säule: Symmetry C18 2.1x150 mm, Säulenofen: 50°C, Fluss = 0.6 $mlmin^{-1}$, Eluent: A = 0.6 g 30%ige HCl/l Wasser, B = CH_3CN, Gradient: 0.0 min 90%A -> 4.0 min 10%A ->9 min 10%A

[5] MHZ-2Q, Instrument Micromass Quattro LCZ

Säule Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, Temperatur: 40°C, Fluss = 0.5 ml min^{-1}, Eluent A = CH_3CN + 0.1% Ameisensäure, Eluent B = Wasser + 0.1% Ameisensäure, Gradient: 0.0 min 10% A -> 4 min 90% A -> 6 min 90% A

[6] MHZ-2P, Instrument Micromass Platform LCZ
Säule Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, Temperatur: 40°C, Fluss = 0.5 $mlmin^{-1}$, Eluent A = CH_3CN + 0.1% Ameisensäure, Eluent B = Wasser + 0.1% Ameisensäure, Gradient: 0.0 min 10% A -> 4 min 90% A -> 6 min 90% A

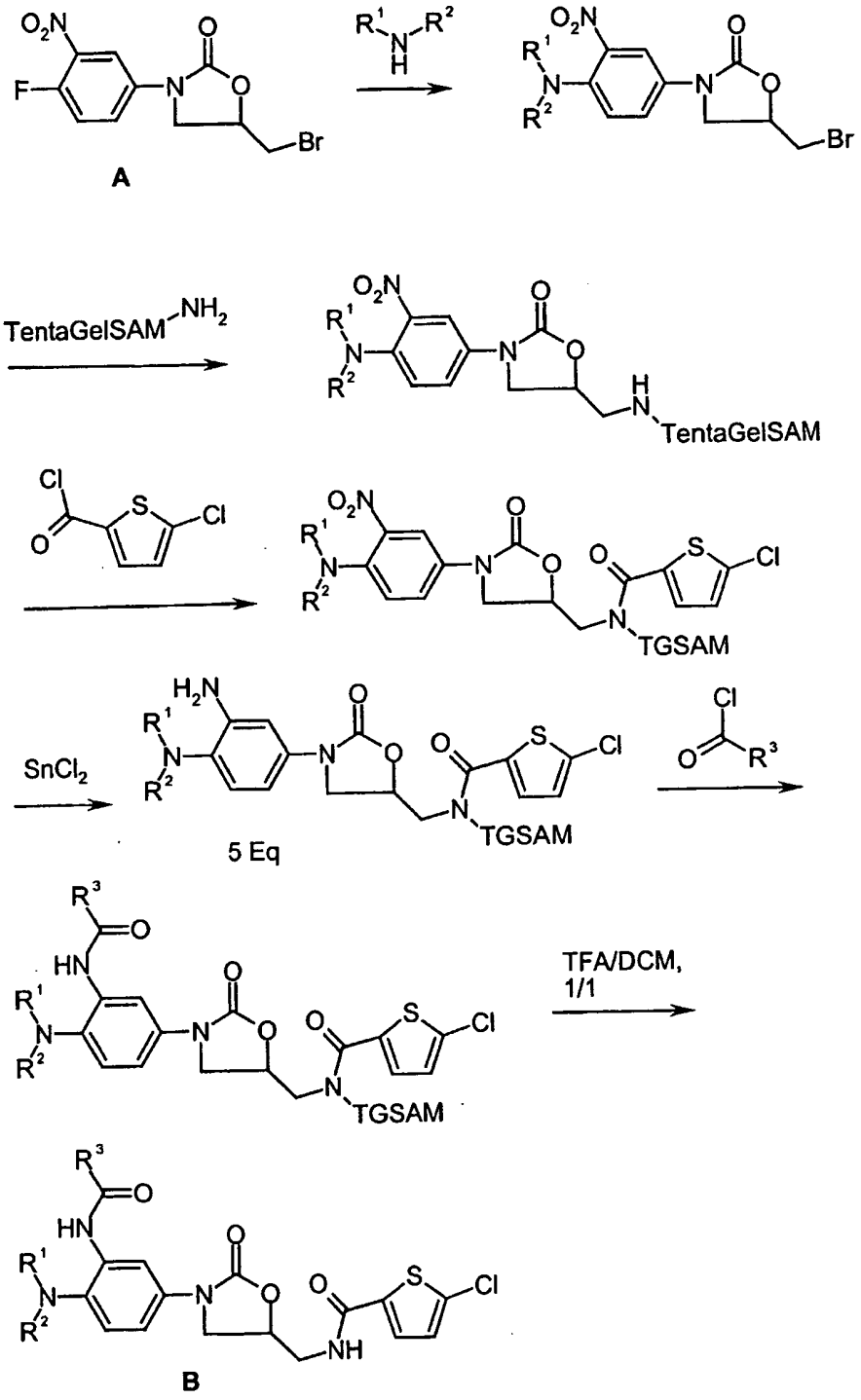
[7] MHZ-7Q, Instrument Micromass Quattro LCZ
Säule Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, Temperatur: 40°C, Fluss = 0.5 $mlmin^{-1}$, Eluent A = CH_3CN + 0.1% Ameisensäure, Eluent B = Wasser + 0.1% Ameisensäure, Gradient: 0.0 min 5% A -> 1 min 5% A -> 5 min 90% A -> 6 min 90% A

Allgemeine Methode zu Darstellung von Oxazolidinonen der allgemeinen Formel B durch festphasenunterstützte Synthese

Umsetzungen mit unterschiedlichen harzgebundenen Produkten fanden in einem Satz von getrennten Reaktionsgefäßen statt.

5-(Brommethyl)-3-(4-fluor-3-nitrophenyl)-1,3-oxazolidin-2-on A (dargestellt aus Epibromhydrin und 4-Fluor-3-nitrophenylisocyanat mit LiBr/Bu_3PO in Xylol analog US 4128654, Bsp.2) (1,20 g, 3,75 mmol) und Ethyldiisoproylamin (DIEA, 1,91 ml, 4,13 mmol) wurden in DMSO (70 ml) gelöst, mit einem sekundären Amin (1,1 eq, Aminkomponente 1) versetzt und 5 h bei 55°C umgesetzt. Zu dieser Lösung wurde TentaGel SAM Harz (5,00 g, 0,25 mmol/g) gegeben und 48 h bei 75°C reagiert. Das Harz wurde filtriert und wiederholt mit Methanol (MeOH), Dimethylformamid (DMF), MeOH, Dichlormethan (DCM) und Diethylether gewaschen und getrocknet. Das Harz (5,00 g) wurde in Dichlormethan (80 ml) suspendiert, mit DIEA (10 eq) und 5-Chlorthiophen-2-carbonsäurechlorid [hergestellt durch Reaktion von 5-Chlorthiophen-2-carbonsäure (5 eq) und 1-Chlor-1-Dimethylamino-2-methylpropen (5 eq) in DCM (20 ml) bei Raumtemperatur für 15 Minuten] versetzt und 5 h bei Raumtemperatur reagiert. Das erhaltene Harz wurde filtriert und wiederholt mit MeOH,

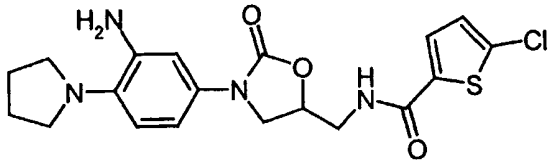
DCM und Diethylether gewaschen und getrocknet. Anschließend wurde das Harz in DMF/Wasser (v/v 9:2, 80 ml) suspendiert, mit $SnCl_2*2H_2O$ (5 eq) versetzt und 18 h bei Raumtemperatur umgesetzt. Das Harz wurde wiederum wiederholt mit MeOH, DMF, Wasser, MeOH, DCM und Diethylether gewaschen und getrocknet. Dieses Harz wurde in DCM suspendiert, mit DIEA (10 eq) und bei 0°C mit einem Säurechlorid (5 eq Säurederivat 1) versetzt und bei Raumtemperatur über Nacht reagiert. Carbonsäuren wurden vor der Umsetzung durch Reaktion mit 1-Dimethylamino-1-chlor-2-methylpropen (1 eq, bezogen auf die Carbonsäure) in DCM bei Raumtemperatur für 15 min in die korrespondierenden Säurechloride überführt. Das Harz wurde wiederholt mit DMF, Wasser, DMF, MeOH, DCM und Diethylether gewaschen und getrocknet. Im Falle der Verwendung von Fmoc-geschützten Aminosäuren als Säurederivat 1 wurde die Fmoc-Schutzgruppe im letzten Reaktionsschritt durch Umsetzung mit Piperidin/DMF (v/v, 1/4) bei Raumtemperatur für 15 Minuten abgespalten und das Harz mit DMF, MeOH, DCM und Diethylether gewaschen und getrocknet. Die Produkte wurden anschließend mit Trifluoressigsäure (TFA)/DCM (v/v, 1/1) von der festen Phase gespalten, das Harz wurde abfiltriert und die Reaktionslösungen wurden eingedampft. Die Rohprodukte wurden über Kieselgel filtriert (DCM/MeOH, 9:1) und eingedampft um einen Satz von Produkten **B** zu erhalten.



Durch festphasenunterstützte Synthese hergestellte Verbindungen:

Beispiel 172

N-({3-[3-Amino-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chlor-2-thiophencarboxamid

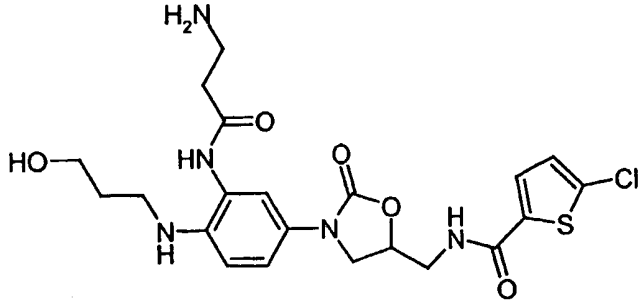


Analog der allgemeinen Arbeitsvorschrift zur Herstellung der Derivate **B** wurden 5 g (1,25 mmol) TentaGel SAM Harz mit Pyrrolidin als Aminderivat 1 umgesetzt. Das nach der Reduktion mit $SnCl_2*2H_2O$ erhaltene Anilin wurde ohne weiteren Acylierungsschritt von der festen Phase abgespalten und eingedampft. Das Rohprodukt wurde zwischen Ethylacetat und $NaHCO_3$-Lösung verteilt, die organische Phase wurde mit NaCl ausgesalzen, dekantiert und zur Trockene eingedampft. Dieses Rohprodukt wurde durch Vakuum-Flashchromatographie an Kieselgel (Dichlormethan/Ethylacetat, 3:1 – 1:2) gereinigt.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.95 – 2.08, br, 4 H; 3.15-3.30, br, 4 H; 3.65-3.81, m, 2 H; 3.89, ddd, 1H; 4.05, dd, 1 H; 4.81, dddd, 1 H; 6.46, dd, 1 H; 6.72, dd, 1 H; 6.90, dd, 1 H; 6.99, dd, 1 H; 7.03, dd, 1 H; 7.29, d, 1 H.

Beispiel 173

N-[(3-{3-(ß-Alanylamino)-4-[(3-hydroxypropyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chlor-2-thiophencarboxamid

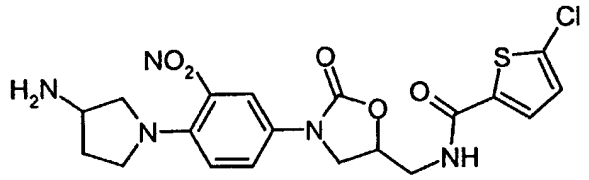


Analog der allgemeinen Arbeitsvorschrift zur Herstellung der Derivate **B** wurden 5 g (1,25 mmol) TentaGel SAM Harz mit Azetidin als Aminderivat 1 und Fmoc-ß-Alanin als Säurederivat 1 umgesetzt. Das nach der Abspaltung erhaltene Rohprodukt wurde 48 h in Methanol bei Raumtemperatur gerührt und zur Trockene eingedampft. Dieses Rohprodukt wurde durch Reversed Phase HPLC mit einem Wasser/TFA/Acetonitril-Gradienten gereinigt.

^{1}H-NMR (400 MHz, CD_3OD): 2.31, tt, 2 H; 3.36, t, 2 H; 3.54, t, 2 H; 3.62, t, 2 H; 3.72, dd, 1 H; 3.79, dd, 1 H; 4.01, dd, 1 H; 4.29, dd, 2 H; 4.43, t, 2 H; 4.85–4.95, m, 1 H; 7.01, d, 1 H; 4.48 – 7.55, m, 2 H; 7.61, d, 1 H; 7.84, d, 1 H.

Beispiel 174

N-({3-[4-(3-Amino-1-pyrrolidinyl)-3-nitrophenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chlor-2-thiophencarboxamid

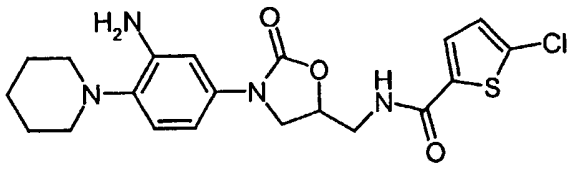


Analog der allgemeinen Arbeitsvorschrift zur Herstellung der Derivate **B** wurden 130 mg (32,5 µmol) TentaGel SAM Harz mit *tert*-Butyl 3-pyrrolidinylcarbamate als Aminderivat 1 umgesetzt. Das nach der Acylierung mit 5-Chlorthiophencarbonsäure erhaltene Nitrobenzolderivat wurde von der festen Phase abgespalten und eingedampft. Dieses Rohprodukt wurde durch Reversed Phase HPLC mit einem Wasser/TFA/Acetonitril-Gradienten gereinigt.

^{1}H-NMR (400 MHz, CD_3OH): 2.07-2.17, m, 1 H; 2.39-2.49, m, 1 H; 3.21-3.40, m, 2 H; 3.45, dd, 1 H; 3.50–3.60, m, 1 H; 3.67, dd, 1 H; 3.76, dd, 1 H; 3.88–4.00, m, 2 H; 4.14 – 4.21, t, 1 H; 4.85 – 4.95, m, 1 H; 7.01, d, 1 H; 7.11, d, 1 H; 7.52, d, 1 H; 7.66, dd, 1 H; 7.93, d, 1 H.

Beispiel 175

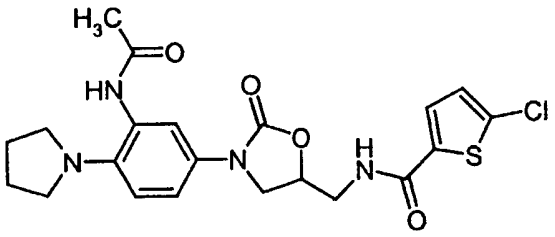
N-({3-[3-amino-4-(1-piperidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophencarboxamid



Analog der allgemeinen Arbeitsvorschrift zur Herstellung der Derivate **B** wurden 130 mg (32,5 µmol) TentaGel SAM Harz mit Piperidin als Aminderivat 1 umgesetzt. Das nach der Reduktion erhaltene Anilin wurde ohne weiteren Acylierungsschritt von der festen Phase abgespalten und eingedampft. Dieses Rohprodukt wurde durch Reversed Phase HPLC mit einem Wasser/TFA/Acetonitril-Gradienten gereinigt.
^{1}H-NMR (400 MHz, CD_3OH): 1.65–1.75, m, 2 H; 1.84-1.95, m, 4 H; 3.20-3.28, m, 4 H; 3.68, dd, 1 H; 3.73, dd, 1H; 3.90, dd, 1 H; 4.17, dd, 1 H; 4.80-4.90, m, 1 H; 7.00, d, 1 H; 7.05, dd, 1 H; 7.30-7.38, m, 2H; 7.50, d, 1 H.

Beispiel 176

N-({3-[3-(Acetylamino)-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chlor-2-thiophencarboxamid

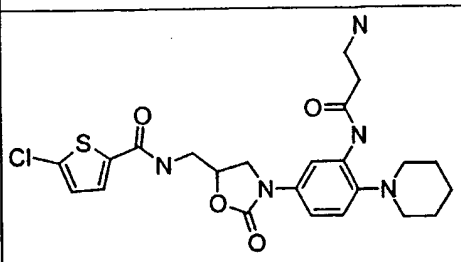
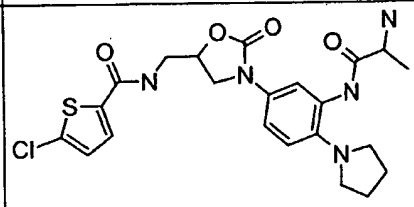
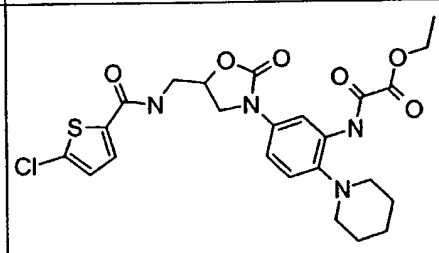
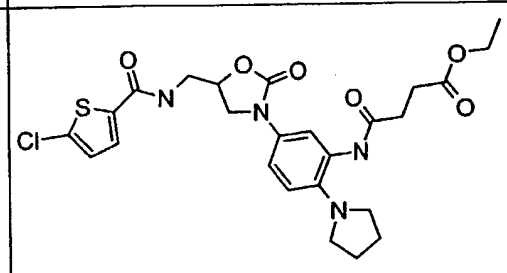
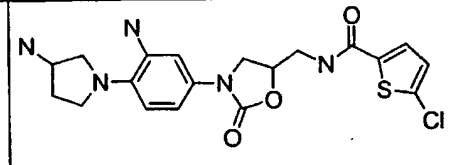


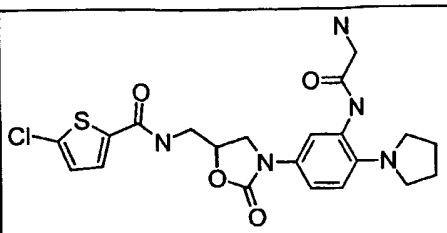
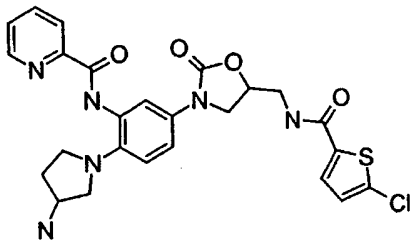
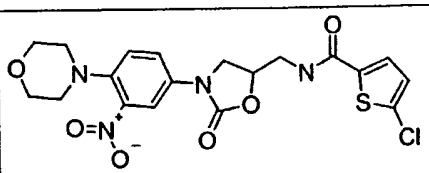
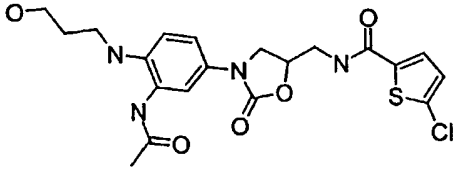
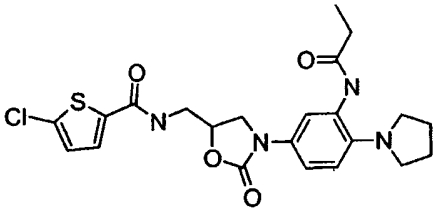
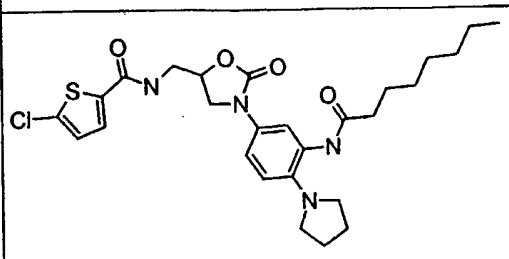
Analog der allgemeinen Arbeitsvorschrift zur Herstellung der Derivate **B** wurden 130 mg (32.5 µmol) TentaGel SAM Harz mit Pyrrolidin als Aminderivat 1 und Acetylchlorid als Säurederivat 1 umgesetzt. Das Rohprodukt wurde zwischen Ethyl-

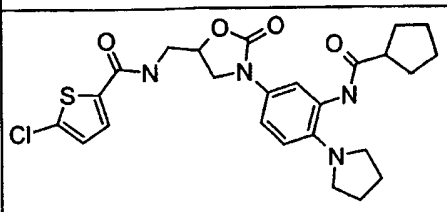
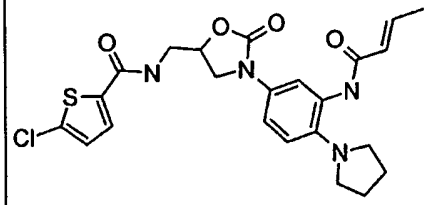
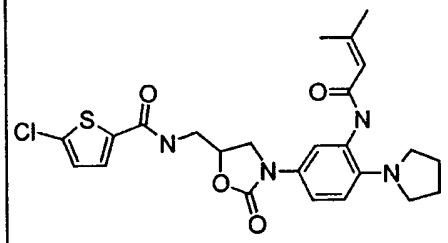
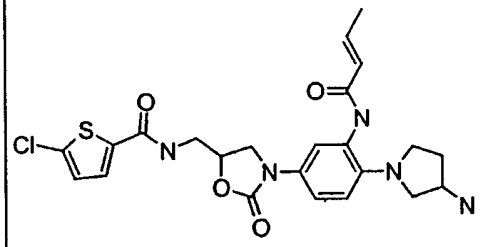
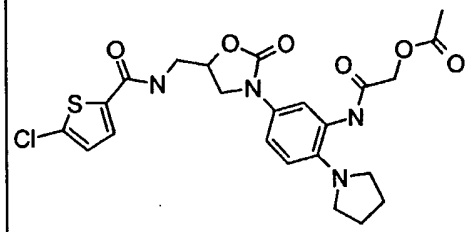
acetat und $NaHCO_3$-Lösung verteilt, die organische Phase wurde mit NaCl ausgesalzen, dekantiert und zur Trockene eingedampft. Dieses Rohprodukt wurde durch Vakuum-Flashchromatographie an Kieselgel (Dichlormethan/Ethylacetat, 1:1-0:1) gereinigt.

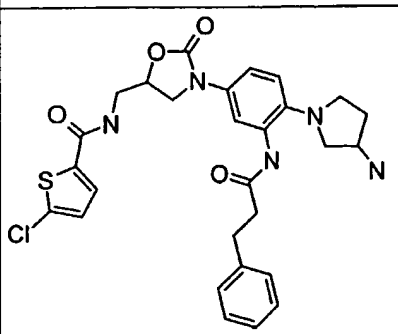
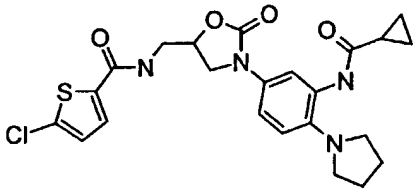
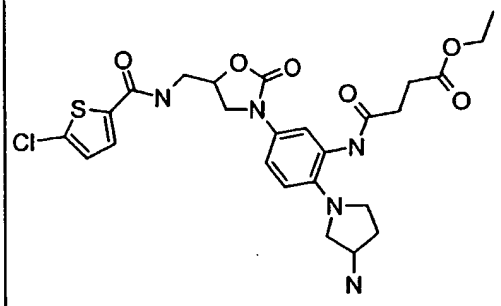
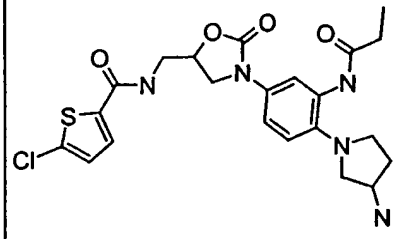
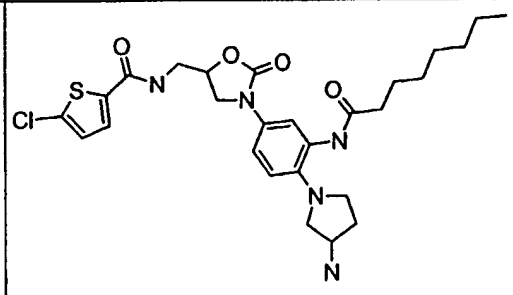
^{1}H-NMR (400 MHz, CD_3OH): 1.93 – 2.03, br, 4 H; 2.16, s, 3 H; 3.20-3.30, br, 4 H; 3.70, d, 2 H; 3.86, dd, 1H; 4.10, dd, 1 H; 4.14, dd, 1 H; 4.80-4.90, m, 1 H; 7.00, d, 1 H; 7.07, d, 1 H; 7.31, dd, 1 H; 7.51, d, 1 H; 7.60, d, 1 H.

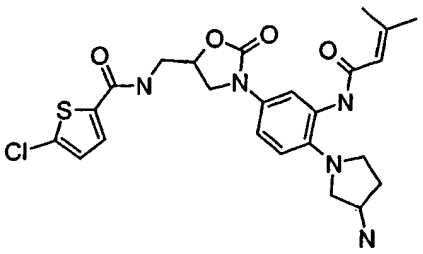
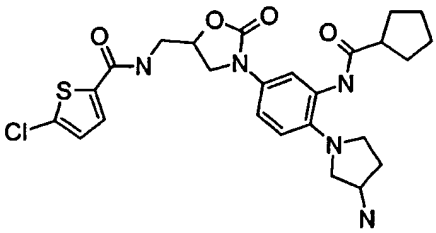
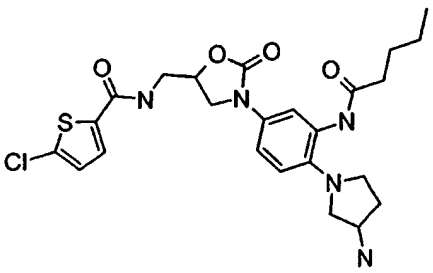
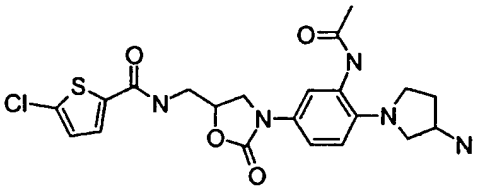
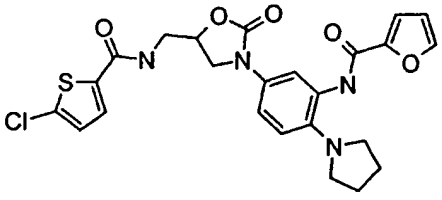
Analog zu der allgemeinen Arbeitsvorschrift wurden die folgenden Verbindungen hergestellt.

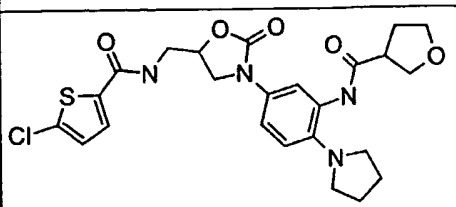
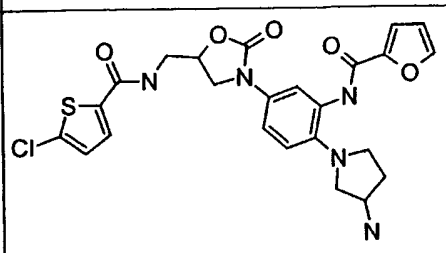
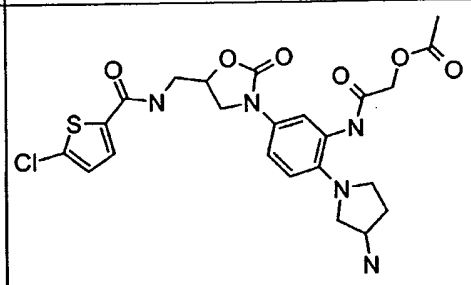
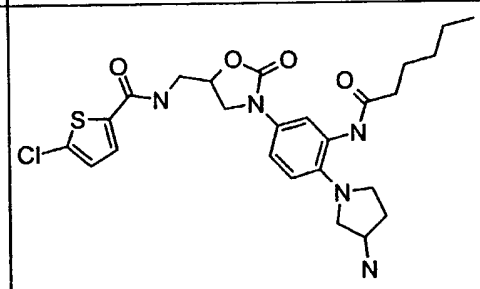
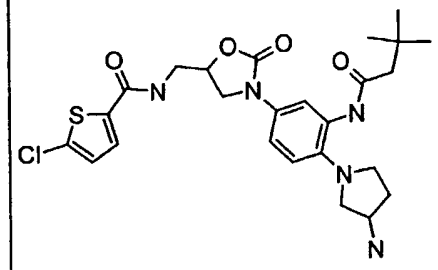
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
177		2,62	79,7
178		2,49	33,7
179		4,63	46,7
180		3,37	44,8
181		2,16	83

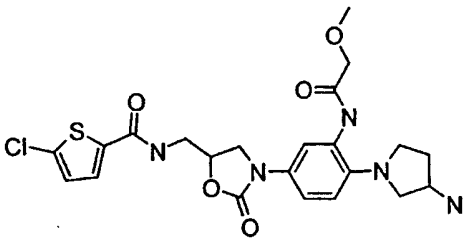
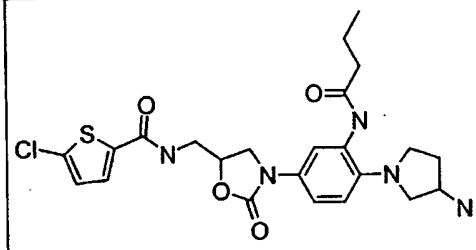
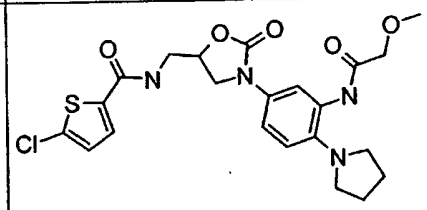
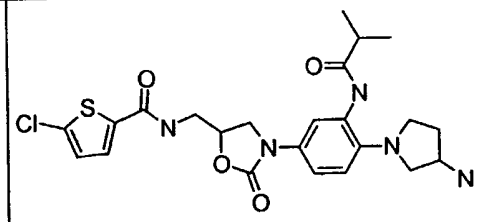
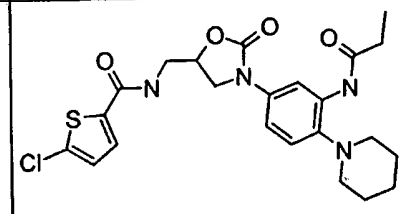
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
182		2,31	93,3
183		2,7	100
184		3,91	51
185		2,72	75,2
186		3,17	46
187		4,61	50,2

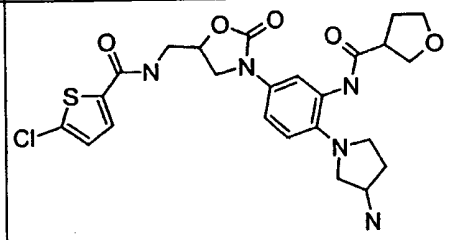
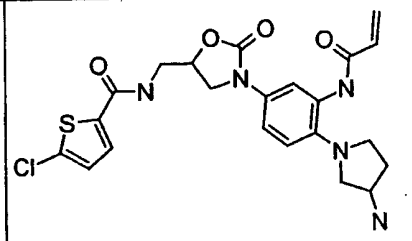
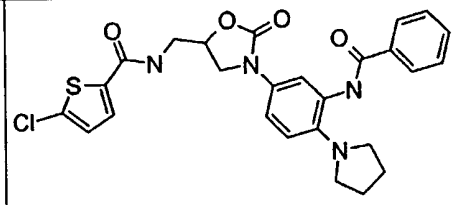
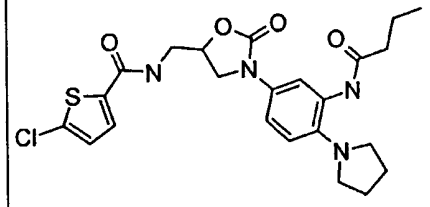
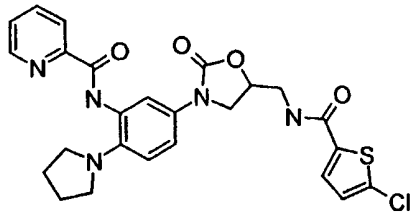
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
188		3,89	56,6
189		3,37	52,9
190		3,6	63,9
191		2,52	70,1
192		3,52	46,6

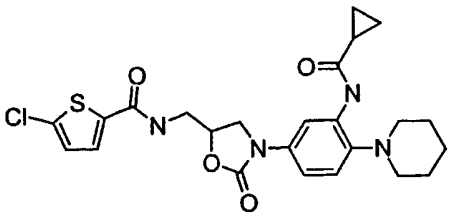
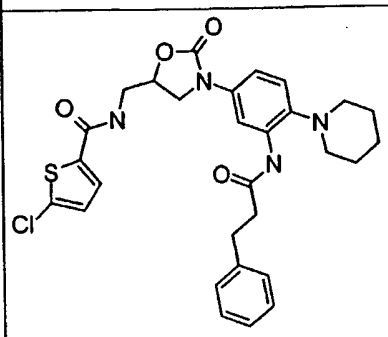
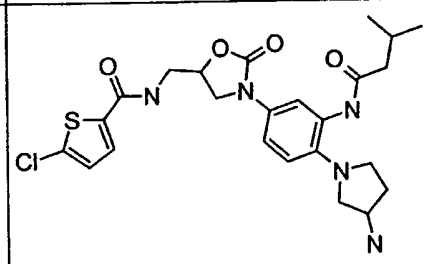
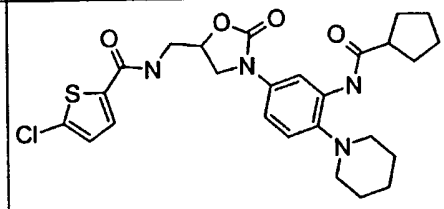
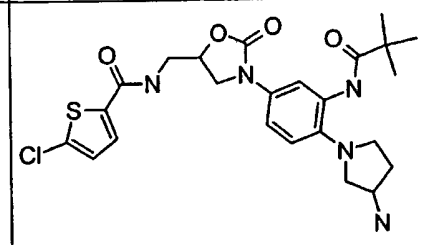
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
193		2,87	50,1
194		3,25	71,1
195		2,66	67
196		2,4	52,1
197		3,13	48,9

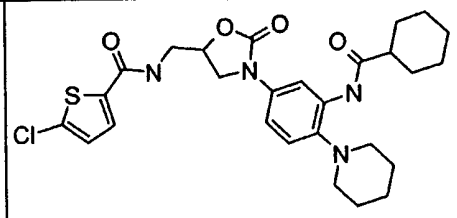
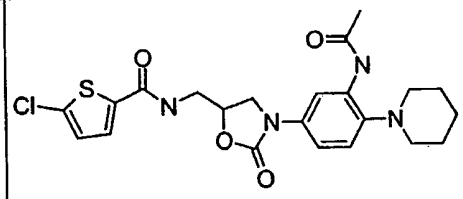
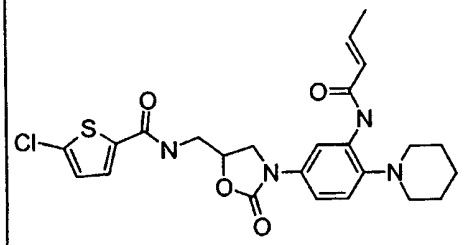
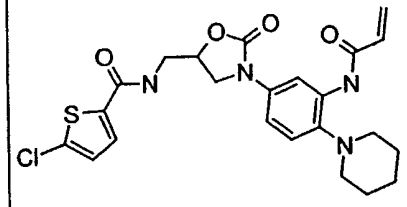
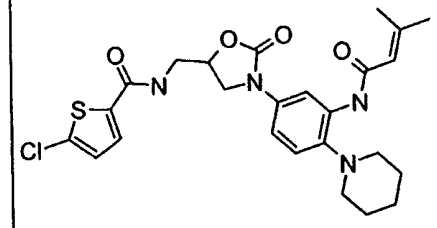
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
198		2,67	75,5
199		2,72	65,7
200		2,71	57,3
201		2,22	100
202		3,89	75,7

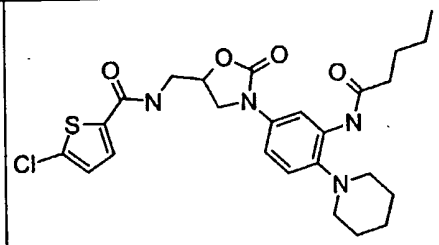
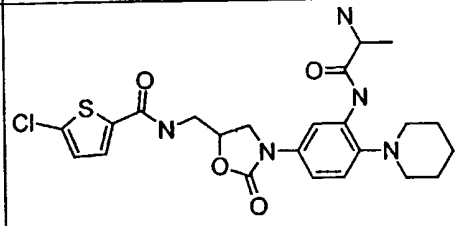
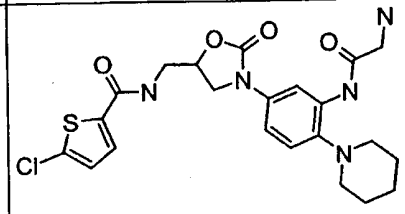
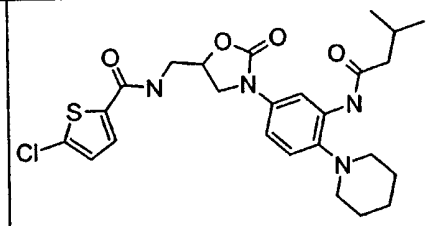
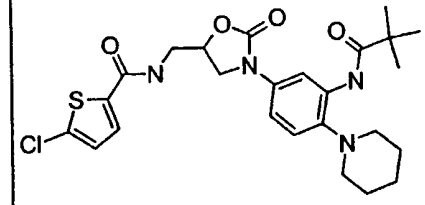
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
203		3,19	49,6
204		2,55	88,2
205		2,44	68,6
206		2,86	71,8
207		2,8	63,6

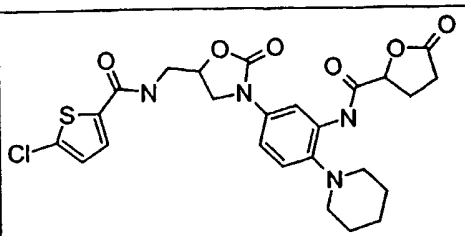
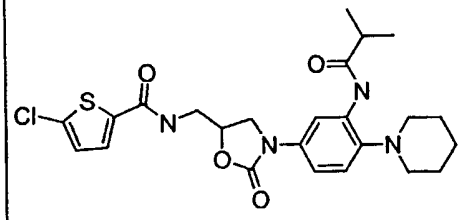
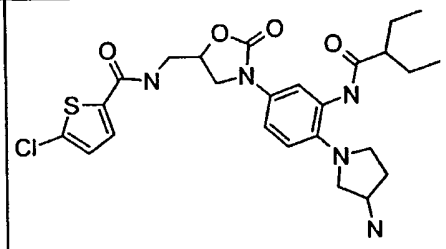
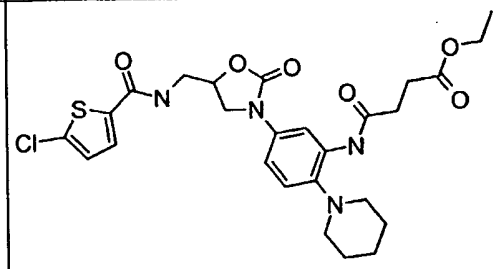
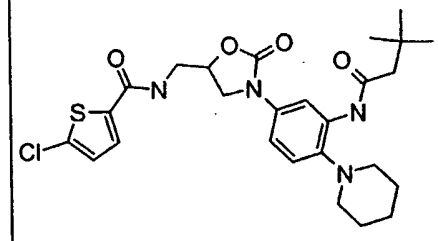
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
208		2,41	77
209		2,56	67,9
210		3,67	78,4
211		2,54	69,8
212		3,84	59,2

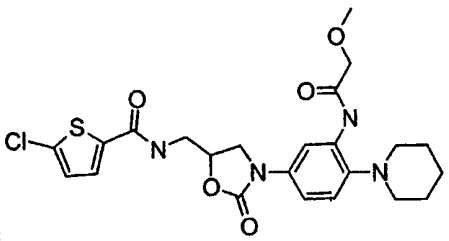
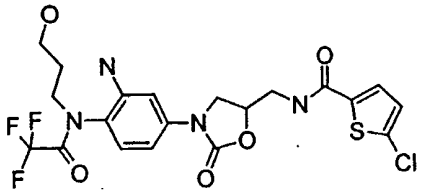
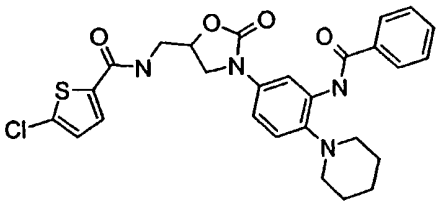
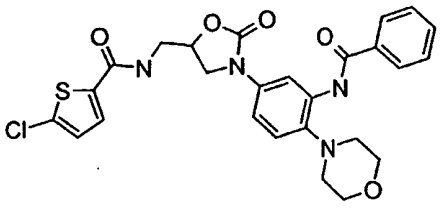
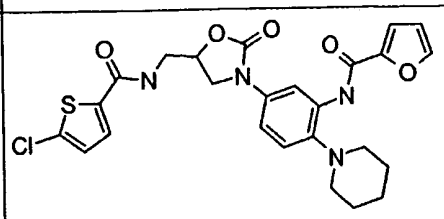
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
213		2,41	67,8
214		2,41	75,4
215		4,01	81,3
216		3,46	49,5
217		4,4	60,2

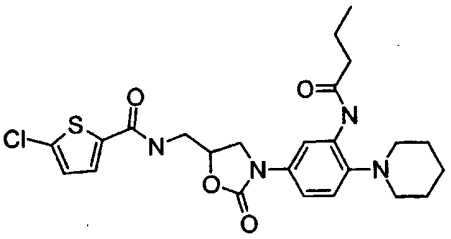
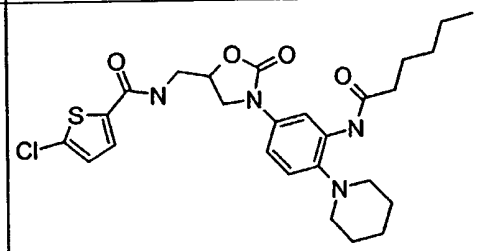
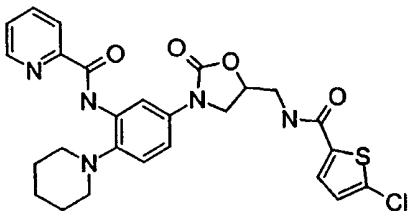
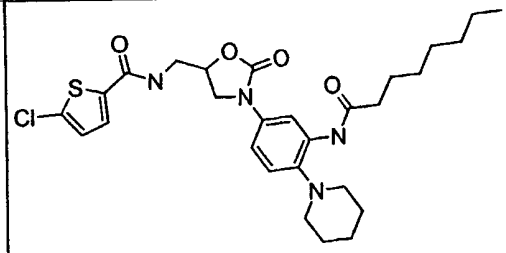
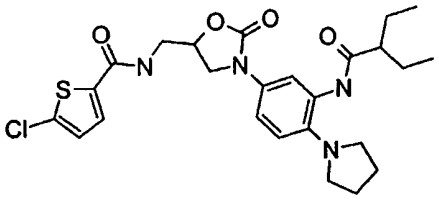
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
218		3,79	70,9
219		4,57	51,5
220		2,68	100
221		4,53	63,5
222		2,66	89,2

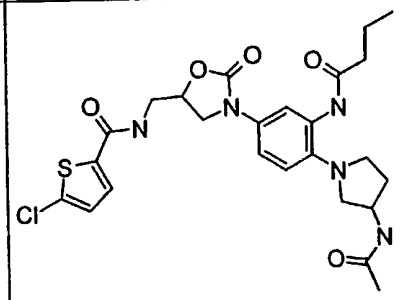
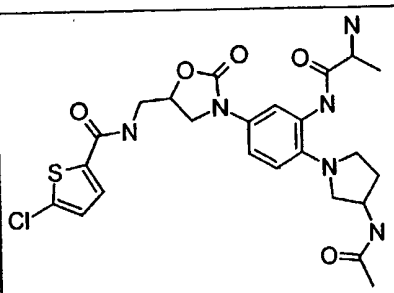
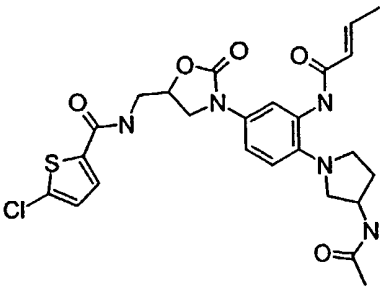
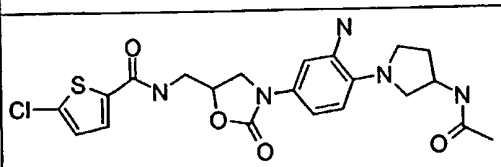
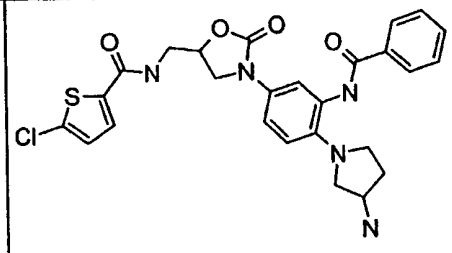
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
223		4,76	69,3
224		3,45	77,4
225		3,97	63,2
226		3,94	61,4
227		4,15	66,3

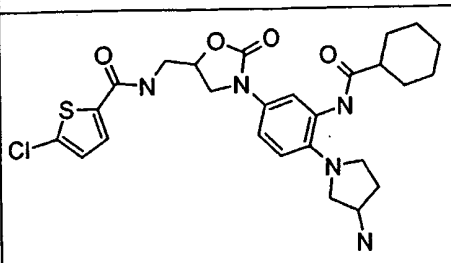
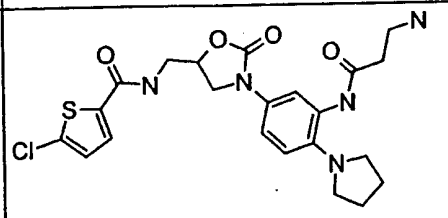
Beispiel	Struktur	Ret.-Zeit	HPLC [%]
228		4,41	55,1
229		2,83	41,1
230		2,7	83
231		4,39	64,2
232		4,85	74,9

Beispiel	Struktur	Ret.-Zeit	HPLC [%]
233		4,17	41
234		4,21	61,8
235		2,75	100
236		3,94	50
237		4,65	75,8

Beispiel	Struktur	Ret.-Zeit	HPLC [%]
238		4,4	75,3
239		4,24	62,2
240		4,76	75,1
241		4,17	72,5
242		4,6	74,8

Beispiel	Struktur	Ret.-Zeit	HPLC [%]
243		4,12	51,6
244		4,71	66,2
245		4,86	62
246		5,23	58,3
247		4,17	72,4

Beispiel	Struktur	Ret.-Zeit	HPLC [%]
248		3,35	59,6
249		2,41	60,3
250		3,31	65,2
251		2,86	36,5
252		2,69	89,8

Beispiel	Struktur	Ret.-Zeit	HPLC [%]
253		2,81	67,4
254		2,19	75,4

Alle Produkte der festphasenunterstützten Synthese wurden mittels LC-MS charakterisiert. Dazu wurde standardmäßig folgendes Trennsystem verwendet: HP 1100 mit UV-Detektor (208 – 400 nm), 40°C Ofentemperatur, Waters-Symmetry C18 Säule (50 mm x 2.1 mm, 3,5 µm), Laufmittel A: 99.9 % Acetonitril/0.1 % Ameisensäure, Laufmittel B: 99.9 % Wasser/0,1 % Ameisensäure; Gradient:

Zeit	A:%	B:%	Fluss
0, 00	10, 0	90, 0	0, 50
4, 00	90, 0	10, 0	0, 50
6, 00	90, 0	10, 0	0, 50
6, 10	10, 0	90, 0	1, 00
7, 50	10, 0	90, 0	0, 50

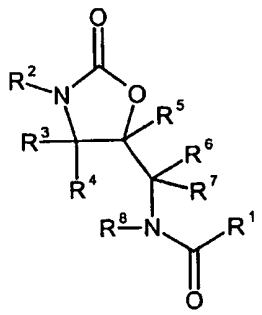
Der Nachweis der Substanzen erfolgte mittels eines Micromass Quattro LCZ MS, Ionisierung: ESI positiv/negativ.

Bei den oben aufgeführten Strukturen, die den oder die Reste  ,  oder -O beinhalten, ist stets eine  ,  oder -OH-Funktion gemeint.

Patentansprüche

1. Kombinationen enthaltend

A) mindestens eine Verbindung der Formel (I)



(I),

in welcher

R^1 für 2-Thiophen, steht, das in der 5-Position substituiert ist durch einen Rest aus der Gruppe Chlor, Brom, Methyl oder Trifluormethyl,

R^2 für D-A- steht:

wobei:
der Rest „A" für Phenylen steht;
der Rest „D" für einen gesättigten 5- oder 6-gliedrigen Heterocyclus steht,
der über ein Stickstoffatom mit „A" verknüpft ist,
der in direkter Nachbarschaft zum verknüpfenden Stickstoffatom eine Carbonylgruppe besitzt und
in dem ein Ring-Kohlenstoffglied durch ein Heteroatom aus der Reihe S, N und O ersetzt sein kann;

wobei
die zuvor definierten Gruppe „A" in der meta-Position bezüglich der Verknüpfung zum Oxazolidinon gegebenenfalls ein- oder zweifach substituiert sein kann mit einem Rest aus der Gruppe von Fluor, Chlor, Nitro, Amino, Trifluormethyl, Methyl oder Cyano,

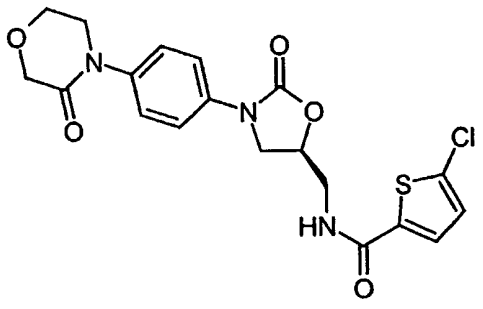
R^3, R^4, R^5, R^6, R^7 und R^8 für Wasserstoff stehen,

deren pharmazeutisch verträglichen Salze, Hydrate, Prodrugs oder deren Mischungen

und

B) mindestens einen weiteren pharmazeutischen Wirkstoff.

2. Kombinationen nach Anspruch 1, dadurch gekennzeichnet, dass die Verbindung A) 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid der Formel



,

seine pharmazeutisch verträglichen Salze, Hydrate, Prodrugs oder deren Mischungen ist.

3. Kombinationen nach Anspruch 1 oder 2, deren weitere pharmazeutische Wirkstoffe B) Plättchenaggregationshemmer, Antikoagulantien, Fibrinolytika, Lipidsenkern, Koronartherapeutika und/oder Vasodilatatoren sind.

4. Verfahren zur Herstellung der Kombinationen nach Ansprüchen 1 bis 3, dadurch gekennzeichnet, dass man Oxazolidinone der Formel (I) und Kombinationswirkstoffe in geeigneter Weise kombiniert oder herrichtet.

5. Kombinationen nach Ansprüchen 1 bis 3 zur Prophylaxe und/oder Behandlung von Erkrankungen.

6. Arzneimittel, enthaltend mindestens eine Kombination gemäß Ansprüchen 1 bis 3 und gegebenenfalls weitere pharmazeutische Wirkstoffe.

7. Arzneimittel enthaltend mindestens eine Kombination gemäß Ansprüchen 1 bis 3 sowie ein oder mehrere pharmakologisch unbedenkliche Hilfs- und/oder Trägerstoffe.

8. Verwendung von Kombinationen der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels zur Prophylaxe und/oder Behandlung von thromboembolischen Erkrankungen.

9. Verwendung von Kombinationen der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels zur Prophylaxe und/oder Behandlung von Herzinfarkt, Angina Pectoris (eingeschlossen instabile Angina), plötzlichem Herztod, Reokklusionen und Restenosen nach einer Angioplastie oder aortokoronarem Bypass, Hirnschlag, transitorischen ischämischen Attacken, peripheren arteriellen Verschlusskrankheiten, Lungenembolien oder tiefen venösen Thrombosen.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/EP 02/06237

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/422 A61K31/435 //(A61K31/435,31:422)

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 7 A61K A61P

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)
EPO-Internal, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 47919 A (POHLMANN JENS ;BAYER AG (DE); LAMPE THOMAS (DE); ROEHRIG SUSANNE () 5 July 2001 (2001-07-05) claims 1-15; examples 1-254	1-9
E	DE 101 05 989 A (BAYER AG) 14 August 2002 (2002-08-14) page 3, line 7 -page 10, line 11; claims 1-11; examples 1-11	1-9

-/--

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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	Date of mailing of the international search report
5 November 2002	15/11/2002

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

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 31092 A (BERNOTAT DANIELOWSKI SABINE ;MERCK PATENT GMBH (DE); DORSCH DIETER) 24 June 1999 (1999-06-24) page 37, line 29-32; example 1 page 40, line 30,31; example 1 page 45, line 35,36; example 2 page 48, line 8,9; example 2 page 54, line 30-32; example 5 page 56, line 9-11; example 5 ---	1-9
A	US 6 159 997 A (HORIKOSHI HIROYOSHI ET AL) 12 December 2000 (2000-12-12) examples 3,4; table 3 ---	1-9
A	EP 0 930 076 A (SANKYO CO) 21 July 1999 (1999-07-21) page 4, line 1 -page 9, line 37 ---	1-9
A	US 5 532 255 A (RADDATZ PETER ET AL) 2 July 1996 (1996-07-02) claims 1-22 -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
EP02/06237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although Claim 5 relates to a method for treatment of the human or animal body, the search was carried out on the basis of the alleged effects of the compound.

2. [X] 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:

see supplemental sheet ADDITIONAL MATTER 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.

Continuation of I.2

The current Claims 1-9 relate to an extremely large number of possible compounds or methods or uses. In fact they comprise so many alternatives, variables, possible permutations and/or restrictions as to appear unclear (and/or too broadly formulated) (PCT Article 6) to the extent that a meaningful search becomes impossible. Therefore, the search was directed to the parts of the claims that can be considered clear (and/or concise), that is the compounds and methods as they are set forth in the examples, including closely related homologous compounds, etc., or in the description on page 3 et seq. in combination with the component B indicated on page 30.

The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/06237

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0147919 A	05-07-2001	DE	19962924 A1	05-07-2001
		AU	2841401 A	09-07-2001
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/06237

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		SK	48494 A3	08-02-1995
		ZA	9402973 A	18-01-1995

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 02/06237

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61K31/422 A61K31/435 //(A61K31/435,31:422)

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

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61K A61P

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)
EPO-Internal, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
P,X	WO 01 47919 A (POHLMANN JENS ;BAYER AG (DE); LAMPE THOMAS (DE); ROEHRIG SUSANNE () 5. Juli 2001 (2001-07-05) Ansprüche 1-15; Beispiele 1-254 ---	1-9
E	DE 101 05 989 A (BAYER AG) 14. August 2002 (2002-08-14) Seite 3, Zeile 7 -Seite 10, Zeile 11; Ansprüche 1-11; Beispiele 1-11 ---	1-9

-/--

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

[X] 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
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"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 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	Absendedatum des Internationalen Recherchenberichts
5. November 2002	15/11/2002

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
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	Kling, I

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

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 99 31092 A (BERNOTAT DANIELOWSKI SABINE ;MERCK PATENT GMBH (DE); DORSCH DIETER) 24. Juni 1999 (1999-06-24) Seite 37, Zeile 29-32; Beispiel 1 Seite 40, Zeile 30,31; Beispiel 1 Seite 45, Zeile 35,36; Beispiel 2 Seite 48, Zeile 8,9; Beispiel 2 Seite 54, Zeile 30-32; Beispiel 5 Seite 56, Zeile 9-11; Beispiel 5 ---	1-9
A	US 6 159 997 A (HORIKOSHI HIROYOSHI ET AL) 12. Dezember 2000 (2000-12-12) Beispiele 3,4; Tabelle 3 ---	1-9
A	EP 0 930 076 A (SANKYO CO) 21. Juli 1999 (1999-07-21) Seite 4, Zeile 1 -Seite 9, Zeile 37 ---	1-9
A	US 5 532 255 A (RADDATZ PETER ET AL) 2. Juli 1996 (1996-07-02) Ansprüche 1-22 -----	1-9

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 02/06237

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. [X] Ansprüche Nr.
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

Obwohl der Anspruch 5 sich auf ein Verfahren zur Behandlung des menschlichen/tierischen Körpers beziehen, wurde die Recherche durchgeführt und gründete sich auf die angeführten Wirkungen der Zusammensetzung.

2. [X] Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

3. [ ] Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. [ ] Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. [ ] Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. [ ] Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. [ ] Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

[ ] Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

[ ] Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN PCT/ISA/ 210

Fortsetzung von Feld I.2

Die geltenden Patentansprüche 1-9 beziehen sich auf eine unverhältnismäßig große Zahl möglicher Verbindungen oder Verfahren oder Verwendungen. In der Tat umfassen sie so viele Wahlmöglichkeiten, Veränderliche, mögliche Permutationen und/oder Einschränkungen, daß sie im Sinne von Art. 6 PCT in einem solchen Maße unklar (und/oder zu weitläufig gefasst) erscheinen, als daß sie eine sinnvolle Recherche ermöglichten. Daher wurde die Recherche auf die Teile der Patentansprüche gerichtet, die als klar (und/oder knapp gefaßt) gelten können, nämlich die Verbindungen und Verfahren recherchiert wurden, z.B. wie diese in den Ausführungsbeispielen angegeben sind, einschliesslich nahverwandter homologer Verbindungen etc., oder wie in der Beschreibung auf Seite 3 unf folgende in Kombination mit der auf Seite 30 angegeben Komponente B.

Der Anmelder wird darauf hingewiesen, daß Patentansprüche, oder Teile von Patentansprüchen, auf Erfindungen, für die kein internationaler Recherchenbericht erstellt wurde, normalerweise nicht Gegenstand einer internationalen vorläufigen Prüfung sein können (Regel 66.1(e) PCT). In seiner Eigenschaft als mit der internationalen vorläufigen Prüfung beauftragte Behörde wird das EPA also in der Regel keine vorläufige Prüfung für Gegenstände durchführen, zu denen keine Recherche vorliegt. Dies gilt auch für den Fall, daß die Patentansprüche nach Erhalt des internationalen Recherchenberichtes geändert wurden (Art. 19 PCT), oder für den Fall, daß der Anmelder im Zuge des Verfahrens gemäß Kapitel II PCT neue Patentansprüche vorlegt.

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 02/06237

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
WO 0147919	A	05-07-2001	DE	19962924 A1	05-07-2001
			AU	2841401 A	09-07-2001
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			AU	744002 B2	14-02-2002
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INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 02/06237

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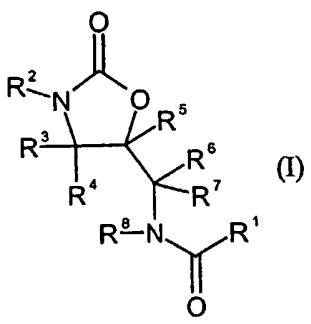
Erklärung gemäß Regel 4.17:
— *hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii) für die folgenden Bestimmungsstaaten AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Veröffentlicht:
— *mit internationalem Recherchenbericht*
— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: STENTS

(54) Bezeichnung: STENTS



(I)

(57) Abstract: The invention concerns stents containing compounds of formula (I) and methods for making said stents as well as their use.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft Stents, enthaltend Verbindungen der Formel (I) (I),Verfahren zur Herstellung dieser Stents und ihre Verwendung.

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Stents

Die vorliegende Erfindung betrifft Blutgerinnungsfaktor Xa enthaltende Stents, Verfahren zur Herstellung dieser Stents und ihre Verwendung, insbesondere zur Behandlung und/oder Prophylaxe von Thrombosen und/oder Restenosen.

Arteriosklerotisch bedingte Koronarerkrankungen werden unter anderem mit der heutzutage üblichen Methode der perkutanen transluminalen Koronarangioplastie (PTCA) behandelt. Hierzu wird ein Ballonkatheter in die verengte oder verschlossene Arterie eingeführt, diese wird dann durch Expansion des Ballons geweitet und der Blutfluss somit wiederhergestellt. Hierbei ist der akute, direkt nach der PTCA auftretende (akute Restenose) oder der spätere, subakute (Restenose) Wiederverschluss des Blutgefäßes ein Problem, das in ca. 30 % der Fälle auftritt.

Das Risiko einer akuten Restenose kann durch Gabe von Thrombozytenaggregationshemmern verringert werden. Außerdem kann eine mechanische Stützung der Koronarwand durch ein üblicherweise zylinderförmiges und expandierbares Geflecht (Stent) erfolgen, das in das erkrankte Gefäß eingeführt und am Ort der Stenose entfaltet wird, um die verengte Stelle zu öffnen und durch Abstützung der Blutgefäßwand dieses offenzuhalten. Auch wenn durch diese Methode das Restenose-Risiko leicht gesenkt werden kann, so steht doch zur Zeit keine überzeugende Therapie für die subakute Restenose zur Verfügung.

Derzeit werden Antikoagulantien wie beispielsweise Heparin; Plättchenaggregationshemmer wie beispielsweise Aspirin, Clopidogrel (Plavix) oder Ticlopidin (Ticlid); oder GlycoproteinIIb/IIIa-Antagonisten wie beispielsweise Abciximab systemisch bei der Stentbehandlung eingesetzt.

Eine neuere Möglichkeit zur Behandlung der Restenose besteht in der lokalen Gabe des Wirkstoffs mittels eines Stents, der den Wirkstoff freisetzt. Die Kombination von

Wirkstoff und Stent ermöglicht eine medikamentöse Behandlung und mechanische Stabilisierung in einer Anwendung.

So ermöglicht die Verbindung von Stents mit Antikoagulantien eine hohe lokale Konzentration an Wirkstoff, ohne dass es zu den unerwünschten systemischen Nebenwirkungen (z.B. Blutungen oder Schlaganfall) kommt.

Hierzu können Stents mit wirkstoffhaltigen Lackmaterialien überzogen werden. Die Wirkstofffreisetzung erfolgt durch Diffusion aus dem Lack oder durch Abbau des Lackes bei Anwendung von bioabbaubaren Lacksystemen.

Eine andere bereits beschriebene Möglichkeit ist die Präparation von kleinen Kavitäten bzw. Mikroporen in der Stentoberfläche, in die der Wirkstoff oder auch wirkstoffhaltige polymere Lacksysteme eingebettet werden (siehe beispielsweise EP-A-0 950 386). Anschließend kann ein wirkstofffreier Lack aufgebracht werden. Die Freisetzung erfolgt durch Diffusion oder Degradation oder durch eine Kombination beider Prozesse.

Darüber hinaus können wirkstoffhaltige Stents durch Schmelzeinbettung des Wirkstoffs in einen polymeren Träger z.B. mit Hilfe von Spritzgussverfahren hergestellt werden. Die Freisetzung des Wirkstoffs erfolgt bei diesen Stents in der Regel durch Diffusion.

Für die Behandlung und/oder Prophylaxe von Thrombosen und Restenosen nach der PTCA sind Blutgerinnungsfaktor Xa-Inhibitoren als Wirkstoffe in besonderer Weise geeignet.

So spielt der Blutgerinnungsfaktor Xa eine Rolle bei der Proliferation vaskulärer Glattmuskelzellen (VSMC, vascular smooth muscle cells). Die Migration und Proliferation der VSMC infolge einer Verletzung des Endothels und die daraus resultierende Bildung einer Neointima tragen hauptsächlich zur Ausbildung von Restenose

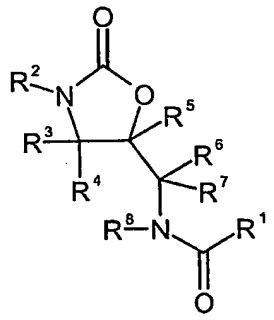
und Atherosklerose bei. Thrombozyten, Thrombin und weitere Komponenten des thrombotischen Prozesses sind wichtige Faktoren in der Neointima-Bildung. Die Serinprotease Thrombin, dessen Bildung durch den Blutgerinnungsfaktor Xa moduliert wird, übt zusätzlich zu ihrer Wirkung im Plasmagerinnungssystem weitere zelluläre Effekte über ihren spezifischen Rezeptor aus. Durch diesen Mechanismus aktiviert es Thrombozyten und wirkt als starkes Mitogen für endotheliale Zellen, VSMC, Bindegewebszellen und Makrophagen.

Die mitogene Wirkung des Blutgerinnungsfaktors Xa erfolgt indirekt über den thrombozytenbasierten Wachstumsfaktor (PDGF, platelet-derived growth factor) Rezeptor-Tyrosinkinase-Pfad und führt zur Aktivierung der mitogenaktivierten Proteinkinasen (MAPK, mitogen-activated protein kinases), bei denen es sich um intrazelluläre Mediatoren der Zellproliferation handelt. Die durch den Blutgerinnungsfaktor Xa modulierte VSMC-Proliferation beeinflusst den Wiederverschluss von Gefäßen und die Restenose nach Angioplastie.

So lässt sich durch spezifische Hemmung des Blutgerinnungsfaktors Xa die intimale Hyperplasie nach vaskulär-endothelialer Beschädigung und damit die Restenosequote nach erfolgreicher Angioplastie verringern, indem die mitogenen Effekte des Blutgerinnungsfaktors Xa selbst verringert werden und/oder die Bildung des potenten Mitogens Thrombin verringert wird (M. M. Samama, J. M. Walenga, B. Kaiser, J. Fareed, Specific Factor Xa Inhibitors, in: M. Verstraete, V. Fuster, E. J. Topol (Hsg.), Cardiovascular Thrombosis: Thrombocardiology and Thromboneurology, Philadelphia 1998, S. 175-176).

Überraschenderweise wurde nun gefunden, dass sich für diese Art von Behandlung Oxazolidinone der Formel (I) eignen, die insbesondere als Antikoagulantien und als selektive Inhibitoren des Blutgerinnungsfaktors Xa wirken und in WO 01/47919 ausführlich beschrieben sind. Die dort im allgemeinen und vor allem die dort spezifisch genannten Verbindungen sind ausdrücklicher Beschreibungsbestandteil der vorliegenden Erfindung.

Die vorliegende Erfindung betrifft somit Stents, enthaltend eine oder mehrere Verbindungen der Formel (I)



(I),

in welcher:

R^1 für gegebenenfalls benzokondensiertes Thiophen (Thienyl) steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann;

R^2 für einen beliebigen organischen Rest steht;

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für $(C_1$-$C_6)$-Alkyl stehen

sowie deren pharmazeutisch verträglichen Salze und/oder Hydrate.

Bevorzugt sind hierbei Stents, enthaltend Verbindungen der Formel (I),

worin

R^1 für gegebenenfalls benzokondensiertes Thiophen (Thienyl) steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch einen Rest aus der Gruppe von Halogen; Cyano; Nitro; Amino; Aminomethyl; $(C_1$-$C_8)$-Alkyl, das gegebenenfalls seinerseits ein- oder mehrfach durch Halogen substituiert

sein kann; (C_3-C_7)-Cycloalkyl; (C_1-C_8)-Alkoxy; Imidazolinyl; -C(=NH)NH_2; Carbamoyl; und Mono- und Di-(C_1-C_4)-alkyl-aminocarbonyl,

R^2 für eine der folgenden Gruppen steht:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,

B-M-B-,

D-M-B-,

wobei:

der Rest „A" für (C_6-C_{14})-Aryl, vorzugsweise für (C_6-C_{10})-Aryl, insbesondere für Phenyl oder Naphthyl, ganz besonders bevorzugt für Phenyl, steht;

der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 3 Heteroatome und/oder Hetero-Kettenglieder, insbesondere bis zu 2 Heteroatome und/oder Hetero-Kettenglieder, aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D" für einen gesättigten oder teilweise ungesättigten, mono- oder bicyclischen, gegebenenfalls benzokondensierten 4- bis 9-gliedrigen Heterocyclus steht, der bis zu drei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;

der Rest „M" für –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- , -SO_2- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Nitro; Carbamoyl; Pyridyl; (C_1-C_6)-Alkanoyl; (C_3-C_7)-Cycloalkanoyl; (C_6-C_{14})-Arylcarbonyl; (C_5-C_{10})-Heteroarylcarbonyl; (C_1-C_6)-Alkanoyloxymethyloxy; (C_1-C_4)-Hydroxyalkylcarbonyl; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl,

wobei (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; $-OR^{27}$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ und $-C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1 bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkanoyl, Carbamoyl, Trifluormethyl, Phenyl oder Pyridyl bedeuten,

und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu drei, vorzugsweise bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, $-CH_2C(NR^{27}R^{28})=NR^{29}$ oder $-COR^{33}$ bedeuten,

wobei

R^{33} (C_1-C_6)-Alkoxy, (C_1-C_4)-Alkoxy-(C_1-C_4)-alkyl, (C_1-C_4)-Alkoxycarbonyl-(C_1-C_4)-alkyl, (C_1-C_4)-Aminoalkyl, (C_1-C_4)-Alkoxycarbonyl, (C_1-C_4)-Alkanoyl-(C_1-C_4)-alkyl, (C_3-C_7)-Cycloalkyl, (C_2-C_6)-Alkenyl, (C_1-C_8)-Alkyl, das gegebenenfalls durch Phenyl oder Acetyl substituiert sein kann, (C_6-C_{14})-Aryl, (C_5-C_{10})-Heteroaryl, Trifluormethyl, Tetrahydrofuranyl oder Butyrolacton bedeutet,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze und/oder Hydrate.

Ebenfalls bevorzugt sind hierbei Stents, enthaltend Verbindungen der Formel (I),

worin

R^1 für Thiophen (Thienyl), insbesondere 2-Thiophen, steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch Halogen, vorzugsweise Chlor oder Brom, Amino, Aminomethyl oder (C_1-C_8)-Alkyl, vorzugsweise Methyl, wobei der (C_1-C_8)-Alkylrest gegebenenfalls seinerseits ein- oder mehrfach durch Halogen, vorzugsweise Fluor, substituiert sein kann,

R^2 für eine der folgenden Gruppen steht:

A-,

A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

wobei:

der Rest „A" für (C_6-C_{14})-Aryl, vorzugsweise für (C_6-C_{10})-Aryl, insbesondere für Phenyl oder Naphthyl, ganz besonders bevorzugt für Phenyl, steht;

der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 3 Heteroatome und/oder Hetero-Kettenglieder, insbesondere bis zu 2 Heteroatome und/oder Hetero-Kettenglieder, aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D" für einen gesättigten oder teilweise ungesättigten 4- bis 7-gliedrigen Heterocyclus steht, der bis zu drei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;

der Rest „M" für –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Nitro; Carbamoyl; Pyridyl; (C_1-C_6)-Alkanoyl; (C_3-C_7)-Cycloalkanoyl; (C_6-C_{14})-Arylcarbonyl; (C_5-C_{10})-Hetero-

arylcarbonyl; (C_1-C_6)-Alkanoyloxymethyloxy; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl,

wobei (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; $-OR^{27}$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ und $-C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1 bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeuten,

und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu drei, vorzugsweise bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_4)-Alkanoyl, (C_6-C_{14})-Arylcarbonyl, (C_5-C_{10})-Heteroarylcarbonyl, (C_1-C_4)-Alkylaminocarbonyl oder $-CH_2C(NR^{27}R^{28})=NR^{29}$ bedeuten,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze und/oder Hydrate.

Besonders bevorzugt sind hierbei Stents, enthaltend Verbindungen der Formel (I),

worin

R^1 für Thiophen (Thienyl), insbesondere 2-Thiophen, steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch Halogen, vorzugsweise Chlor oder Brom, oder (C_1-C_8)-Alkyl, vorzugsweise Methyl, wobei der (C_1-C_8)-Alkylrest gegebenenfalls seinerseits ein- oder mehrfach durch Halogen, vorzugsweise Fluor, substituiert sein kann,

R^2 für eine der folgenden Gruppen steht:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

wobei:
der Rest „A" für Phenyl oder Naphthyl, insbesondere für Phenyl, steht;

der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 2 Heteroatome aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D" für einen gesättigten oder teilweise ungesättigten 5- oder 6-gliedrigen Heterocyclus steht, der bis zu zwei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;

der Rest „M" für –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Pyridyl; (C_1-C_3)-Alkanoyl; (C_6-C_{10})-Arylcarbonyl; (C_5-C_6)-Heteroarylcarbonyl; (C_1-C_3)-Alkanoyloxymethyloxy; -$C(NR^{27}R^{28})$=NR^{29}; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-Alkyl; und Cyclopropyl, Cyclopentyl oder Cyclohexyl,

wobei (C_1-C_4)-Alkyl und Cyclopropyl, Cyclopentyl oder Cyclohexyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; -OH; -OCH_3; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ und -$C(NR^{27}R^{28})$=NR^{29},

wobei:

v entweder 0 oder 1, vorzugsweise 0, bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder aber Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeuten

und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden können, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-Alkanoyl oder Phenylcarbonyl bedeuten,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze und/oder Hydrate.

Insbesondere bevorzugt sind hierbei Stents, enthaltend Verbindungen der Formel (I),

worin

R^1 für 2-Thiophen, steht, das gegebenenfalls in der 5-Position substituiert sein kann durch einen Rest aus der Gruppe Chlor, Brom, Methyl oder Trifluormethyl,

R^2 für eine der folgenden Gruppen steht:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,
B-M-B-,
D-M-B-,

wobei:

der Rest „A" für Phenyl oder Naphthyl, insbesondere für Phenyl, steht;

der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 2 Heteroatome aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D" für einen gesättigten oder teilweise ungesättigten 5- oder 6-gliedrigen Heterocyclus steht, der ein Stickstoffatom und gegebenenfalls ein weiteres Heteroatom und/oder Hetero-Kettenglied aus der Reihe S, SO, SO_2 und O; oder bis zu zwei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2 und O enthält;

der Rest „M" für –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Pyridyl; (C_1-C_3)-Alkanoyl; (C_6-C_{10})-Arylcarbonyl; (C_5-C_6)-Heteroarylcarbonyl; (C_1-C_3)-Alkanoyloxymethyloxy; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-Alkyl; und Cyclopropyl, Cyclopentyl oder Cyclohexyl,

wobei (C_1-C_4)-Alkyl und Cyclopropyl, Cyclopentyl oder Cyclohexyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe

von Cyano; -OH; $-OCH_3$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ und $-C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1, vorzugsweise 0, bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder aber Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeuten

und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden können, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-Alkanoyl oder Phenylcarbonyl bedeuten,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_4)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze und/oder Hydrate.

Ganz besonders bevorzugt sind hierbei Stents, enthaltend Verbindungen der Formel (I),

worin

R^1 für 2-Thiophen, steht, das in der 5-Position substituiert ist durch einen Rest aus der Gruppe Chlor, Brom, Methyl oder Trifluormethyl,

R^2 für D-A- steht:

wobei:
der Rest „A" für Phenylen steht;

der Rest „D" für einen gesättigten 5- oder 6-gliedrigen Heterocyclus steht,

der über ein Stickstoffatom mit „A" verknüpft ist,

der in direkter Nachbarschaft zum verknüpfenden Stickstoffatom eine Carbonylgruppe besitzt und

in dem ein Ring-Kohlenstoffglied durch ein Heteroatom aus der Reihe S, N und O ersetzt sein kann;

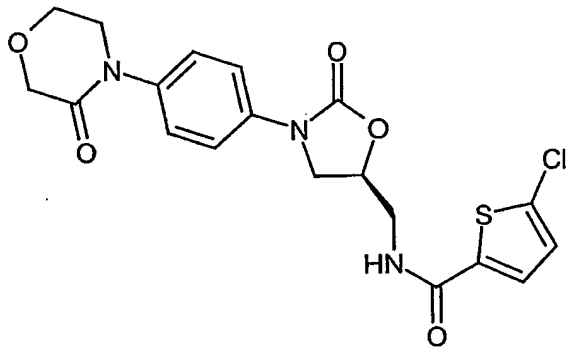
wobei

die zuvor definierten Gruppe „A" in der meta-Position bezüglich der Verknüpfung zum Oxazolidinon gegebenenfalls ein- oder zweifach substituiert sein kann mit einem Rest aus der Gruppe von Fluor, Chlor, Nitro, Amino, Trifluormethyl, Methyl oder Cyano,

R^3, R^4, R^5, R^6, R^7 und R^8 für Wasserstoff stehen

und deren pharmazeutisch verträglichen Salze und/oder Hydrate.

Ebenfalls ganz besonders bevorzugt ist hierbei ein Stent, enthaltend die Verbindung aus Beispiel 44 der WO 01/47919 mit der folgenden Formel



und ihre pharmazeutisch verträglichen Salze und/oder Hydrate.

Hinsichtlich der Offenbarung der Verbindungen der Formel (I), beispielsweise was ihre Herstellung betrifft, wird ausdrücklich auf die Offenbarung der WO 01/47919 Bezug genommen.

Die vorliegende Erfindung beschreibt die Verwendung von einer oder mehreren Verbindungen der Formel (I), gegebenenfalls in Kombination mit einem oder mehreren anderen Wirkstoffen, zur Herstellung eines Arzneistoff(e) enthaltenden Freisetzungssystems, insbesondere eines Arzneistoff(e) enthaltenden Stents.

Außerdem beschreibt die vorliegende Erfindung ein Freisetzungssystem, insbesondere einen Stent, das eine oder mehrere Verbindungen der Formel (I), gegebenenfalls in Kombination mit einem oder mehreren anderen Wirkstoffen, enthält, das eine gezielte Freisetzung von einer oder mehreren Verbindungen der Formel (I) sowie von weiteren gegebenenfalls vorhandenen Wirkstoffen am Wirkort (drug targeting) ermöglicht und somit zur Prophylaxe und/oder Behandlung von Restenose und/oder Thrombosen, insbesondere nach PTCA geeignet sind.

Die vorliegende Erfindung beschreibt ebenfalls ein Verfahren zur Behandlung und/oder Prophylaxe von Thrombosen und/oder Restenose, wobei eine oder mehrere Verbindungen der Formel (I) in Kombination mit einem Stent angewendet werden. Bei dieser Anwendung kann die Verbindungen der Formel (I) entweder systemisch oder vorzugsweise in Form eines Verbindungen der Formel (I) enthaltenden Stents eingesetzt werden.

Während mit den bisher zur Verfügung stehenden Wirkstoffen und Stents nicht in allen Fällen ein ausreichender Therapieerfolg erzielt werden kann, ermöglicht die neue Kombination von Verbindungen der Formel (I) mit einem Stent eine effektivere Behandlung und/oder Prophylaxe von Thrombosen und/oder Restenose. Durch lokale Applikation von Verbindungen der Formel (I) in Kombination mit einem Stent gelingt es, die zur Verhinderung von Thrombosen und/oder Restenose erforderliche Dosis des Arzneistoffs zu senken. Somit können unverwünschte systemische Effekte minimiert werden. Gleichzeitig kann die lokale Konzentration gesteigert werden und somit die Wirksamkeit erhöht werden.

Außerdem kann, zusätzlich zu der erfindungsgemäßen Applikation, eine systemische und/oder lokale Gabe von weiteren zur Behandlung und/oder Prophylaxe von Thrombosen und/oder Restenose geeigneten Wirkstoffen wie beispielhaft und vorzugsweise Abciximab, Eptifibatid, Tirofiban, Acetylsalicylsäure, Ticlopidin oder Clopidogrel erfolgen. Bevorzugt ist eine zusätzliche systemische Behandlung mit Verbindungen der Formel (I), insbesondere durch orale Gabe.

Zur Herstellung der erfindungsgemäßen Verbindungen der Formel (I) enthaltenden Freisetzungssysteme werden übliche Stents verwendet, wobei der Stentgrundkörper entweder aus Metallen oder nicht abbaubaren Kunststoffen wie beispielhaft und vorzugsweise Polyethylen, Polypropylen, Polycarbonat, Polyurethan und/oder Polytetrafluorethylen (PTFE) besteht. Weiterhin werden als Stentgrundkörper Stents mit verschiedenen Konstruktionen des Metallgeflechts, die verschiedene Oberflächen und

Faltungsprinzipien ermöglichen und wie zum Beispiel in der WO 01/037761, WO 01/037892 beschrieben, verwendet.

Diese Stents werden mit den Verbindungen der Formel (I) beschichtet und/oder befüllt. Alternativ können Verbindungen der Formel (I) bei nichtmetallischen Stents direkt in das zur Herstellung der Stents verwendete Material eingearbeitet werden.

Zur Beschichtung oder Befüllung werden Trägermaterialien mit den Verbindungen der Formel (I) gemischt. Als Trägermaterialien dienen dabei vorzugsweise polymere Träger, insbesondere biokompatible, nicht-bioabbaubare Polymere oder Polymergemische, wie beispielhaft und vorzugsweise Polyacrylate und deren Copolymerisate wie beispielhaft und vorzugsweise Poly(hydroxyethyl)methylmethacrylate; Polyvinylpyrrolidone; Celluloseester und -ether; fluorierte Polymere wie beispielhaft und vorzugsweise PTFE; Polyvinylacetate und deren Copolymere; vernetzte und unvernetzte Polyurethane, Polyether oder Polyester; Polycarbonate; Polydimethylsiloxane. Alternativ werden auch biokompatible, bioabbaubare Polymere oder Polymergemische, wie beispielhaft und vorzugsweise Polymere oder Copolymerisate aus Lactid und Glycolid, oder aus Caprolacton und Glycolid; andere Polyester; Polyorthoester; Polyanhydride; Polyaminosäuren; Polysaccharide; Polyiminocarbonate; Polyphosphazene und Poly(ether-ester)-Copolymere als polymere Träger verwendet.

Als polymere Träger eignen sich weiterhin auch Gemische aus bioabbaubaren und/oder nicht-bioabbaubaren Polymeren. Durch diese Mischungen wird die Freisetzungsrate des Wirkstoffs optimal eingestellt.

Zur Herstellung von beschichteten oder gefüllten Stents werden die Mischungen von Verbindungen der Formel (I) und Träger, vorzugsweise in geeigneten Lösungsmitteln, gelöst. Diese Lösungen werden dann durch verschiedene Techniken wie z.B. Sprühen, Tauchen oder Aufbürsten auf den Stent aufgetragen. Nach anschließender oder gleichzeitiger Entfernung des Lösungsmittels entsteht so der mit wirkstoffhaltigem Lack versetzte Stent. Alternativ können auch Mischungen von Verbindungen

der Formel (I) und Träger aufgeschmolzen werden und nach den gleichen Auftragungsmethoden aufgetragen werden.

Vorzugsweise werden die Stents vorbehandelt, um eine Vergrößerung der äußeren und/oder inneren Stentoberfläche zu bewirken. Damit wird das Beladungspotential erhöht und größere Lack-(Wirkstoff/Polymer-)mengen können aufgebracht werden. Zur Vorbehandlung der Stents werden beispielsweise verschiedene Ätztechniken aber auch Behandlungen mit ionisierter Strahlung angewendet. Ebenso können Mikroporen oder Kavitäten mit Hilfe verschiedener Techniken in den Stents erzeugt werden.

Die Wirkstoffgehalte der mit Verbindungen der Formel (I) beschichteten bzw. gefüllten Stents betragen in der Regel von 0,001 Gew.-% bis 50 Gew.-%, bevorzugt von 0,01 Gew.-% bis 30 Gew.-%, besonders bevorzugt 0,1 Gew.-% bis 15 Gew.-%.

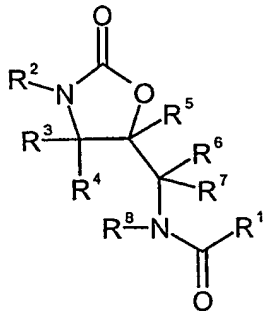
Bei nichtmetallischen Stents können die Verbindungen der Formel (I) auch direkt zum Beispiel als Schmelzeinbettung in die Stentgrundkörper eingearbeitet werden. Dabei werden wirkstoffhaltige polymere Trägermassen nach üblichen Verfahren, zum Beispiel durch Spritzgussverfahren zu der endgültigen wirkstoffhaltigen Form verarbeitet. Die Freisetzung des Wirkstoffs erfolgt hierbei in der Regel durch Diffusion.

Die Wirkstoffgehalte von Stents mit eingebetteten Verbindungen der Formel (I) betragen in der Regel von 0,001 Gew.-% bis 70 Gew.-%, bevorzugt von 0,01 Gew.-% bis 50 Gew.-%, besonders bevorzugt 0,1 Gew.-% bis 30 Gew.-%.

Die Verbindungen der Formel (I) enthaltenden Stents werden gegebenenfalls zusätzlichen mit einer Membran überzogen. Diese Membran dient beispielhaft und vorzugsweise zur Steuerung der Arzneistofffreisetzung und/oder zum Schutz der wirkstoffhaltigen Stents vor äußeren Einflüssen..

Patentansprüche

1. Stents enthaltend eine oder mehrere Verbindungen der Formel (I)



(I),

in welcher

R^1 für 2-Thiophen, steht, das in der 5-Position substituiert ist durch einen Rest aus der Gruppe Chlor, Brom, Methyl oder Trifluormethyl,

R^2 für D-A- steht:

wobei:

der Rest „A" für Phenylen steht;

der Rest „D" für einen gesättigten 5- oder 6-gliedrigen Heterocyclus steht,

der über ein Stickstoffatom mit „A" verknüpft ist,

der in direkter Nachbarschaft zum verknüpfenden Stickstoffatom eine Carbonylgruppe besitzt und

in dem ein Ring-Kohlenstoffglied durch ein Heteroatom aus der Reihe S, N und O ersetzt sein kann;

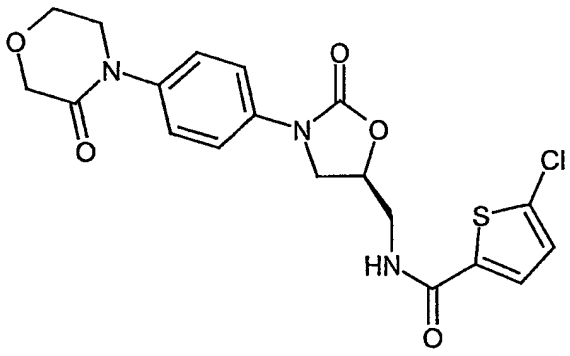
wobei

die zuvor definierten Gruppe „A" in der meta-Position bezüglich der Verknüpfung zum Oxazolidinon gegebenenfalls ein- oder zweifach substituiert sein kann mit einem Rest aus der Gruppe von Fluor, Chlor, Nitro, Amino, Trifluormethyl, Methyl oder Cyano,

R^3, R^4, R^5, R^6, R^7 und R^8 für Wasserstoff stehen,

deren pharmazeutisch verträglichen Salze, Hydrate und/oder deren Mischungen.

2. Stents nach Anspruch 1, dadurch gekennzeichnet, dass die Verbindung 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid der Formel



,

seine pharmazeutisch verträglichen Salze, Hydrate und/oder deren Mischungen ist.

3. Stents nach Anspruch 1 oder 2, die mit einer zusätzlichen Membran überzogen sind.

4. Stents nach einem der Ansprüche 1 bis 3, enthaltend mindestens einen weiteren Wirkstoff.

5. Stents nach einem der Ansprüche 1 bis 4 zur Behandlung von Restenose nach PTCA.

6. Stents nach einem der Ansprüche 1 bis 4 zur Behandlung und/oder Prophylaxe von Thrombosen nach PTCA.

7. Verwendung von Verbindungen der Formel (I), wie in Anspruch 1 definiert, zur oder bei der Herstellung von Stents.

8. Verwendung von Verbindungen der Formel (I), wie in Anspruch 1 definiert, zur Herstellung von Stents zur Behandlung und/oder Prophylaxe von Restenose und/oder Thrombosen.

9. Verfahren zur Herstellung von Stents, dadurch gekennzeichnet, dass man Stents mit einer oder mehreren Verbindungen der Formel (I), wie in Anspruch 1 definiert, beschichtet oder befüllt.

10. Verfahren zur Herstellung von Stents, dadurch gekennzeichnet, dass man einen oder mehrere Verbindungen der Formel (I), wie in Anspruch 1 definiert, enthaltenden polymere Trägermassen zu Stents formt.

11. Verfahren zur Behandlung von Patienten mit restenotischen Arterien durch gleichzeitige Anwendung von einer oder mehreren Verbindungen der Formel (I), wie in Anspruch 1 definiert, und einem Stent.

12. Verfahren gemäß Anspruch 11, dadurch gekennzeichnet, dass Verbindungen der Formel (I), wie in Anspruch 1 definiert, in oder auf dem Stent enthalten

sind und lokal freigesetzt werden.

13. Verfahren zur Behandlung und/oder Prophylaxe von Restenose und/oder Thrombosen durch Anwendung von Stents nach einem der vorhergehenden Ansprüche in Kombination mit lokaler und/oder systemischer Verabreichung von anderen zur Restenose- und/oderThrombose- Behandlung und/oder Prophylaxe geeigneten Wirkstoffen.

14. Verfahren zur Behandlung und/oder Prophylaxe von Restenose und/oder Thrombosen durch Anwendung von Stents nach einem der vorhergehenden Ansprüche in Kombination mit systemischer Gabe von Verbindungen der Formel (I), wie in Anspruch 1 definiert.

INTERNATIONAL SEARCH REPORT

Internatio[redacted]pplication No
PCT/EP 02/11402

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/16

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 7 A61L

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)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 47919 A (POHLMANN JENS ;BAYER AG (DE); LAMPE THOMAS (DE); ROEHRIG SUSANNE () 5 July 2001 (2001-07-05) cited in the application the whole document	1-14
Y	EP 0 950 386 A (CORDIS CORP) 20 October 1999 (1999-10-20) cited in the application column 3, line 50 -column 4, line 31 column 5, line 1-13	1-14
A	EP 0 623 615 A (MERCK PATENT GMBH) 9 November 1994 (1994-11-09) page 2, line 39-47 claims	1

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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	Date of mailing of the international search report
14 February 2003	26/02/2003

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

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11402

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 98 46628 A (COR THERAPEUTICS INC) 22 October 1998 (1998-10-22) abstract claims	1
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 02/11402

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61L31/16

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

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61L

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)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	WO 01 47919 A (POHLMANN JENS ;BAYER AG (DE); LAMPE THOMAS (DE); ROEHRIG SUSANNE () 5. Juli 2001 (2001-07-05) in der Anmeldung erwähnt das ganze Dokument ---	1-14
Y	EP 0 950 386 A (CORDIS CORP) 20. Oktober 1999 (1999-10-20) in der Anmeldung erwähnt Spalte 3, Zeile 50 -Spalte 4, Zeile 31 Spalte 5, Zeile 1-13 ---	1-14
A	EP 0 623 615 A (MERCK PATENT GMBH) 9. November 1994 (1994-11-09) Seite 2, Zeile 39-47 Ansprüche --- -/--	1

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

[X] 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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"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	Absendedatum des internationalen Recherchenberichts
14. Februar 2003	26/02/2003

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
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	Böhm, I

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

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 02/11402

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. [X] Ansprüche Nr. –
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

2. [ ] Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

3. [ ] Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die Internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. [ ] Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. [ ] Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. [ ] Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. [ ] Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

[ ] Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

[ ] Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN **PCT/ISA/ 210**

Fortsetzung von Feld I.1

Obwohl die Ansprüche 11-14 sich auf ein Verfahren zur Behandlung des menschlichen/tierischen Körpers beziehen, wurde die Recherche durchgeführt und gründete sich auf die angeführten Wirkungen der Verbindung.

Fortsetzung von Feld I.1

Regel 39.1(iv) PCT - Verfahren zur chirurgischen Behandlung des menschlichen oder tierischen Körpers

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 02/11402

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	WO 98 46628 A (COR THERAPEUTICS INC) 22. Oktober 1998 (1998-10-22) Zusammenfassung Ansprüche	1
A,P	WO 02 064575 A (PERNERSTORFER JOSEF ;POHLMANN JENS (DE); BAYER AG (DE); LAMPE THOM) 22. August 2002 (2002-08-22) das ganze Dokument	1-14

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 02/11402

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		WO 9846628 A1	22-10-1998
WO 02064575 A	22-08-2002	DE 10105989 A1	14-08-2002
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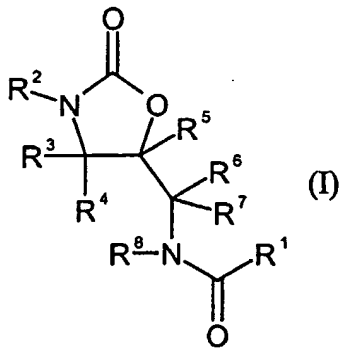


(I)

(57) Abrégé/Abstract:
The invention concerns stents containing compounds of formula (I) and methods for making said stents as well as their use.

ABSTRACT

The invention concerns stents containing compounds of formula (I) and methods for making said stents as well as their use.

Stents

The present invention relates to stents comprising coagulation factor Xa, processes for producing these stents and their use, especially for the treatment and/or prophylaxis of thromboses and/or restenoses.

Coronary diseases caused by arteriosclerosis are treated inter alia by the currently usual method of percutaneous transluminal coronary angioplasty (PTCA). For this purpose, a balloon catheter is introduced into the narrowed or blocked artery, which is then widened through expansion of the balloon, and the blood flow is thus restored. A problem in this connection, occurring in about 30% of cases, is the acute reocclusion, occurring immediately after the PTCA (acute restenosis), or the later, subacute (restenosis) reocclusion, of the blood vessel.

The risk of acute restenosis can be reduced by administration of platelet aggregation inhibitors. An additional possibility is mechanical support of the coronary wall by a normally cylindrical and expandable mesh (stent) which is introduced into the diseased vessel and unfolds at the site of the stenosis in order to open the narrowed place and keep it open by supporting the blood vessel wall. Although it is possible by this method to reduce the risk of restenosis slightly, at present there is still no convincing therapy available for subacute restenosis.

Currently employed systemically in stent treatment are anticoagulants such as, for example heparin; platelet aggregation inhibitors such as, for example aspirin, clopidogrel (Plavix) or ticlopidine (Ticlid); or glycoproteinIIb/IIIa antagonists such as, for example, abciximab.

A newer possibility for the treatment of restenosis is local administration of the active ingredient by means of a stent which releases the active ingredient. The combination of active ingredient and stent makes medical treatment and mechanical stabilization possible in one application.

Thus, the combination of stents with anticoagulants makes it possible for the local concentration of active ingredient to be high without unwanted systemic side effects (e.g. hemorrhages or stroke) occurring.

It is possible for this purpose to coat stents with active ingredient-containing coating materials. The active ingredient release takes place by diffusion from the coating or through breakdown of the coating when biodegradable coating systems are used.

Another possibility which has already been described is the preparation of small cavities or micropores in the stent surface, into which the active ingredient or else active ingredient-containing polymeric coating systems are embedded (see, for example, EP-A 0 950 386). An active ingredient-free coating can subsequently be applied. Release takes place by diffusion or degradation or by a combination of the two processes.

In addition, active ingredient-containing stents can be produced by melt embedding the active ingredient in a polymeric carrier, e.g. with the aid of injection molding processes. Release of the active ingredient from these stents usually takes place through diffusion.

Active ingredients particularly suitable for the treatment and/or prophylaxis of thromboses and restenoses after PTCA are coagulation factor Xa inhibitors.

Thus, coagulation factor Xa is involved in the proliferation of vascular smooth muscle cells (VSMC). The migration and proliferation of VSMC following an injury to the endothelium, and the formation of a neointima resulting therefrom, make a major contribution to the development of restenosis and atherosclerosis. Platelets, thrombin and other components of the thrombotic process are important factors in neointima formation. The serine protease thrombin, whose production is modulated by coagulation factor Xa, exerts further cellular effects, in addition to its effect in the plasma coagulation system, via its specific receptor. By this mechanism it activates platelets and acts as strong mitogen for endothelial cells, VSMC, connective tissue

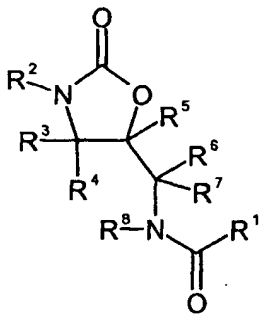
cells and macrophages.

The mitogenic effect of coagulation factor Xa takes place indirectly via the platelet-derived growth factor (PDGF) receptor tyrosine kinase pathway and leads to activation of the mitogen-activated protein kinases (MAPK), which are intracellular mediators of cellular proliferation. The VSMC proliferation modulated by coagulation factor Xa influences the reocclusion of vessels and the restenosis following angioplasty.

Thus, it is possible by specific inhibition of coagulation factor Xa to reduce the intimal hyperplasia after vascular endothelial damage, and thus the restenosis rate after successful angioplasty, since the mitogenic effects of coagulation factor Xa so far reduced and/or the production of the potential mitogen thrombin is reduced (M. M. Samama, J. M. Walenga, B. Kaiser, J. Fareed, Specific Factor Xa Inhibitors, in: M. Verstraete, V. Fuster, E. J. Topol (Ed.), Cardiovascular Thrombosis: Thrombocardiology and Thromboneurology, Philadelphia 1998, pp. 175-176).

It has now been found, surprisingly, that oxazolidinones of the formula (I) which act, in particular, as anticoagulants and as selective inhibitors of coagulation factor Xa, and are described in detail in WO 01/47919, are suitable for this type of treatment. The compounds mentioned generally therein and, in particular, those mentioned specifically therein form an express part of the description of the present invention.

The present invention thus relates to stents comprising one or more compounds of the formula (I)



(I),

in which:

R^1 is optionally benzo-fused thiophene (thienyl) which may optionally be substituted one or more times;

R^2 is any organic radical;

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and are hydrogen or (C_1-C_6)-alkyl,

and the pharmaceutically acceptable salts and/or hydrates thereof.

Preference is given in this connection to stents comprising compounds of the formula (I)

in which

R^1 is optionally benzo-fused thiophene (thienyl) which may optionally be substituted one or more times by a radical from the group of halogen; cyano; nitro; amino; aminomethyl; (C_1-C_8)-alkyl which may in turn be optionally substituted one or more times by halogen; (C_3-C_7)-cycloalkyl; (C_1-C_8)-alkoxy; imidazolinyl; $-C(=NH)NH_2$; carbamoyl; and mono- and di-(C_1-C_4)-alkylaminocarbonyl,

R^2 is one of the following groups:

A-,

A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" is (C_6-C_{14})-aryl, preferably (C_6-C_{10})-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;
the radical "B" is a 5- or 6-membered aromatic heterocycle which comprises up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the series S, N, NO (N-oxide) and O;
the radical "D" is a saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused 4- to 9-membered heterocycle which comprises up to three heteroatoms and/or hetero chain members from the series S, SO, SO_2, N, NO (N-oxide) and O;
the radical "M" is –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- , -SO_2- or a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be substituted one or more times by a radical from the group of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; (C_1-C_6)-alkanoyl; (C_3-C_7)-cycloalkanoyl; (C_6-C_{14})-arylcarbonyl; (C_5-C_{10})-heteroarylcarbonyl; (C_1-C_6)-alkanoyloxymethyloxy; (C_1-C_4)-hydroxyalkylcarbonyl; -$COOR^{27}$;

$-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl,

where (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl in turn may optionally be substituted by a radical from the group of cyano; $-OR^{27}$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ and $-C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

R^{27}, R^{28} and R^{29} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_4)-alkanoyl, carbamoyl, trifluoromethyl, phenyl or pyridyl,

and/or

R^{27} and R^{28}, or R^{27} and R^{29}, form, together with the nitrogen atom to which they are bonded, a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group of N, O and S, and

R^{30} and R^{31} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, $-CH_2C(NR^{27}R^{28})=NR^{29}$ or $-COR^{33}$,

where

R^{33} is (C_1-C_6)-alkoxy, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl-(C_1-C_4)-alkyl, (C_1-C_4)-aminoalkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl-(C_1-C_4)-alkyl, (C_3-C_7)-cyclo-

alkyl, (C_2-C_6)-alkenyl, (C_1-C_8)-alkyl which may optionally be substituted by phenyl or acetyl, or is (C_6-C_{14})-aryl, (C_5-C_{10})-heteroaryl, trifluoromethyl, tetrahydrofuranyl or butyrolactone,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and are hydrogen or (C_1-C_6)-alkyl,

and the pharmaceutically acceptable salts and/or hydrates thereof.

Preference is likewise given in this connection to stents comprising compounds of the formula (I)

in which

R^1 is thiophene (thienyl), in particular 2-thiophene, which may optionally be substituted one or more times by halogen, preferably chlorine or bromine, amino, aminomethyl or (C_1-C_8)-alkyl, preferably methyl, where the (C_1-C_8)-alkyl radical may optionally in turn be substituted one or more times by halogen, preferably fluorine,

R^2 is one of the following groups:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" is (C_6-C_{14})-aryl, preferably (C_6-C_{10})-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;

the radical "B" is a 5- or 6-membered aromatic heterocycle which comprises up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the series S, N, NO (N-oxide) and O;

the radical "D" is a saturated or partially unsaturated 4- to 7-membered heterocycle which comprises up to three heteroatoms and/or hetero chain members from the series S, SO, SO_2, N, NO (N-oxide) and O;

the radical "M" is –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- or a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be substituted one or more times by a radical from the group of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; (C_1-C_6)-alkanoyl; (C_3-C_7)-cycloalkanoyl; (C_6-C_{14})-arylcarbonyl; (C_5-C_{10})-heteroarylcarbonyl; (C_1-C_6)-alkanoyloxymethyloxy; -$COOR^{27}$; -SO_2R^{27}; -$C(NR^{27}R^{28})=NR^{29}$; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OR^{30}; -$NR^{30}R^{31}$, (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl,

where (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl may in turn optionally be substituted by a radical from the group of cyano; -OR^{27}; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ and -$C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1, and

R^{27}, R^{28} and R^{29} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl or (C_3-C_7)-cycloalkyl,

and/or

R^{27} and R^{28}, or R^{27} and R^{29}, form, together with the nitrogen atom to which they are bonded, a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group of N, O and S, and

R^{30} and R^{31} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, (C_6-C_{14})-arylcarbonyl, (C_5-C_{10})-heteroarylcarbonyl, (C_1-C_4)-alkylaminocarbonyl or $-CH_2C(NR^{27}R^{28})=NR^{29}$,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and are hydrogen or (C_1-C_6)-alkyl,

and the pharmaceutically acceptable salts and/or hydrates thereof.

Particular preference is given in this connection to stents comprising compounds of the formula (I)

in which

R^1 is thiophene (thienyl), in particular 2-thiophene, which may optionally be substituted one or more times by halogen, preferably chlorine or bromine, or (C_1-C_8)-alkyl, preferably methyl, where the (C_1-C_8)-alkyl radical may in turn optionally be substituted one or more times by halogen, preferably fluorine,

R^2 is one of the following groups:

A-,

A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

the radical "A" is phenyl or naphthyl, in particular phenyl;
the radical "B" is a 5- or 6-membered aromatic heterocycle which comprises up to 2 heteroatoms from the series S, N, NO (N-oxide) and O;
the radical "D" is a saturated or partially unsaturated 5- or 6-membered heterocycle which comprises up to two heteroatoms and/or hetero chain members from the series S, SO, SO_2, N, NO (N-oxide) and O;
the radical "M" is –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be substituted one or more times by a radical from the group of halogen; trifluoromethyl; oxo; cyano; pyridyl; (C_1-C_3)-alkanoyl; (C_6-C_{10})-arylcarbonyl; (C_5-C_6)-heteroarylcarbonyl; (C_1-C_3)-alkanoyloxymethyloxy; -$C(NR^{27}R^{28})$=NR^{29}; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

where (C_1-C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl may in turn optionally be substituted by a radical from the group of cyano; -OH; -OCH_3; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ and -$C(NR^{27}R^{28})$=NR^{29},

where:

v is either 0 or 1, preferably 0, and

R^{27}, R^{28} and R^{29} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl,
and/or

R^{27} and R^{28}, or R^{27} and R^{29}, may form, together with the nitrogen atom to which they are bonded, a saturated or partially unsaturated 5- to 7-membered heterocycle having up to two identical or different heteroatoms from the group of N, O and S, and

R^{30} and R^{31} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-alkanoyl or phenylcarbonyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and are hydrogen or (C_1-C_6)-alkyl,

and the pharmaceutically acceptable salts and/or hydrates thereof.

Special preference is given in this connection to stents comprising compounds of the formula (I)

in which

R^1 is 2-thiophene which may optionally be substituted in position 5 by a radical from the group chlorine, bromine, methyl or trifluoromethyl,

R^2 is one of the following groups:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,

B-M-B-,

D-M-B-,

where:

the radical "A" is phenyl or naphthyl, in particular phenyl;

the radical "B" is a 5- or 6-membered aromatic heterocycle which comprises up to 2 heteroatoms from the series S, N, NO (N-oxide) and O;

the radical "D" is a saturated or partially unsaturated 5- or 6-membered heterocycle which comprises a nitrogen atom and optionally a further heteroatom and/or hetero chain member from the series S, SO, SO_2 and O; or up to two heteroatoms and/or hetero chain members from the series S, SO, SO_2 and O;

the radical "M" is –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or a covalent bond;

where

the groups "A", "B" and "D" defined above may in each case optionally be substituted one or more times by a radical from the group of halogen; trifluoromethyl; oxo; cyano; pyridyl; (C_1-C_3)-alkanoyl; (C_6-C_{10})-arylcarbonyl; (C_5-C_6)-heteroarylcarbonyl; (C_1-C_3)-alkanoyloxymethyloxy; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

where (C_1-C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl may in turn optionally be substituted by a radical from the group of cyano; -OH; -OCH_3; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ and -$C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1, preferably 0, and

R^{27}, R^{28} and R^{29} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl,

and/or

R^{27} and R^{28}, or R^{27} and R^{29}, may form, together with the nitrogen atom to which they are bonded, a saturated or partially unsaturated 5- to 7-membered heterocycle having up to two identical or different heteroatoms from the group of N, O and S, and

R^{30} and R^{31} are identical or different and are, independently of one another, hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-alkanoyl or phenylcarbonyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and are hydrogen or (C_1-C_4)-alkyl,

and the pharmaceutically acceptable salts and/or hydrates thereof.

Very particular preference is given in this connection to stents comprising compounds of the formula (I)

in which

R^1 is 2-thiophene which is substituted in position 5 by a radical from the group of chlorine, bromine, methyl or trifluoromethyl,

R^2 is D-A-:

where:

the radical "A" is phenylene;
the radical "D" is a saturated 5- or 6-membered heterocycle which is linked via a nitrogen atom to "A",
which has a carbonyl group in direct vicinity to the linking nitrogen atom, and in which a ring carbon member may be replaced by a heteroatom from the series S, N and O;

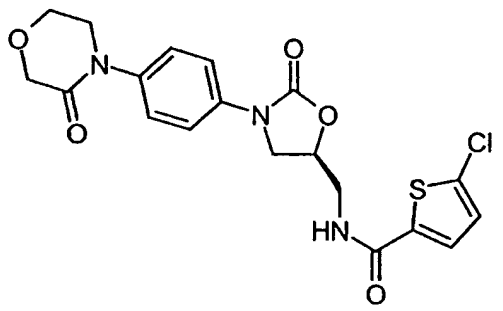
where

the group "A" defined above may optionally be substituted once or twice in the meta position relative to the linkage to the oxazolidinone by a radical from the group of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl or cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 are hydrogen,

and the pharmaceutically acceptable salts and/or hydrates thereof.

Very particular preference is likewise given in this connection to a stent comprising the compound of example 44 of WO 01/47919 having the following formula



and the pharmaceutically acceptable salts and/or hydrates thereof.

Concerning the disclosure of compounds of the formula (I), for example relating to their preparation, express reference is made to the disclosure in WO 01/47919.

The present invention describes the use of one or more compounds of the formula (I), where appropriate in combination with one or more other active ingredients, for producing a release system comprising medicinal substance(s), in particular a stent comprising medicinal substance(s).

In addition, the present invention describes a release system, in particular a stent, which comprises one or more compounds of the formula (I), where appropriate in combination with one or more other active ingredients, and which makes targeted release of one or more compounds of the formula (I), and of other active ingredients present where appropriate, at the site of action (drug targeting) possible, and are thus suitable for the prophylaxis and/or treatment of restenosis and/or thromboses, in particular after PTCA.

The present invention likewise describes a method for the treatment and/or prophylaxis of thromboses and/or restenosis using one or more compounds of the formula (I) in combination with a stent. In this use it is possible for the compounds of the formula (I) to be employed either systemically or, preferably, in the form of a stent comprising compounds of the formula (I).

Whereas it is not possible with the active ingredients and stents currently available to achieve an adequate success of therapy in all cases, the novel combination of compounds of formula (I) with a stent makes more effective treatment and/or prophylaxis of thromboses and/or restenosis possible. Local administration of compounds of the formula (I) in combination with a stent makes it possible to reduce the dose of the medicinal substance necessary to prevent thromboses and/or restenosis. It is thus possible to minimize undeplored systemic effects. At the same time, the local concentration can be increased and thus the efficacy enhanced.

It is moreover possible, in addition to the administration according to the invention, for a systemic and/or local administration of other active ingredients suitable for the treatment and/or prophylaxis of thromboses and/or restenosis to take place, such as, for example and preferably, abciximab, eptifibatide, tirofiban, acetylsalicylic acid, ticlopidine or clopidogrel. Additional systemic treatment with compounds of the formula (I) is preferred, especially by oral administration.

Release systems comprising the compounds of the invention of the formula (I) are produced by using conventional stents where the basic body of the stent consists either of metals or undegradable plastics such as, for example and preferably, polyethylene, polypropylene, polycarbonate, polyurethane and/or polytetrafluoro-ethylene (PTFE). In addition, stents with various designs of the metal mesh, which make various surfaces and folding principles possible and as described, for example, in WO 01/037761, WO 01/037892 are used as basic body of the stent.

These stents are coated and/or filled with compounds of the formula (I). An alternative possibility in the case of nonmetallic stents is to incorporate compounds of the formula (I) directly into the material used to produce the stents.

Carrier materials are mixed with the compounds of the formula (I) for the coating or filling. Carrier materials used for this purpose are preferably polymeric carriers, in particular biocompatible, nonbiodegradable polymers or polymer mixtures, such as,

for example and preferably, polyacrylates and copolymers thereof such as, for example and preferably, poly(hydroxyethyl)methylmethacrylates; polyvinylpyrrolidones; cellulose esters and ethers; fluorinated polymers such as, for example and preferably, PTFE; polyvinyl acetates and copolymers thereof; crosslinked and uncrosslinked polyurethanes, polyethers or polyesters; polycarbonates; polydimethylsiloxanes. As an alternative, biocompatible, biodegradable polymers or polymer mixtures such as, for example and preferably, polymers or copolymers of lactide and glycolide, or of caprolactone and glycolide; other polyesters, polyorthoesters; polyanhydrides; polyamino acids; polysaccharides; polyiminocarbonates; polyphosphazenes and poly(ether-ester) copolymers are also used as polymeric carriers.

Also suitable as polymeric carriers are mixtures of biodegradable and/or non-biodegradable polymers. The rate of release of the active ingredient is adjusted optimally through these mixtures.

Coated or filled stents are produced by dissolving the mixtures of compounds of the formula (I) and carrier, preferably in suitable solvents. These solutions are then applied to the stent by various techniques such as, for example, spraying, dipping or brush-coating. Subsequent or simultaneous removal of the solvent results in the stent provided with the active ingredient-containing coating. An alternative possibility is also for mixtures of compounds of the formula (I) and carrier to be melted and applied by the same application methods.

The stents are preferably pretreated in order to enlarge the outer and/or inner surface area of the stent. This increases the loading potential and larger amounts of coating (active ingredient/polymer) can be applied. Various etching techniques, but also treatments with ionizing radiation, for example, are used for pretreatment of the stents. It is likewise possible to produce micropores or cavities in the stents with the aid of various techniques.

The active ingredient contents of the stents coated or filled with compounds of the

formula (I) are usually from 0.001% by weight to 50% by weight, preferably from 0.01% by weight to 30% by weight, particularly preferably 0.1% by weight to 15% by weight.

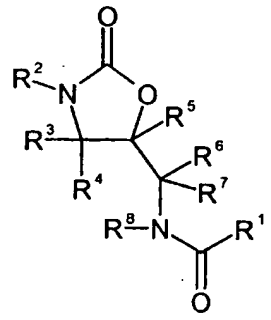
In the case of nonmetallic stents, the compounds of the formula (I) can also be incorporated directly for example as melt embedding in the basic body of the stent. In theses cases, active ingredient-containing polymeric carrier materials are processed by conventional methods, for example by injection molding processes, to give the final active ingredient-containing form. In these cases, the active ingredient is usually released by diffusion.

The active ingredient contents of stents with embedded compounds of the formula (I) are usually from 0.001% by weight to 70% by weight, preferably from 0.01% by weight to 50% by weight, particularly preferably 0.1% by weight to 30% by weight.

The stents comprising compounds of the formula (I) are, where appropriate, additionally coated with a membrane. This membrane serves, for example and preferably, for controlling the release of medicinal substances and/or for protecting the active ingredient-containing stents from external influences.

Claims

1. Stents comprising one or more compounds of the formula (I)



(I),

in which

R^1 is 2-thiophene which is substituted in position 5 by a radical from the group of chlorine, bromine, methyl or trifluoromethyl,

R^2 is D-A-:

where:

the radical "A" is phenylene;
the radical "D" is a saturated 5- or 6-membered heterocycle which is linked via a nitrogen atom to "A",
which has a carbonyl group in direct vicinity to the linking nitrogen atom, and
in which a ring carbon member may be replaced by a heteroatom from the series S, N and O;

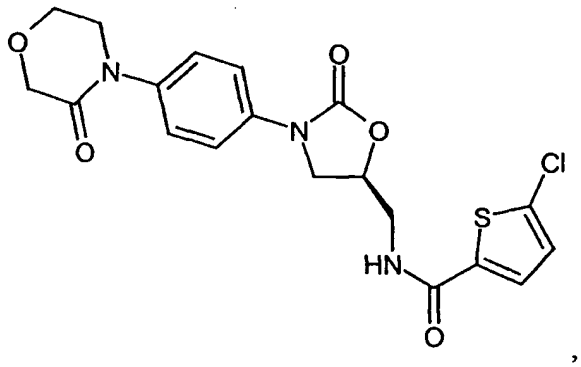
where

the group "A" defined above may optionally be substituted once or twice in the meta position relative to the linkage to the oxazolidinone by a radical from the group of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl or cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 are hydrogen,

the pharmaceutically acceptable salts, hydrates thereof and/or mixtures thereof.

2. Stents as claimed in claim 1, characterized in that the compound is 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide of the formula



,

its pharmaceutically acceptable salts, hydrates and/or mixtures thereof.

3. Stents as claimed in claim 1 or 2, which are coated with an additional membrane.

4. Stents as claimed in any of claims 1 to 3, comprising at least one other active ingredient.

5. Stents as claimed in any of claims 1 to 4 for the treatment of restenosis after PTCA.

6. Stents as claimed in any of claims 1 to 4 for the treatment and/or prophylaxis of thromboses after PTCA.

7. The use of compounds of the formula (I) as defined in claim 1 for or in the production of stents.

8. The use of compounds of the formula (I) as defined in claim 1 for producing stents for the treatment and/or prophylaxis of restenosis and/or thromboses.

9. A process for producing stents, characterized in that stents are coated or filled with one or more compounds of the formula (I) as defined in claim 1.

10. A process for producing stents, characterized in that polymeric carrier materials comprising one or more compounds of the formula (I) as defined in claim 1 are shaped to stents.

11. A method for treating patients with restenoic arteries by simultaneous use of one or more compounds of the formula (I) as defined in claim 1, and of a stent.

12. The method as claimed in claim 11, characterized in that compounds of the formula (I) as defined in claim 1 are present in or on the stent and are released locally.

13. A method for the treatment and/or prophylaxis of restenosis and/or thromboses by using stents as claimed in any of the preceding claims in combination with local and/or systemic administration of other active ingredients suitable for the treatment and/or prophylaxis of restenosis and/or thrombosis.

14. A method for the treatment and/or prophylaxis of restenosis and/or

thromboses by using stents as claimed in any of the preceding claims in combination with systemic administration of compounds of the formula (I) as defined in claim 1.

Patent Agents
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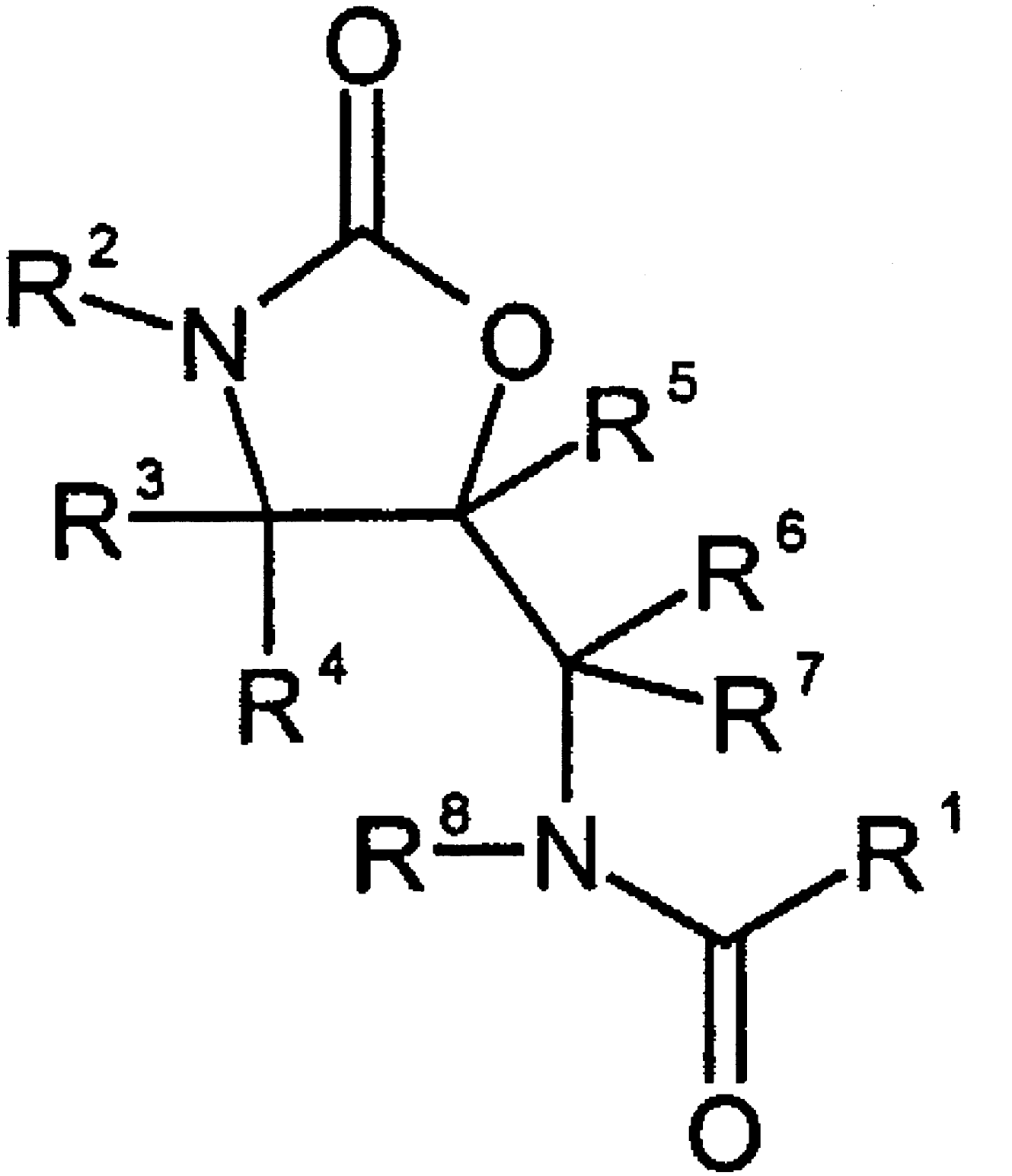

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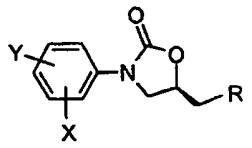
(54) Title: ANTIBACTERIAL HETEROBICYCLIC SUBSTITUTED PHENYL OXAZOLIDINONES



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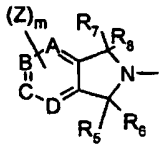

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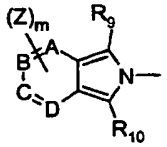


(III)

(57) Abstract: Bicyclic heterocyclic substituted phenyl oxazolidinone compounds of formula (I): wherein Y is a radical of formulae (II) or (III) in which the substituents have the meaning indicated in the description. These compounds are useful as antibacterial agents.

WO 01/42242 A1

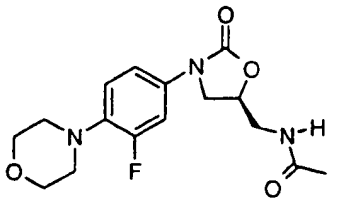
ANTIBACTERIAL HETEROBICYCLIC SUBSTITUTED PHENYL OXAZOLIDINONES

FIELD OF THE INVENTION

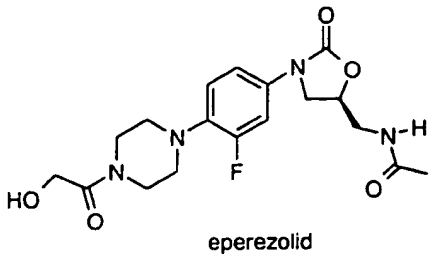
The present invention relates to the field of phenyl oxazolidinone compounds having antibacterial activity against Gram-positive and Gram-negative bacteria, pharmaceutical compositions containing the compounds, and methods of treating bacterial infections with the compounds.

BACKGROUND OF THE INVENTION

Oxazolidinones have been identified, within the last twenty years, as a new class of antibacterials which are active against numerous multidrug-resistant gram positive organisms. Particularly problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate resistant *Staphylococcus aureus* (GISA), vancomycin-resistant *enterocci* (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. As a class, oxazolidinones exhibit a unique mechanism of action. Studies have shown that these compounds selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis. Exemplary members of oxazolidinones are linezolid (see WO 95/07271) and eperezolid.



linezolid



eperezolid

U.S. Pat. No. 5,792,765 to Riedl et al. discloses a series of substituted oxazolidinones (cyanoguanidine, cyanoamidines, and amidines) useful as antibacterial medicaments.

U. S. Patent No. 5,910,504 to Hutchinson discloses a series of hetero-aromatic ring substituted phenyl oxazolidinones, including indolyl substituted compounds useful as antibacterial agents.

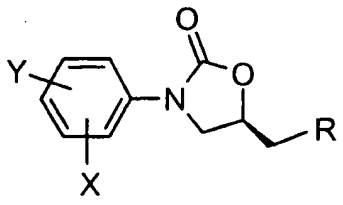
WO 98/54161 (Hester et al.) discloses amides, thioamides, ureas, and thioureas which are antibacterial agents.

WO 95/07271 (Barbachyn et al.) discloses oxazine and thiazine oxazolidinone derivatives such as linezolid and its analogs which are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiple-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*

WO 93/09103 (Barbachyn et al.) discloses substituted aryl- and heteroarylphenyloxazolidinones which are useful as antibacterial agents.

SUMMARY OF THE INVENTION

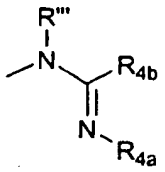
The invention provides phenyl oxazolidinone compounds of Formula I:



Formula I

wherein:

R is selected from the group consisting of OH, N_3, OR', O-Aryl, O-Heteroaryl OSO_2R'', -NR'''R'''', or



wherein:

(i) R' is straight-chain or branched acyl having up to 6 carbon atoms or benzyl;

(ii) R'' is straight-chain or branched alkyl, having up to 5 carbon atoms, phenyl or tolyl; and

(iii) R''' and R'''' are independently selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, phenyl or tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by cyano or alkoxycarbonyl having up to 4 carbon atoms, $-CO_2-R_1$, $-CO-R_1$, $-CO-SR_1$, $-CS-R_1$, $P(O)(OR_2)(OR_3)$, and $-SO_2-R_4$, in which

R_1 is selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, trifluoromethyl or phenyl, benzyl, or acyl each having up to 5 carbon atoms, straight-chain or branched alkyl having up to 6 carbon atoms, said alkyl optionally substituted by straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms, OH, cyano, up to 3 halogen atoms, and $-NR_5\ R_6$ in which R_5 and R_6 are identical or different and are selected from H, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms;

R_2 and R_3 are identical or different and are selected from hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms; and

R_4 is selected from straight-chain or branched alkyl having up to 4 carbon atoms or phenyl and;

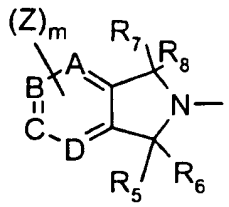
R_{4a} is CN, COR_{4c}, $COOR_{4c}$, $CONHR_{4c}$, $CO\text{-}NR_{4c}$ R_{4d}, SO_2R_{4c}, SO_2NHR_{4c}, $SO_2\text{-}NR_{4c}$ R_{4d}, or NO_2;

R_{4b} is H, alkyl, OR_{4c}, SR_{4c}, amino, NHR_{4c}, $NR_{4c}R_{4d}$, C1-C8-alkylaryl or mono-, di-, tri-, and per-halo C1-C8-alkyl;

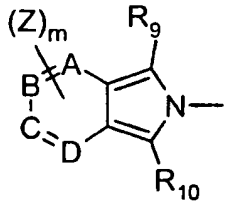
R_{4c} and R_{4d} are independently selected from H, alkyl, aryl, or in the case of any $NR_{4c}R_{4d}$ group R_{4c} and R_{4d} taken together with the nitrogen atom to which they are attached form a unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl group;

X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-$C_{1\text{-}8}$-alkyl, $C_{1\text{-}8}$ alkoxy, thio-$C_{1\text{-}8}$-alkyl, $C_{1\text{-}8}$ alkyl-amino, di($C_{1\text{-}8}$-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, $C_{1\text{-}8}$ alkyl-CO-O-, $C_{1\text{-}8}$ alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, amine, $C_{3\text{-}6}$ cycloalkyl, $C_{1\text{-}8}$ alkyl optionally substituted with one or more members selected from the group consisting of F, Cl, OH, $C_{1\text{-}8}$ alkoxyl and $C_{1\text{-}8}$ acyloxy; and

Y is a radical of Formulae II or III:



Formula II



Formula III

wherein

R_5, R_6, R_7, and R_8 are each independently H, alkyl, CN, nitro, $C_{1\text{-}8}$ alkyl, halo-$C_{1\text{-}8}$-alkyl, formyl, carboxy, alkoxycarbonyl, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, or R_5 and R_6 and/or R_7 and R_8 together form an oxo group;

R_9, and R_{10} are each independently H, halogen, alkyl, OH, CN, mercapto, nitro, C_{1-8} alkyl, halo-C_{1-8}-alkyl, C_{1-8} alkoxy, thio-C_{1-8}-alkyl, amino, C_{1-8}-alkyl-amino, di(C_{1-8}-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8}-alkyl-CO-O-, C_{1-8}-alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, or amine;

A, B, C, and D are selected from C, S, O, and N to form any five to ten membered aromatic or heteroaromatic ring, said heteroaromatic ring having one to four members selected from the group consisting of S, O, and N;

Z is selected from halogen, alkyl, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, CHO, COalkyl, amine, (dialkylamino)alkyl, said dialkylamino consisting of straight-chain or branched alkyl having up to 6 carbon atoms or phenyl or constituting a ring of 2 to 5 carbons having 0 to 2 atoms selected from S, O and N or alkoxy, or NHCO-(C_1-C_8-alkyl); and

m is 0 or 1,

and the pharmaceutically acceptable salts and esters thereof.

Compounds of the above formula are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

The present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound of Formula I.

The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a

prophylactically effective dose of the pharmaceutical composition of a compound of Formula I.

Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing specification.

DETAILED DESCRIPTION

Relative to the above description of the phenyl oxazolidinone compounds of the present invention, the following definitions apply.

Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl" may be straight or branched groups with 1-8 carbon atoms.

"Acyl" means an organic radical having the designated number of carbon atoms, derived from an organic acid by the removal of a hydroxyl group having the formula RCO, as in the case of acetyl where R is CH_3.

"Aryl" is an unsubstituted carbocyclic aromatic group including, but not limited to, phenyl, 1- or 2-naphthyl and the like. "Heteroaryl" refers to a cyclic aromatic radical having from five to ten atoms in the ring; where one to three ring atoms are independent heteroatoms such as S, O, and N, and the remaining ring atoms are carbon, for example, a pyridinyl, pyrazinyl, pyrimidinyl, pyrroyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thienyl, furanyl, quinolinyl, or isoquinolinyl, radical and the like.

"Substituted aryl" or "substituted heteroaryl" refers to an aryl or heteroaryl substituted by independent replacement of 1-3 of the hydrogen atoms thereon with halogen, OH, CN, mercapto, nitro, C_{1-8}-alkyl, halo-C_{1-8}-alkyl, C_{1-8}-alkoxy, thio-C_{1-8}-alkyl, amino, C_{1-8}-alkyl-amine, di(C_1-C_8-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8}-alkyl-CO-O-, C_{1-8}-alkyl-CO-NH-, or carboxamide. Further, substituted-heteroaryl may be substituted with a

mono-oxo to give, for example, a 4-oxo-1-H-quinoline. Substituted-heteroaryl may also be substituted with a substituted-aryl or a second substituted-heteroaryl to give, for example, a 4-phenyl-imidazol-1-yl or a 3-pyridinyl-imidazol-1-yl, and the like.

The term "halo" or "halogen" means fluoro, chloro, bromo and iodo. (mono-, di-, tri-, and per-) halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen. P denotes phosphorus.

The compounds of the instant invention are asymmetric in the oxazolidinone ring at the 5- position and thus exist as optical antipodes. As such, all possible optical antipodes, enantiomers or diastereomers resulting from additional asymmetric centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography on a Pirkle column.

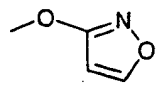
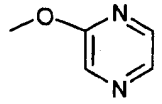
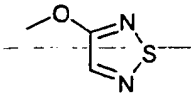
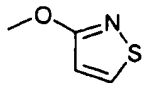
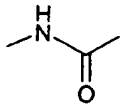
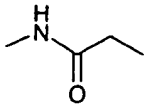
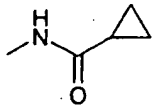
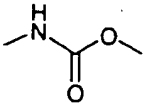
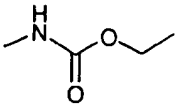
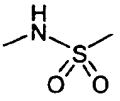
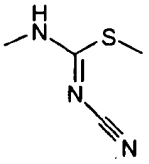
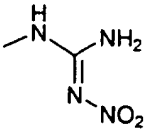
The phrase "pharmaceutically acceptable salts" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicyclic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $Ca(OH)_2$, $Al(OH)_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

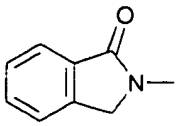
The term "subject" includes, without limitation, any animal or artificially modified animal. In the preferred embodiment, the subject is a human.

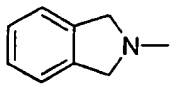
The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in presence of a currently available antimicrobial agent at its routine, effective concentration.

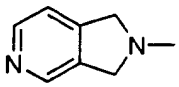
The compounds of the present invention possess antibacterial activity against Gram-positive and certain Gram-negative bacteria. They are useful as antibacterial agents for the treatment of bacterial infections in humans and animals. Particularly, these compounds have antimicrobial activity against *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *Moraxella catarrhalis*, and *H. influenzae*. More particularly, these compounds are useful against resistant bacteria such as MRSA and GISA, and have a low susceptibility to acquired resistance mechanisms. Compounds of Formula I which are most preferred for such purposes are those in which R is any of the following:

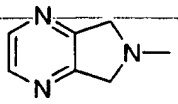













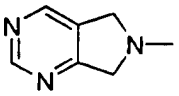
In addition Compounds of Formula I which are most preferred for such purposes are those in which Y is any of the following:

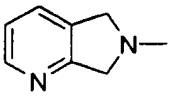
 isoindolone-;

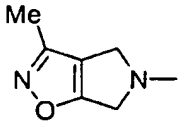

(1,3-dihydro-2H-isoindol-2-yl)-

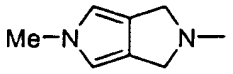

(1,3-dihydro-2H-pyrrolo[3,4-*c*]pyridin-2-yl)-

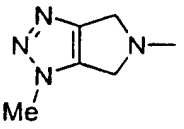

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyrazin-6-yl)-

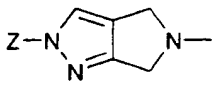

(5,7-dihydro-6H-pyrrolo[3,4-*d*]pyrimidin-6-yl)-

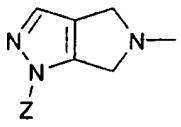

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)-


(4,6-dihydro-3-methyl-5H-pyrrolo[3,4-*d*]isoxazol-5-yl)-


(3,5-dihydro-5-methylpyrrolo[3,4-c]pyrrol-2(1H)-yl)-


(4,6-dihydro-1-methylpyrrolo[3,4-d]-1,2,3-triazol-5(1H)-yl)-





Particular examples of the present invention include the following compounds:

N-[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

N-[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

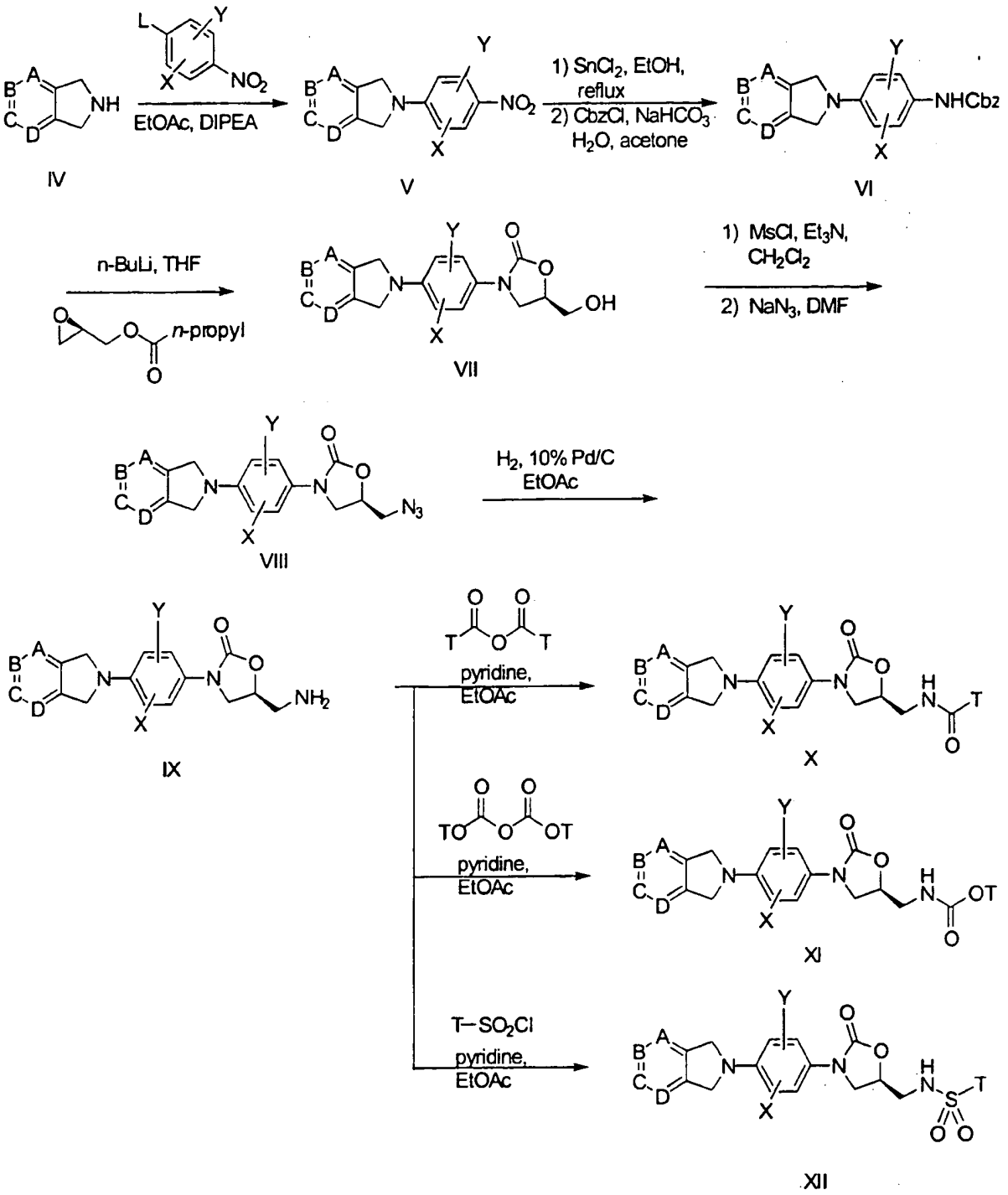
N-[[(5*S*)-3-[3-Fluoro-4-(5-oxido-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

N-[[(5*S*)-3-[4-(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

N-[[(5*S*)-3-[4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

(5*R*)-3-[4-(5,7-Dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-3-fluorophenyl]-5-(hydroxymethyl)-2-oxazolidinone.

The compounds of Formula I that are the subject of this invention may be prepared from readily available starting materials such as isoindole (Gawley et al., *J. Org. Chem.*, 1988, *53*:5381), 6,7-dihydro-5H-pyrrolo[3,4-*c*]pyridine and 6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridine (US Pat. No. 5,371,090 to Petersen et al.) in accordance with synthetic methods well known in the art. Representative proceduresare outlined in Scheme I-V:



Scheme I

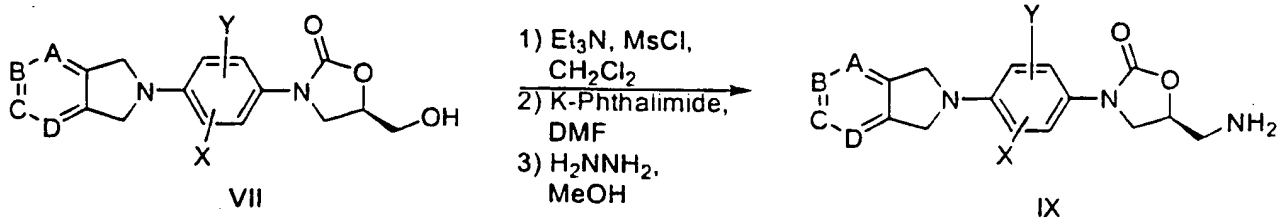
In accordance with Scheme I, bicyclic heterocycles of general formula IV are treated with a substituted nitrobenzene derivative (L is an appropriate leaving group such as a halogen of trifluoromethanesulfonyloxy) in a suitable base

and solvent, such as diisopropylamine and ethyl acetate, to give the substituted nitrophenyl compound V.

The nitrobenzene derivative V is then reduced to the aniline by an appropriate reaction, for instance by treatment with $SnCl_2$ or by catalytic hydrogenation in the presence of a suitable catalyst, such as palladium on carbon. The aniline is then treated with benzyl or methyl chloroformate and sodium bicarbonate to form the corresponding benzyl or methyl carbamate derivative VI.

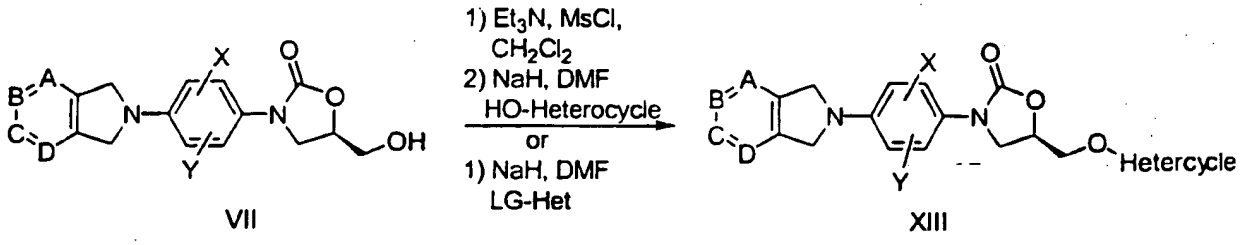
The Cbz aniline VI is then deprotonated with a lithium base such as n-butyllithium and reacted with (R)– glycidyl butyrate to afford the oxazolidinone VII. The hydroxymethyl group can then be converted to an amide as shown in Scheme I by preparation of the mesylate, conversion to azide VIII, and reduction to amine IX by an appropriate procedure such as hydrogenation. Alternatively displacement of a mesylate (Scheme II) or appropiate leaving group such as tosylate or chlorine with potassium phthalimide and removal of the phthaloyl protecting group by hydrazinolysis would provide amine IX. The amine IX can be converted to amide X by an acylation reaction using techniques known in the art, such as treatment with acetic anhydride in the presence of a base such as pyridine. Alternatively, amine IX can be converted to a carbamate XI by treatment with methylchloroformate and pyridine, or reacted with a sulfonyl chloride in an inert solvent in the presence of an organic base like pyridine to form a sulfonamide XII

Scheme II



VII IX

Scheme III

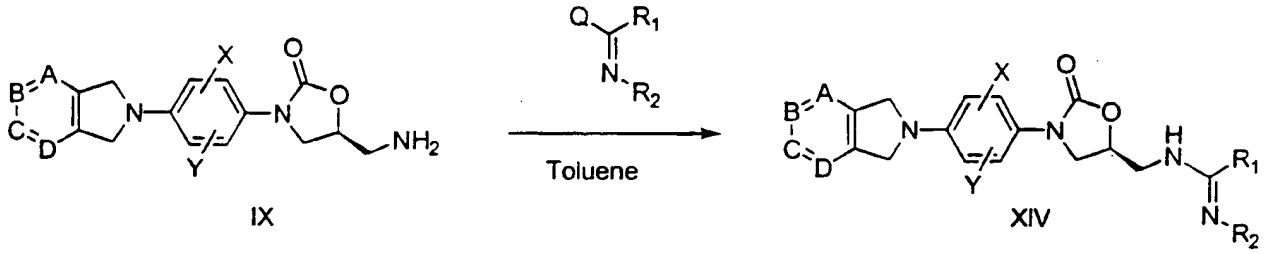


VII XIII

For the formation of oxazolidione in which R = O-Heteroaryl (XIII), the oxazolidinone carbinol VII can be converted to the corresponding mesylate or other appropriate leaving group and reacted with HO-Het (a suitible hydroxyl containing heterocycle), either in the presence of base or with HO-Het as a preformed alkoxide, in an appropriate solvent, for example DMF or acetonitrile (Scheme III). Alternatively, Mitsunobu conditions can be used to couple VII with HO-Heterocycle by treating with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in an appropriate solvent, such as THF, at a suitable temperature, preferably room temperature. Reaction conditions and leading references can be found in Gravestock et al, WO99/64416.

Furthermore, by treating VII with a suitable, non-nucleophilic base, for example NaH, the displacement of a leaving group (LG), such as chlorine or bromine, can be effected from an appropriately reactive aza-heterocycle (LG-Het)(Scheme III).

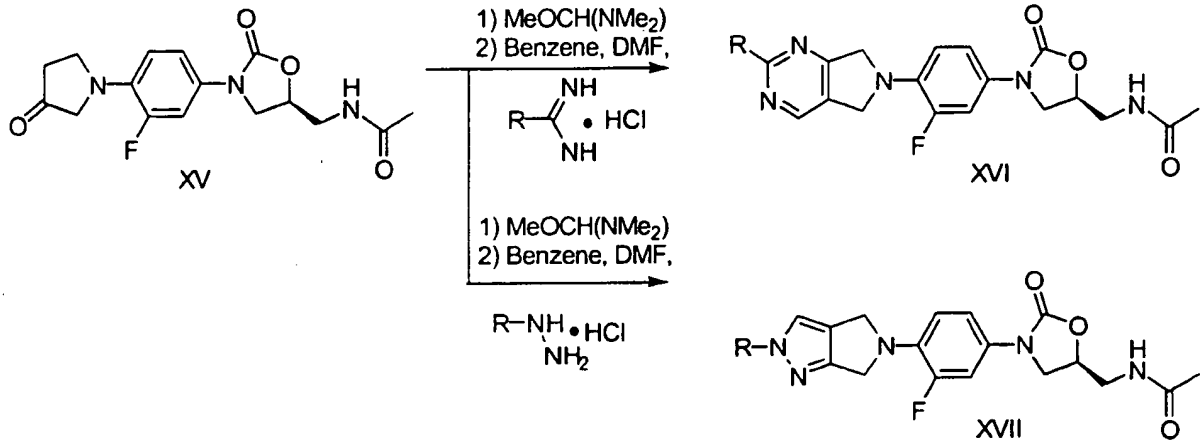
Scheme IV



IX XIV

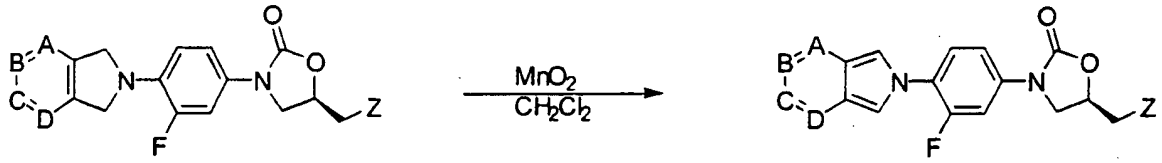
Compounds of structure XIV can be prepared as shown in Scheme IV. Amine IX can be converted to various functionalized amidines by reaction with activated imines, where Q is a leaving group such as methylthio or methoxy, in a suitable solvent, for example toluene or methanol, with or without a catalyst (such $AgNO_3$) present at a temperature range of 0-110°C.

Scheme V



In accordance with Scheme V pyrrolidinone XV (prepared as in WO96/13502) is first reacted with methoxy-bis(dimethylamine) or other activated dimethylformamide reagent and, second, heated in a suitable solvent (for example DMF and benzene) with either substituted amidines, to form pyrrolopyrimidines oxazolidinones such as XVI, or substituted hydrazines, to form pyrrolopyrazole oxazolidinones such as XVII. Formation of the enamine, alkoxymethylene or alkoxycarbonyl derivatives of pyrrolidinone XV, according to Brighty et al in US 5037834A, would also allow access to these systems.

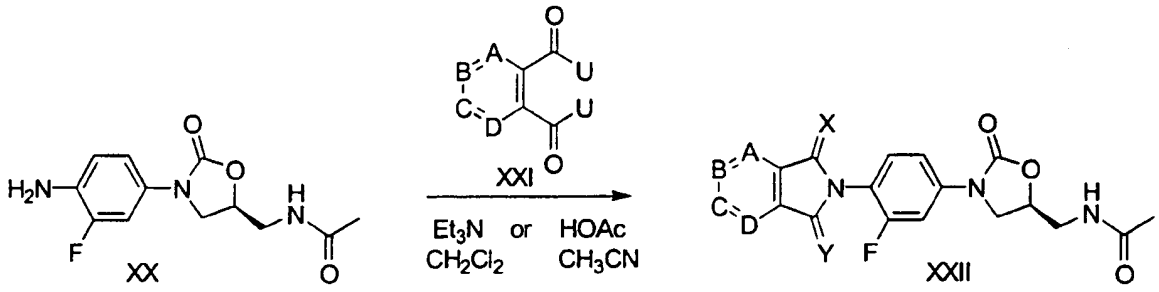
Scheme VI



XVIII XIX

As shown in Scheme VI compounds with the structure XIX can be achieved by oxidation of the various compounds, XVIII, using an appropriate oxidant (for example manganese dioxide, peroxyacetic acid, DDQ or air) in a suitable solvent such as methylene chloride.

Scheme VII



XX XXII

Oxo-derivatives of structure XXII in Scheme VII, (X = O, Y = H_2 or X = H_2, Y = O) can be constructed by reacting 1,2-aryl dicarboxaldehydes (where XXI, U = H) with aniline XX (prepared as in WO96/23788) in the presence of acids, such as acetic acid, in a suitable solvent such as methylene chloride. The di-oxo-derivatives (structure XXII where X = Y = O) are prepared from the reaction of aniline XX with selected 1,2-aryl dicarbonyl reagents with a suitable leaving group (XXI where U = Cl, Br, etc).

Definitions

All temperatures are in degrees Centigrade

Brine refers to an aqueous saturated sodium chloride solution

DMF refers to N,N-dimethylformamide

THF refers to tetrahydrofuran

Cbz refers to carbobenzyloxy

n-BuLi refers to n-butyl lithium

MS refers to mass spectrometry expressed as m/e or mass/charge unit

[M + H] refers to the positive ion of a parent plus a hydrogen atom

Ether refers to diethyl ether

rt refers to room temperature

Mp refers to melting point

CH_2Cl_2 refers to methylene chloride

NaOH refers to sodium hydroxide

MeOH refers to methanol

EtOAc refers to ethyl acetate

ppt refers to a precipitate

These compounds have antimicrobial activity against susceptible and drug resistant bacterial pathogens such as *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus spp., Moraxella catarrhalis* and *H. influenzae*. These compounds are particularly useful against drug resistant Gram-positive cocci such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci. These compounds are useful in the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital-acquired lung infections, bone and joint infections, and other bacterial infections.

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically--Fourth Edition", which is incorporated herein by reference.

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFU/well.

Following inoculation of the microdilution trays, the trays are incubated at 35°C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Table 1, some compounds of the present invention were tested against a variety of pathogenic bacteria resulting in a range of activities, from 1 to ≥128 μg/mL depending on the organism tested. *S. aureus* OC2878 is a MRSA and *E. faecium* OC3312 is a vancomycin resistant enterococcus.

Table 1. MIC Values of Some Compounds of Formula I

Compound No.	MIC (mg/mL) in Test Strains		
	S. aureus OC4172	*S. aureus* OC2878	*E. faecium* OC3312
1	2	2	2
2	2	1	4
3	0.5	0.25	0.5
4	1	0.5	1
5	>32	>32	>32
6	64	32	32
7	>32	8	16
8	8	4	8
9	>32	>32	>32
10	>32	8	64
11	2	1	2
12	8	2	4

13	2	1	2
14	32	16	16
15	2	2	2
16	8	8	8
17	4	2	2
18	16	16	16
19	8	4	8
20	4	2	4
21	>64	>64	>64
22	2	2	2
23	8	8	8
24	8	8	8
25	64	>128	32
26	1	0.5	1
27	8	4	8
28	0.5	0.5	0.5
29	>32	8	16
30	>128	>128	>128
31	>16	>16	>16
32	4	2	2
33	32	32	32
34	8	2	4
35	0.5	0.25	2
36	1	0.5	1
37	1	1	0.5
38	2	2	1
39	1	2	1
40	1	1	1
41	2	2	2
42	2	2	2
43	1	1	1
44	1	1	1

45	4	4	4
46	4	4	8
47	32	16	32
48	8	8	8
49	16	4	8

This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in a subject having conditions caused by or contributed to by bacterial infection, which comprises administering to the animals a compound of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention. The terms of "treating" and "treatment" include administering, either simultaneously, separately or sequentially, a pharmaceutically effective amount of a composition containing one or more of the compounds disclosed herein to a subject that desires inhibition of bacterial growth. The pharmaceutically effective amount of the compound used to practice the present invention for treatment varies depending on the manner of administration, the age, weight, and general health of the subject treated, and ultimately will be decided by physicians or veterinarians.

The compounds of the present invention may be administered to a subject such as a human by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route may vary with, for example, the condition of the recipient as well as the ease of preparation and administration.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms

as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene

glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

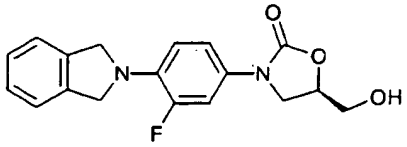
The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredients(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

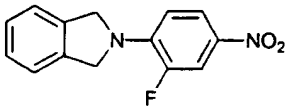
Example 1

(5*R*)-3-[4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-5-(hydroxymethyl)-2-oxazolidinone



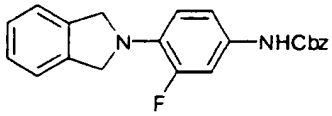
Isoindoline was synthesized employing the method of R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar *J. Org. Chem.* 1988, *53*, 5381.

Step 1:



To 3,4-difluoronitrobenzene (3.02 mL, 27.3 mmols) in ethyl acetate at rt was added diisopropylethylamine (5.03 mL, 28.9 mmols) and then isoindoline (3.50 g, 29.4 mmols) and stirred overnight. A yellow precipitate (ppt) formed and was collected on a filter, washed with water and ether and dried in a vacuum oven (30°C) to provide the product as a bright yellow solid (6.69 g, 95% yield). Mp = 200-202°C. MS (M + 1) = 327 m/z.

Step 2:



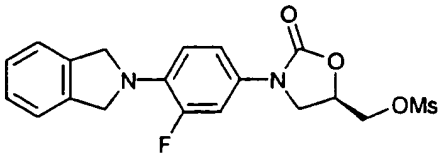
To the above nitro compound (2.62 g, 10.2 mmols) in ethanol (100 mL) was added $SnCl_2$ (9.84 g, 50.9mmols) and was refluxed for 16hrs. After cooling to rt the reaction mixture was added to 10% aq. NaOH (300 mL) and extracted with CH_2Cl_2 (6x50 mL). The combined organic washings were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give 2.63 g of an olive green solid (aniline), which was used without further purification. To this aniline in acetone (150 mL) and water (20 mL) was added $NaHCO_3$ (1.84 g, 21.9 mmols) and then benzylchloroformate (1.68 mL, 11.8 mmols). After stirring overnight the mixture was poured into ice water (100 mL) and the resulting tan precipitate was collected on a filter, washed with water and dried in a vacuum to give the Cbz aniline as a tan solid (3.50 g, 95% yield). Mp = 146-148 °C. MS (M + 1) = 363 m/z.

Step 3:

To the above Cbz aniline (0.74 g, 2.04 mmols) in THF (10 mL) at –78 °C was added *n*-BuLi (2.5 M, 0.82 mL, 2.05 mmols) dropwise. After stirring for 40 min, (R)-glycidyl butyrate (0.31 mL, 2.10 mmols) in THF (0.5 mL) was added dropwise and the resulting mixture was allowed to warm to RT overnight. A white precipitate had formed and was collected on a filter and washed with water and ether. Chromatography on silica gel with 25% ethyl acetate/hexane as eluent provided the product as a white solid (0.58 g, 87% yield). MS (M + 1) = 329 m/z.

Example 2

(5*R*)-3-[4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

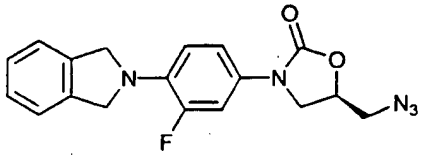


To the oxazolidinone carbinol from Example 1 (0.58 g, 1.78 mmols), in DMF (10 mL) and acetonitrile (10 mL) at 0 °C was added triethylamine (0.74 mL, 5.31 mmols) and, after 10 min, methanesulfonyl chloride (0.28 mL, 3.62 mmols). After allowing the reaction mixture to warm to RT over an hour

starting material was still present so cooling and addition of triethyl amine (0.37 mL, 2.65 mmols) and methanesulfonyl chloride (0.14 mL, 1.81 mmols) was repeated. The mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (6 X 20 mL), washed with brine (4 x 10mL), dried over Na_2SO_4, concentrated to afford the crude product as a brown oil (0.95 g). MS (M + 1) = 407 m/z.

Example 3

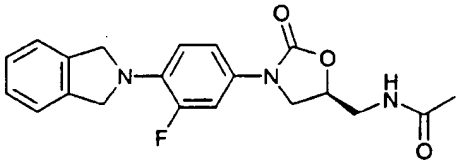
(5*R*)-5-(Azidomethyl)-3-[4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxazolidinone



To the mesylate from Example 2 (0.95 g, 1.78 mmols) in DMF (25 mL) was added sodium azide (0.47 g, 7.23 mmols) and heated to 70°C for 16 hrs. After cooling to rt water was added and the mixture extracted with ethyl acetate (6X25 mL), washed with brine (4x10 mL), dried over Na_2SO_4, concentrated to give 0.48 g of a tan solid. MS (M + 1) = 354 m/z.

Example 4

N-[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

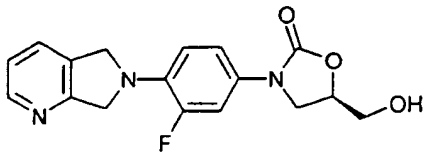


Compound 1

The azide from Example 3 in ethyl acetate (25 mL) was placed in a Paar flask and nitrogen bubbled through for 15 min whereupon 10% Pd/C (0.15 g, 0.14 mmol) was added. The mixture was pressurized with 50 psi of H_2 (*g*) and shaken for 16 hrs whereupon an additional amount of 10% Pd/C (0.15 g, 1.4 mmols) was added and the mixture shaken for an additional 6 hrs (at this

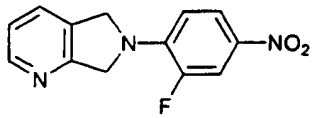
point MS (M + 1) = 328 m/z). After placing the mixture under nitrogen, pyridine (0.22 mL, 2.72 mmol) and then Ac_2O (0.51 mL, 5.30 mmol) were added and the mixture stirred for 2 hrs. The mixture was filtered through celite, washing with ethyl acetate (100 mL), concentrated, and chromatographed on silica (gradient elution 1%-5% $MeOH/CH_2Cl_2$) and then triturated with ethyl acetate (3X3 mL) to give 0.19 g of a white solid (Compound 1, 29% yield for 4 steps). Mp = 240-242 °C. MS (M + 1) = 370 m/z.

Example 5



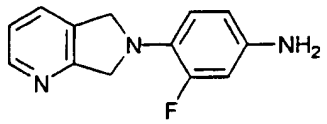
Compound 2

Step 1:



6,7-Dihydro-6-(2-fluoro-4-nitrophenyl)-5H-pyrrolo[3,4-b]pyridine: To 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine dihydrochloride salt (as described by Petersen, et al. (Bayer) EP0520277A2)(42.8 g, 222 mmols) in DMF (1.2 L) was added 2,4-difluoronitrobenzene (25 mL, 224 mmols). The mixture was heated to 60°C and DIPEA (195 mL, 1.12 mols) was added dropwise from an addition funnel over 2 hrs. After heating overnight the reaction mixture was cooled to rt, poured into water (3 L), filtered and dried in a vacuum oven (50 °C) to provide a yellow-green solid (53.8 g, 94% yield). MS (M + 1) = 260 m/z.

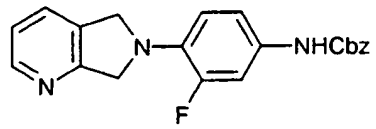
Step 2:



6,7-Dihydro-6-(2-fluoro-4-aminophenyl)-5H-pyrrolo[3,4-b]pyridine

To the above nitro compound (53.8 g, 208 mmol) in THF (175 mL) and methanol (600 mL) was added ammonium formate (59.0 g, 907 mmol). Nitrogen was bubbled through the reaction for approximately 30 minutes whereupon 10% Pd/C (2.20 g, 21 mmols) was added. After stirring overnight at rt under an atmosphere of nitrogen the reaction mixture was filtered through a pad of Celite, washing thoroughly with methanol (400 mL), and concentrated to a volume of ca. 200 mL. Water (300 mL) was added and the mixture extracted with ethyl acetate (5X200 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and utilized directly in the next step without further purification. MS (M + 1) = 230 m/z.

Step 3:



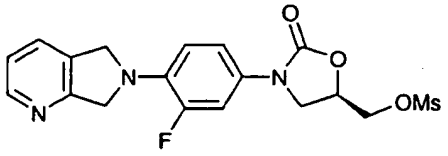
6,7-Dihydor-6-(2-fluoro-4-(Aminocarboxybenzyl)phenyl)-5H-pyrrolo[3,4-b]pyridine The above aniline (~208 mmols) in acetone (1 L) and water (160 mL) was cooled to 0°C whereupon sodium bicarbonate (37.4 g, 445 mmols) was added followed by the dropwise addition of benzylchloroformate (34.2 mL, 228 mmols). The reaction mixture was allowed to warm to room temperature and stirred overnight whereupon a ppt formed. The reaction was poured into ice water (2 L) and the resulting precipitate was collected by filtration. The solid was washed with water and dried in a vacuum oven (50°C) to afford the Cbz derivative (73.0 g, 97% yield) as a salmon colored powder. MS (M + 1) = 364 m/z.

Step 4:

(Compound 2). The above Cbz derivative (40.8 g, 112 mmols) in THF (1 L) was cooled to –78°C under a nitrogen atmosphere. To this mixture was added n-BuLi (2.5 M, 45.8 mL, 114.5 mmols) dropwise via syringe over fifteen minutes. The reaction was warmed to room temperature and allowed to stir

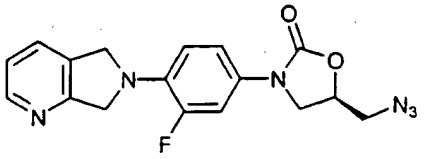
for 45 minutes before again being cooled to –78°C. At this point (R)-glycidyl butyrate (17.2 mL, 117 mmols) was added and the reaction mixture allowed to warm to rt overnight during which time a precipitate formed. The ppt was collected, washed with several portions of ether (5X100 mL) and dried in a vacuum oven (50°C) to afford 40.6 g of the ether solvate of the lithium alkoxide as a tan fluffy powder. This material was then washed with several portions of water (4X200 mL) and dried in a vacuum oven (50°C) to afford the oxazolidinone alcohol (34.1 g, 92% yield) as a tan granular solid. Mp = 208-212°C, decomp. MS (M + 1) = 330 m/z.

Example 6



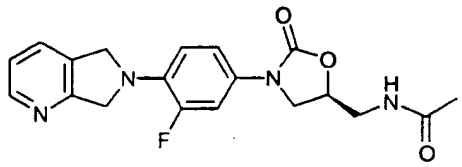
Oxazolidinone Mesylate. The above oxazolidinone carbinol (from Example 4) (33.8 g, 103 mmols) was suspended in DMF (1.25 L, previously degassed with nitrogen) at rt under a nitrogen atmosphere. Triethylamine (50 mL, 360 mmols) was added followed by the dropwise addition of methanesulfonyl chloride (13.5 mL, 174 mmols). After stirring for 3 hrs the reaction mixture was poured into water (200 mL) and methylene chloride (1 L) added. A ppt was filtered off, washed with water (3X200 mL) and dried in a vac oven (50°C) to afford the mesylate as a tan solid (28.1 g, 67%). The organic layer was dried (Na_2SO_4), filtered and evaporated to also afford the mesylate (11.7 g, 28% yield) as a tan solid. Both where characterized with MS (M + 1) = 408 m/z.

Example 7



Oxazolidinone Azide. The above mesylate (from Example 5) (27.8 g, 68.2 mmols) and sodium azide (17.7 g, 271 mmols) in anhydrous DMF (1 L), previously degassed with nitrogen, were heated 95°C for 6 hr under a nitrogen atmosphere. After cooling, the mixture was poured into stirred ice water (2 L) and formed a flocculant white ppt. The ppt was collected on a filter and washed with water (4X200 mL), dried in a vac oven (50°C) to afford the azide as a light beige solid (22.7 g, 94% yield). Mp = 175-180°C, decomp. MS (M + 1) = 355 m/z.

Example 8

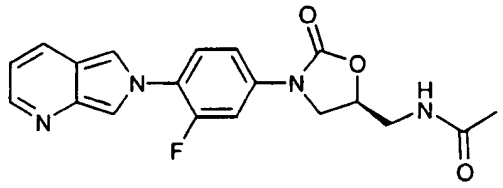


Compound 3

Oxazolidinone Acetamide. The above azide (from Example 6)(21.67 g, 61.16 mmol) dissolved in DMF (400 mL) and THF (500 mL) was degassed with nitrogen for 30 minutes whereupon 10% Pd/C (4.74 g, 4.4 mmols) was added and the reaction hydrogenated on a Parr apparatus (60 psi of hydrogen) for 14 hr. The reaction mixture was removed from the Parr apparatus and placed under a nitrogen atmosphere whereupon pyridine (5.44 mL, 67.3 mmols) and acetic anhydride (6.35 mL, 67.3 mmols) were added. After stirring for 1 hr the

reaction mixture was filtered through a pad of Celite, washing thoroughly with methanol and then copious amounts of 50% $MeOH/CH_2Cl_2$ (ca. 2 L). The filtrate was evaporated to afford the crude acetamide in DMF. The mixture was slowly added to water (2 L) and the ppt collected on a filter, washed with water (5X400 mL) and dried in a vac oven (50 °C) to provide the acetamide as an analytically pure white solid (14.2 g, 63% yield). The combined filtrates were extracted with methylene chloride (5X200 mL), dried over Na_2SO_4 and concentrated. Water was added to the residue and the resulting ppt was filtered off and dried in a vac oven (50 °C) to afford a second crop of the acetamide as a light tan, fluffy solid (5.61 g, 25%). For the analytically pure material Mp = 229-230 °C, decomp. MS (M + 1) = 371 m/z.

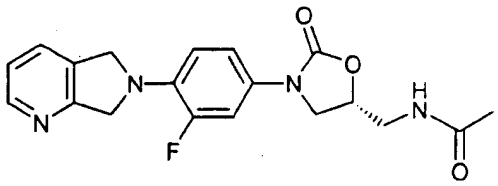
Example 9



Compound 4

The above acetamide from Example 8 (2.51 g, 6.78 mmols) was taken up in CH_2Cl_2 and MnO_2 added (23.9 g, 234 mmols). After stirring overnight the reaction mixture was filtered through celite, concentrated and chromatography on silica with 10% $MeOH/CH_2Cl_2$ as eluent to afford the product as a light yellow solid (0.48 g, 19% yield). Mp = 220-225 °C decomp. MS (M + 1) = 369 m/z.

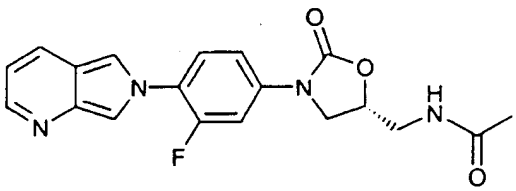
Example 10



Compound 5

Compound 5 was prepared as in Example 8 except (S)-glycidyl butyrate was employed in the oxazolidinone formation. The product was isolated as a light tan solid. Mp = 227-230°C decomp. MS (M + 1) = 371 m/z.

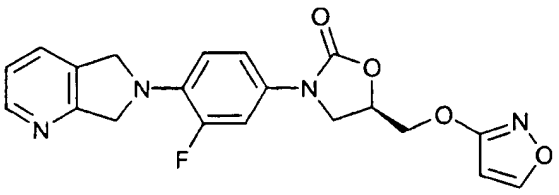
Example 11



Compound 6 oxidized enantiomer

Compound 6 was prepared as in Example 9 and isolated as a light yellow solid. Mp = 181-185°C decomp. MS (M + 1) = 369 m/z.

Example 12

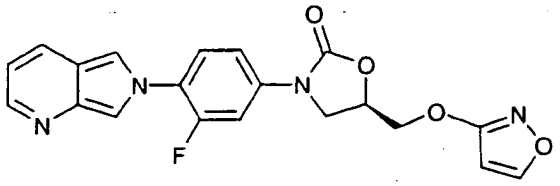


Compound 7

To 5-hydroxyisoxazole (prepared as in *Chem Pharm Bull* **1966**, *14*(11), 1277) (0.174 g, 2.04 mmols) in DMF was added NaH (60% in oil)(0.105 g, 2.62 mmols). After stirring for 30 min the mesylate (from Example 6) (0.744g, 1.82

mmols) was added in one portion and the mixture stirred at 60°C overnight. After cooling to rt water was added and a ppt was collected on a filter, air dried and chromatographed on silica with 2.5% MeOH/CH_2Cl_2 as eluent to afford the product as a white solid (0.140 g, 19 % yield). Mp = 182-185°C. MS (M + 1) = 397 m/z.

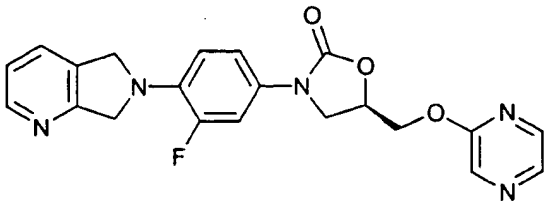
Example 13



Compound 8

To the above oxazolidinone (from Example 12) (0.264 g, 6.66 mmols) was taken up in CH_2Cl_2 and MnO_2 added (1.66 g, 16.2 mmols) in two portions over two days. After stirring for two days the reaction mixture was filtered through celite, concentrated and chromatographed on silica with 10% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.086 g, 32% yield). Mp = 133-135°C. MS (M + 1) = 395 m/z.

Example 14

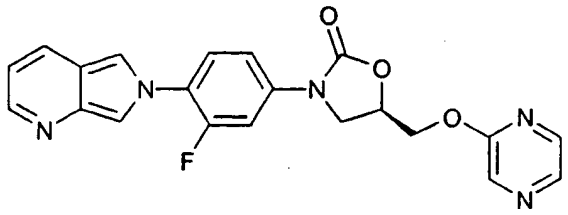


Compound 9

To NaH (60% by wt in oil)(0.03 g, 0.76 mmol) in DMF (5 mL) was added oxazolidinone carbinol (from Example 5) (0.23 g, 0.71 mmol) in four portions. After stirring for 30 min 2-chloropyrazine (0.065 mL, 0.71 mmol) was added

via syringe and stirred overnight at rt. Water was added and a ppt was collected on a filter, air dried and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a white solid (0.067 g, 23 % yield). Mp = 225-230°C. MS (M + 1) = 408 m/z.

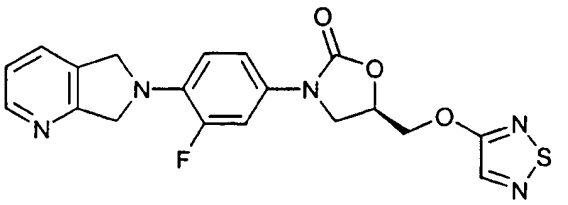
Example 15



Compound 10

The above oxazolidinone (from Example 14) (0.024 g, 0.058 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (0.07 g, 0.7 mmol). After stirring overnight the reaction mixture was filtered through Celite and concentrated to afford the product as a very light yellow solid (0.015 g, 64% yield). Mp = 192-194°C. MS (M + 1) = 406 m/z.

Example 16

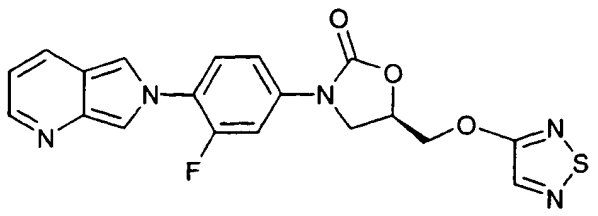


Compound 11

To a suspension of the oxazolidinone carbinol (prepared in Example 5) (330 mg, 1.0 mmol), triphenylphosphine (260 mg, 1.1 mmols) and 4-hydroxy-1, 2, 5-thiadiazole (100 mg, 1.0 mmol) (as prepared in U.S Patent 3,391,150 [7/2/68]) in THF (8 mL) was added diisopropylazodicarboxylate (0.20 mL, 1.1 mmols). After stirring overnight at rt the reaction mixture was filtered, washed

with methanol, and air dried to afford a yellow crystalline solid (60 mg, 15% yield). Mp = 185-187°C. MS (M + 1) = 414 m/z.

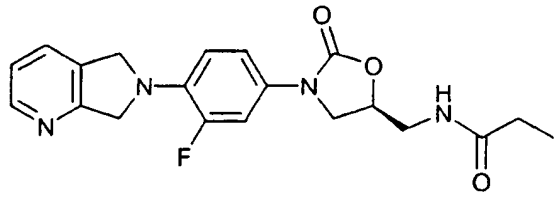
Example 17



Compound 12

To the oxazolidinone (prepared in Example 16) (160 mg, 0.39 mmol) suspended in CH_2Cl_2 (1.0 mL) was added MnO_2 (four additions of 150 mg over four days). The reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (15 mL), and concentrated under reduced pressure to afford the product as a white crystalline solid (63 mg, 40% yield). Mp = 185-188°C. MS (M + 1) = 412 m/z.

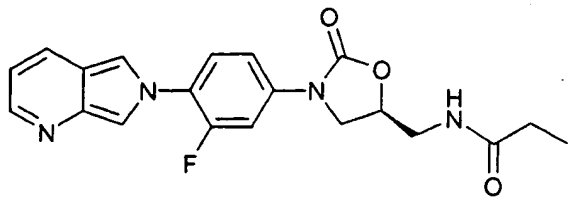
Example 18



Compound 13

To the amine (as prepared in Example 8) (100 mg, 0.30 mmol) and potassium carbonate (100 mg, 0.72 mmol) suspended in methanol (1.0 mL), was added propionyl chloride (50 mg, 0.54 mmol). After stirring overnight at 80°C the reaction mixture was cooled and water was added. A precipitate was filtered off, washed with methanol and air dried to afford the product as a brown crystalline solid (15 mg, 13 % yield). Mp = 110-112°C. MS (M + 1) = 385 m/z.

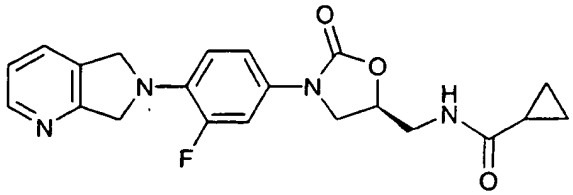
Example 19



Compound 14

To the amide (prepared in Example 18) (15 mg, 0.04 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (200 mg) at rt. After stirring overnight, the reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as an light brown crystalline solid (1.6 mg, 8 % yield). MS (M + 1) = 383 m/z.

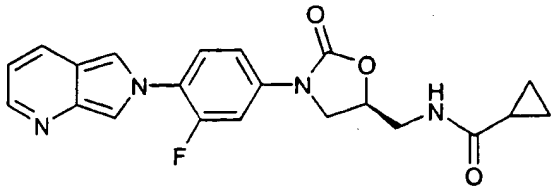
Example 20



Compound 15

To the amine (as prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL), was added cyclopropyl carbonyl chloride (120 mg, 1.15 mmols). After stirring at rt overnight, the reaction mixture was filtered, rinsed with methanol, and then concentrated to dryness under reduced pressure. The resulting solid residue was triturated with water and filtered to afford the product as a brown crystalline solid (36 mg, 50 % yield). Mp = 235-240°C. MS (M + 1) = 397 m/z.

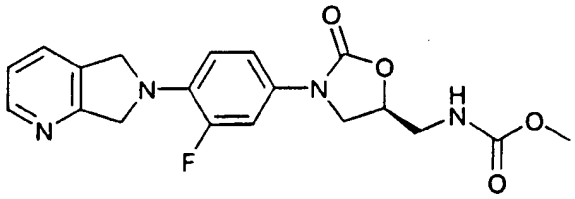
Example 21



Compound 16

To the amide (prepared in Example 20) (36 mg, 0.09 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (three portions of 100 mg over three days) at rt. The reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as an off-white crystalline solid (3 mg, 8 % yield). MS (M + 1) = 395 m/z.

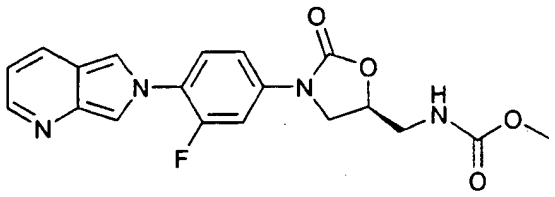
Example 22



Compound 17

To the amine (prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL), was added dropwise methyl chloroformate (120 mg, 1.27 mmols). After stirring for four hours at rt, the reaction mixture was filtered, diluted with water, and concentrated under reduced pressure to remove the methanol. The aqueous solution was extracted with ethyl acetate (5X5 mL). The combined organics were washed with water, dried over $MgSO_4$, filtered, and concentrated to provide an oil which was triturated with ether to afford a brown crystalline solid (35 mg, 50% yield). MS (M + 1) = 387 m/z.

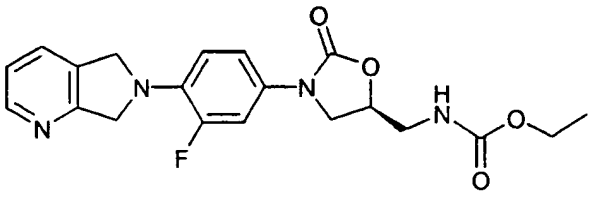
Example 23



Compound 18

To the carbamate (prepared in Example 22) (33 mg, 0.08 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (150 mg). After stirring overnight at rt the reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as a yellow crystalline solid (6.0 mg, 18% yield). MS (M + 1) = 385 m/z.

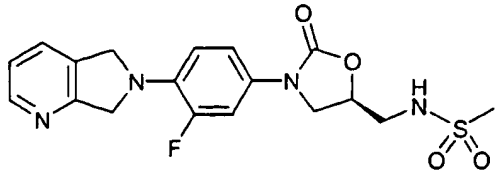
Example 24



Compound 19

To the amine (prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL) was added dropwise ethyl chloroformate (0.1 mL, 1.04 mmols). After stirring overnight at rt the reaction mixture was filtered, diluted with water, and concentrated under reduced pressure to remove the methanol. The aqueous solution was extracted with ethyl acetate (5X5 mL). The combined organics were washed with water, dried over $MgSO_4$, filtered, and concentrated. The resulting semi-solid was treated with water, filtered and air-dried to afford a brown crystalline solid (18 mg, 30% yield). MS (M + 1) = 401 m/z.

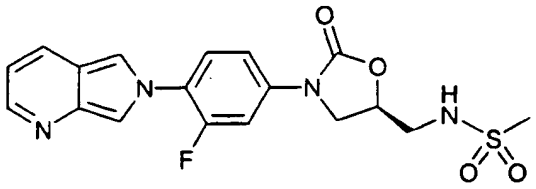
Example 25



Compound 20

To the amine (prepared in Example 8) (95 mg, 0.29 mmol) suspended in pyridine (0.5 mL) was added methane sulfonylchloride (0.08 mL, 1.0 mmol). After stirring overnight at rt the pyridine was removed under a stream of nitrogen. The residue was treated with water, filtered and air-dried to afford a brown solid (45 mg, 38% yield). Mp = 172-176 °C. MS (M + 1) = 407 m/z.

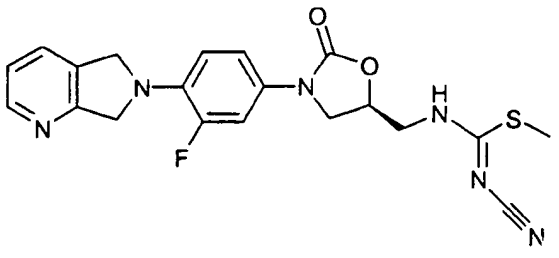
Example 26



Compound 21

To the sulfonamide (prepared in Example 25) (10 mg, 0.02 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (100 mg, 10 mmols). After stirring overnight the reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as a brown crystalline solid (0.5 mg, 5% yield). MS (M + 1) = 405 m/z.

Example 27

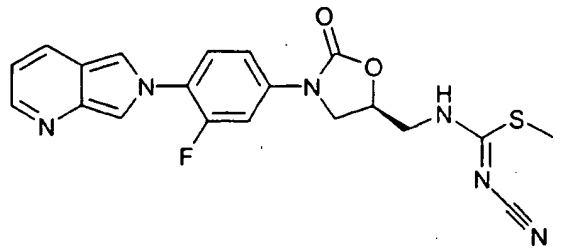


38

Compound 22

To the amine (prepared in Example 8) (200 mg, 0.61 mmol) suspended in toluene (8 mL), was added dimethyl-N-cyanodithioiminocarbonate (89 mg, 0.61 mmol). After stirring overnight at reflux the toluene was decanted and the oily residue treated with methanol, filtered, and air-dried to afford a brown crystalline solid (62 mg, 20% yield). Mp = 204-207°C. MS (M + 1) = 427 m/z.

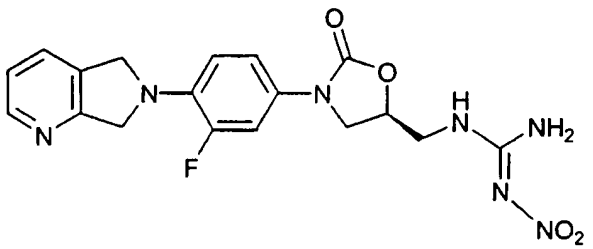
Example 28



Compound 23

A suspension of the thioimidate (from Example 27) (45 mg, 0.10 mmol) and MnO_2 (200 mg, 2.0 mmols) in CH_2Cl_2 were stirred at rt for one day whereupon a second addition of MnO_2 (150 mg, 1.5 mmols) was added. After an additional day of stirring the mixture was filtered through Celite, washed with CH_2Cl_2 (10 mL), concentrated to afford a yellow crystalline solid (20 mg, 45% yield). MS (M + 1) = 426 m/z.

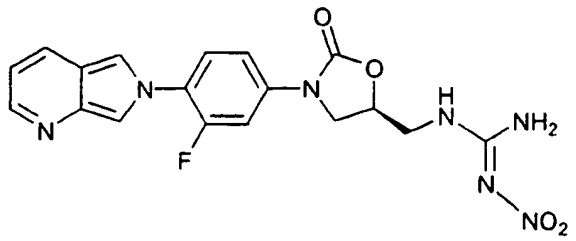
Example 29



Compound 24

A suspension of the amine (prepared in Example 8) (165 mg, 0.5 mmol) and 2-methyl-1-nitro-2-thiopseudourea (94 mg, 0.70 mmol) (as prepared as in EP 0539204/ 1993) in methanol (2 mL) was refluxed for four hours. After cooling to rt the reaction mixture was filtered and air dried to afford a yellow crystalline solid (50 mg, 24% yield). Mp = 202-206 °C. MS (M + 1) = 416 m/z.

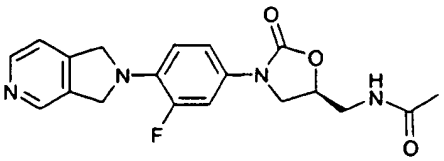
Example 30



Compound 25

To the nitroguanidine (prepared in Example 29) (35 mg, 0.08 mmol) suspended in CH_2Cl_2 (1.0 mL) was added MnO_2 (three additions of 100 mg over three days). The reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as a yellow crystalline solid (1.6 mg, 4% yield). MS (M + 1) = 414 m/z.

Example 31

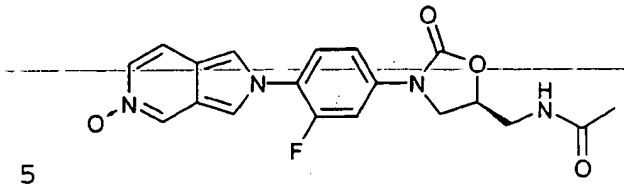


Compound 26

The starting material 6,7-dihydro-5H-pyrrolo[3,4-*c*]pyridine was prepared as in US Pat. No. 5,371,090 to Petersen et al. Compound 26 was then prepared as

in Example 8 except the acetamide was recrystallized from acetonitrile to give a light tan solid. Mp = 182-190°C decomposition. MS (M + 1) = 371 m/z.

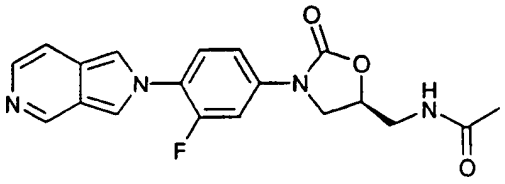
Example 32



Compound 27

Compound 27 was isolated from the final step of Example 31 via chromatography (5% MeOH/CH_2Cl_2 as eluent) of the mother liquors collected from recrystallization. Light yellow solid, Mp = 219-225°C decomp. MS (M + 1) = 385 m/z.

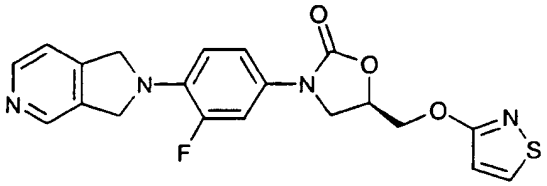
Example 33



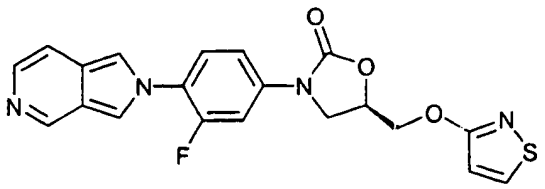
Compound 28

Compound 28 was prepared as in Example 9 except with 10% MeOH/CH_2Cl_2 as eluent. Light yellow solid, Mp = 219-225°C decomposition. MS (M + 1) = 369 m/z.

Example 34



Compound 29

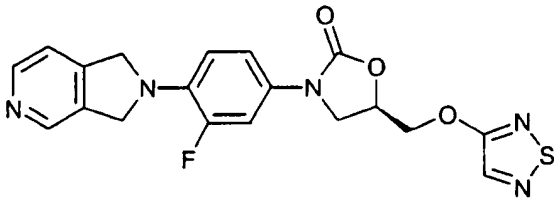


Compound 30

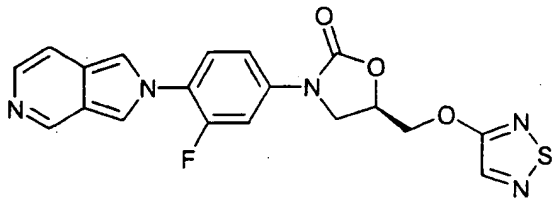
Isothiazole (0.088 g, 0.87mmol)(prepared as in *J Heterocyclic Chem* **1971**, *8*, 591) was added portionwise at rt to a suspension of sodium hydride (0.036 g, 0.91 mmol, 60% in oil) in DMF (4 mL) under nitrogen. The mixture was stirred for 30 minutes whereupon the mesylate from Example 31 (0.31 g, 0.76 mmol), in DMF (10 mL), was added all at once. After stirring for 6 hours at 60°C the reaction mixture was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3x50 mL). The combined organics were washed several times with water, then once with brine, dried over sodium sulfate, concentrated, and chromatographed on silica with 5% MeOH/EtOAc as eluent. Two products were isolated from the chromatography: 0.050g of Compound 29; and 0.022 g of Compound 30. Overall yield, 30%.

Compound 29 MS (M+1) = 413.0
Compound 30 MS (M+1) = 411.1

Example 35



Compound 31



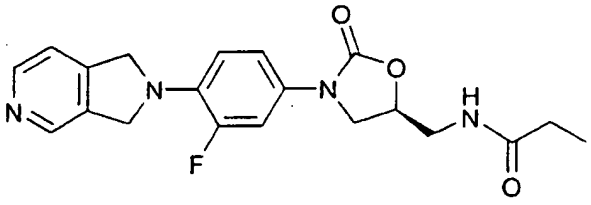
Compound 32

To a suspension of sodium hydride (0.036 g, 0.91mmol, 60% in oil) in DMF (4 mL) at rt under nitrogen was added portion wise 4-hydroxy-1, 2, 5-thiadiazole (0.088 g, 0.87 mmol) (as prepared in U.S Patent 3,391,150 [7/2/68]). After stirring for 30 min the mesylate from Example 31 (0.310 g, 0.76 mmol), in DMF (10 mL), was added all at once. After stirring for 6 hours at 60 C the reaction mixture was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3x50 mL). The combined organics were washed several times with water, then once with brine, dried over sodium sulfate, concentrated, and chromatographed on silica with 2% MeOH/EtOAc as eluent. Two products were isolated from the chromatography: 0.035 g of Compound 31; and 0.0093 g of Compound 32. Overall yield, 14%.

Compound 31 MS (M+1) = 414.0

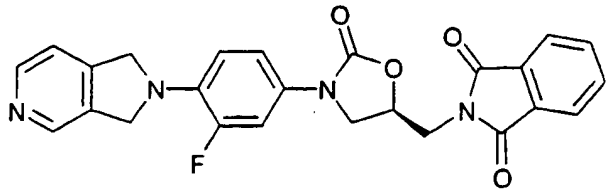
Compound 32 MS (M+1) = 412.1

Example 36

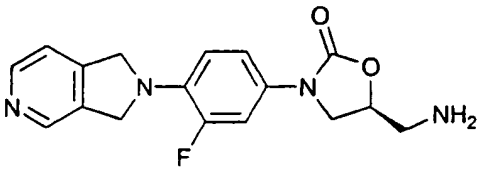


Compound 33

Step 1:



To the mesylate from Example 31 (2.45 g, 6.01 mmol) dissolved in degassed DMF (100 mL) under nitrogen was added potassium phthalimide (2.23 g, 12.0 mmols). After heating at 65°C for 3 hours the reaction mixture was cooled, poured into water (300 mL), and extracted with methylene chloride (3x200 mL). The combined organics were washed with water (3x150 mL) dried over sodium sulfate, concentrated to a tan solid. This solid was washed with water and dried in a high vacuum oven at 50°C to afford 2.20 g (80%) of the oxazolidinone phthalimide. MS= 459.1 (M+1)



Step 2:

To the above phthalimide (0.97 g, 2.1 mmols) in degassed methanol (30 mL) under nitrogen was added hydrazine monohydrate (0.2 mL, 4.3 mmols) dropwise. After refluxing for 12 hours the reaction mixture was cooled to rt, and concentrated, suspended CH_2Cl_2 and filtered. The crude oxazolidinone amine was concentrated and used without further purification.

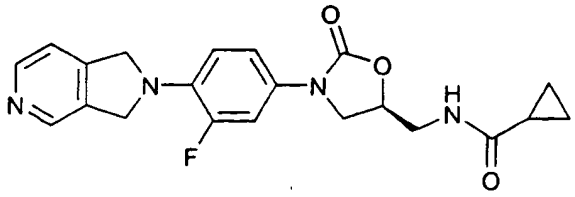
Step 3:

Compound 33,

To the crude amine (0.14 g, 0.44 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.14 mL, 18 mmols) followed by propionyl chloride (0.76 mL, 0.88 mmol).

After stirring for 5 hrs at rt the solution was poured into water (20 mL) and extracted with methylene chloride (3x10 mL). The combined extracts were washed with water (10 mL) and 1 M NaOH (aq) (10 mL), dried over sodium sulfate, concentrated and chromatographed using neat EtOAc as eluent to afford the propionyl amide as a gold oil (0.020 g, 12% yield). MS= 385.2 (M+1)

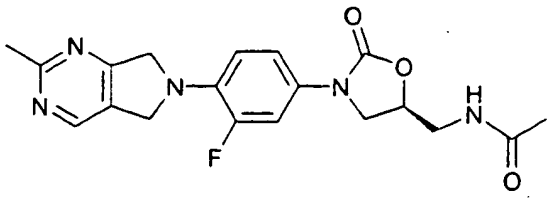
Example 37



Compound 34

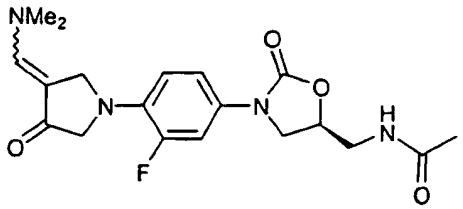
To the crude amine (as prepared in Example 36) (0.144 g, 0.437 mmol) in methylene chloride (5 mL) was added pyridine (0.14 mL, 1.7 mmols), followed by cyclopropane carbonyl chloride (0.08 mL, 0.88 mmol). After stirring for 5 hrs at rt the solution was poured into water (20 mL) and extracted with methylene chloride (3x10 mL). The combined extracts were washed with water (10 mL) and 1 M NaOH (aq) (10 mL), dried over sodium sulfate, concentrated and chromatographed using a gradient elution of 1% to 5% to 10% MeOH/ EtOAc. The desired product eluted with 5% MeOH/ EtOAc and was concentration to afford the product as a white powder (0.012 g, 7% yield). MS= 397.2 (M+1)

Example 38



Compound 35

Step 1:



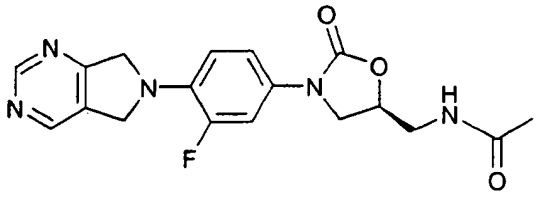
To *N*-[(3-pyrrolidinone-3-fluorophenyl) 5-oxazolidinyl]methyl acetamide (prepared according to W096/13502)(0.150 g, 0.447 mmols) was added methoxy-bis(dimethylamino)methane (1 mL). After heating at 50°C for 15 min the reaction mixture was concentrated to provide the crude β-ketoenamine which was used without further purification.

Step 2;

Compound 35

To ethanolic NaOEt (made from 0.027 g Na in 3 mL EtOH) was added acetamidine hydrochloride (0.113 g, 1.19 mmols) and the above β-ketoenamine oxazolidinone acetamide. After refluxing for 3 hrs the reaction mixture was cooled to rt, concentrated, taken up in chloroform, and washed with water (3x8 mL). After drying over sodium sulfate the crude product was concentrated, dissolved in 5% MeOH/ EtOAc, and filtered to afford the product as an off-white solid (0.052 g, 45% yield). Mp = 234°C, decomp. MS = 385.9 (M+1)

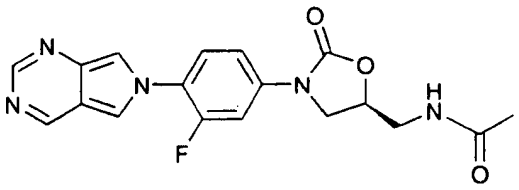
Example 39



Compound 36

To *N*-[(3-pyrrolidinone-3-fluorophenyl) 5-oxazolidinyl]methyl acetamide (prepared according to W096/13502)(0.099 g, 0.29 mmol) was added methoxy-bis(dimethylamino)methane (1.0 mL). After heating at 50°C for 2 hrs the reaction mixture was concentrated to provide the crude β-ketoenamine. To this mixture was added benzene (5 mL), DMF (1 mL) and formamidine acetate (0.55 g, 5.3 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a white powder (0.037 g, 34% yield). Mp = 230-232°C. MS (M + 1) = 372 m/z.

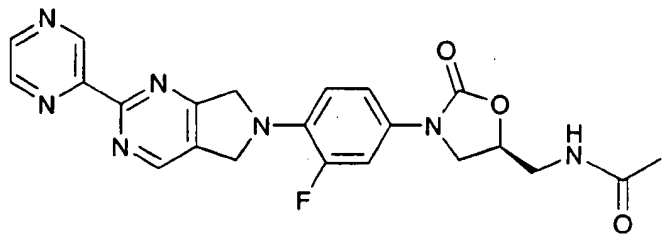
Example 40



Compound 37

The above acetamide from Example 39 (0.020 mg, 0.054 mmol) was taken up in CH_2Cl_2 (5 mL) and MnO_2 added (0.10 g, 0.98 mmol). After stirring overnight at rt the reaction mixture was filtered through Celite and concentrated to afford the product as a light yellow solid (0.016 g, 80% yield). Mp = 164-166°C. MS (M + 1) = 370 m/z.

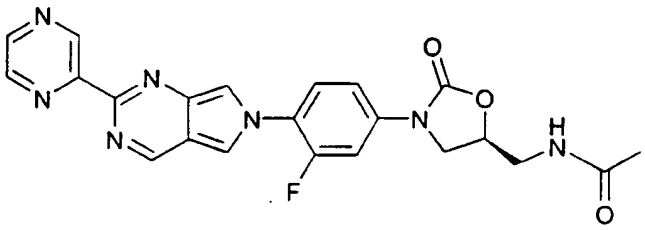
Example 41



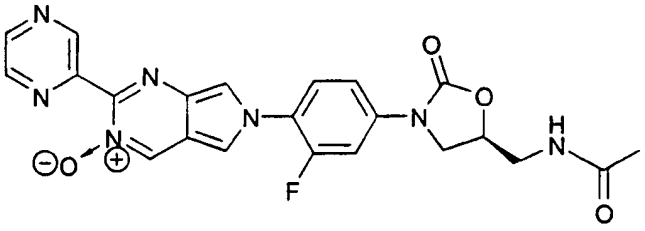
Compound 38

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and pyrazine-2-carboxamidine hydrochloride (0.62 g, 3.9 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.0026 g, 2% yield). Mp = 212-214°C. MS (M + 1) = 450 m/z.

Example 42



Compound 39



Compound 40

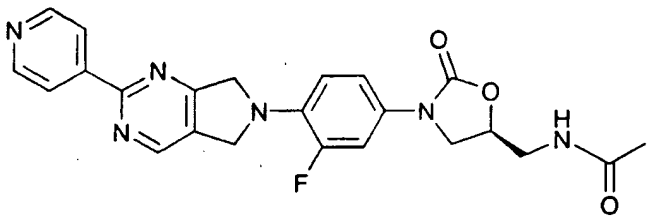
The above acetamide from Example 39 (0.040 g, 0.088 mmols) was taken up in CH_2Cl_2 (10 mL) and MnO_2 (0.36 g, 3.5 mmols) added in three portions over three days. After stirring for three days the reaction mixture was filtered through Celite, concentrated and chromatography on silica with 7%

MeOH/CH_2Cl_2 as eluent. Two products were isolated from the chromatography: 0.001 g of Compound 39 as a light yellow solid (4% yield); and 0.002 g of Compound 40 as a yellow solid (4% yield).

Compound 39: MS (M + 1) = 448 m/z.

Compound 40: MS (M + 1) = 464 m/z.

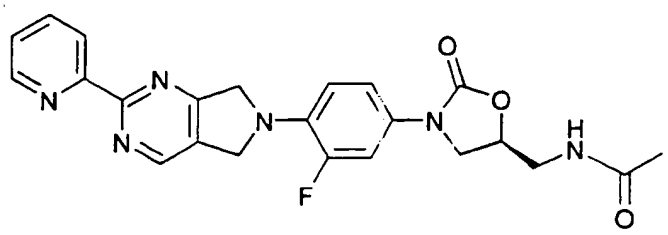
Example 43



Compound 41

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and 4-amidinopyridine hydrochloride (0.81 g, 5.2 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.072 g, 55% yield). Mp = 245-250°C, decomp. MS (M + 1) = 449 m/z.

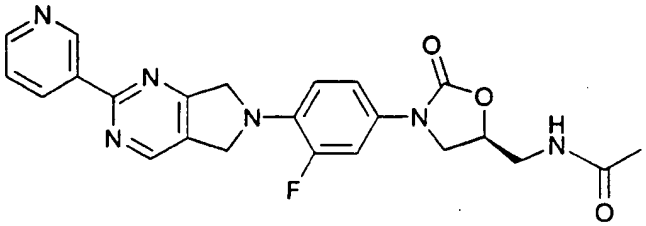
Example 44



Compound 42

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and 2-amidinopyridine hydrochloride (0.61 g, 3.9 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a yellow powder (0.054 g, 40% yield). Mp = 216-220°C. MS (M + 1) = 449 m/z.

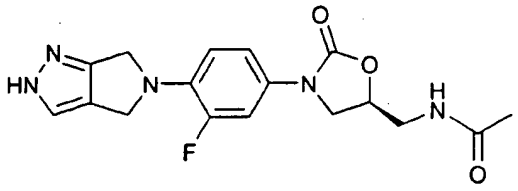
Example 45



Compound 43

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and 3-amidinopyridine hydrochloride (0.49 g, 3.1 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light purple, crystalline solid (0.044 g, 33% yield). Mp = 265-270°C, decomp. MS (M + 1) = 449 m/z.

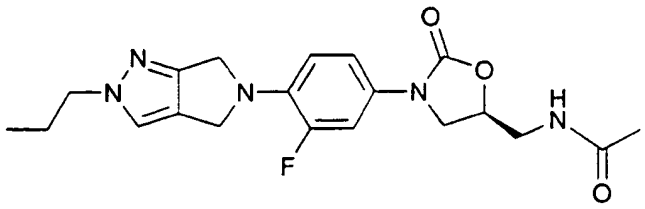
Example 46



Compound 44

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and hydrazine hydrochloride (0.22 g, 3.2 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as off-white powder (0.022 g, 21% yield). Mp = 244-247°C, decomp. MS (M + 1) = 360 m/z.

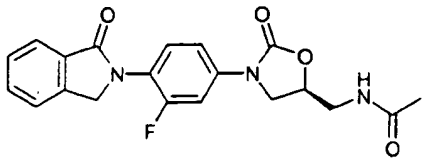
Example 47



Compound 45

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and n-propylhydrazine oxalate (0.87 g, 5.3 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.081 g, 55% yield). Mp = 204-208°C. MS (M + 1) = 402 m/z.

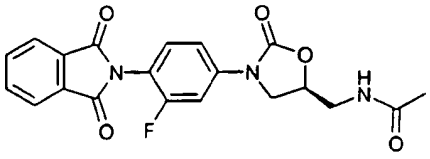
Example 48



Compound 46

The starting material aniline (N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide) was prepared as in World Patent WO 96/23788. To phthalic dicarboxaldehyde (0.0522 g, 0.378 mmol) in acetonitrile (1 mL) was added glacial acetic acid (0.05 mL, 0.87 mmol) and then the above aniline (0.0955 g, 0.357 mmol) in acetonitrile (5 mL) dropwise. After 4 hrs water (10 mL) was added and a precipitate was collected on a filter and washed with water and ether to provide Compound 46 as a light green solid (0.0655g, 48%). Mp = 211-214 °C. MS (M + 1) = 384 m/z.

Example 49

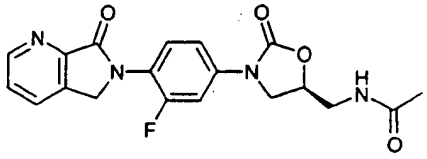


Compound 47

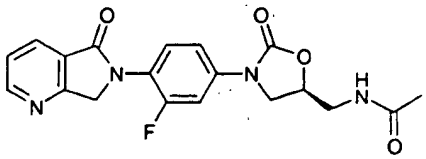
To starting material aniline (N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide)(0.095 g, 0.36 mmol)(as prepared in World Patent WO 96/23788) in CH_2Cl_2 (5 mL) was added triethylamine (0.15 mL, 1.1 mmols) and phthaloyl dichloride (0.056 mL, 0.39 mmol). After stirring overnight a solid was collected on a filter, washed with water (10 mL) and

dried in vacuum oven (50°C) to afford the product as a off-white solid (0.060, 42%). Mp = 240-242°C. MS (M + 1) = 398 m/z.

Example 50



Compound 48



Compound 49

To starting material aniline (N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide)(0.20 g, 0.75 mmol)(as prepared in World Patent WO 96/23788) in acetonitrile (5 mL) was added 2,3-pyridine dicarboxaldehyde (0.10 g, 6.6 mmols) and glacial acetic acid (0.050 mL, 0.87 mmol). After stirring for 5hrs the reaction mixture was concentrated and chromatographed on silica with 2.5% MeOH/CH_2Cl_2 as eluent to afford the two products: 0.035 g of Compound 52 (12%) as a yellow solid; and 0.011 g of Compound 53 (4%) as a yellow solid.

Compound 48: Mp = 230-232°C. MS (M + 1) = 385 m/z.

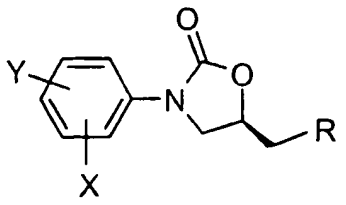
Compound 49: Mp = 207-209°C. MS (M + 1) = 385 m/z.

The invention has been described in detail with particular reference to the above embodiments thereof. The above embodiments and examples are given to illustrate the scope and spirit of the present invention. These embodiments and examples will make apparent, to those skilled in the art, other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. It will be understood that variations and modifications can be effected within the spirit and scope of the invention; therefore, the instant invention should be limited only by the appended claims.

CLAIMS

We claim:

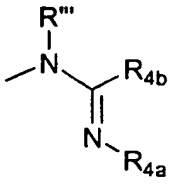
1. A compound of Formula I



Formula I

wherein:

R is selected from the group consisting of OH, O-Aryl, O-Heteroaryl, N_3, OR', OSO_2R'', -NR'''R'''', or



wherein:

(i) R' is straight-chain or branched acyl having up to 6 carbon atoms or benzyl;

(ii) R'' is straight-chain or branched alkyl, having up to 5 carbon atoms, phenyl or tolyl; and

(iii) R''' and R'''' are independently selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, phenyl or tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by cyano or alkoxycarbonyl having up to 4 carbon atoms, $-CO_2-R_1$, $-CO-R_1$, $-CO-SR_1$, $-CS-R_1$, $P(O)(OR_2)(OR_3)$, and $-SO_2-R_4$, in which

R_1 is selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, trifluoromethyl or phenyl, benzyl\ or acyl having up to 5 carbon atoms, straight-chain or branched alkyl having up to 6 carbon

atoms, said alkyl optionally substituted by straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms, OH, cyano, up to 3 halogen atoms, and -NR_5 R_6 in which R_5 and R_6 are identical or different and are selected from H, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms;

R_2 and R_3 are identical or different and are selected from hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms; and

R_4 is selected from straight-chain or branched alkyl having up to 4 carbon atoms or phenyl and;

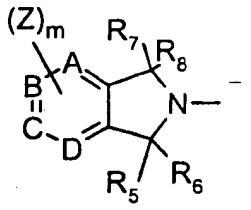
R_{4a} is CN, COR_{4c}, $COOR_{4c}$, $CONHR_{4c}$, CO-NR_{4c} R_{4d}, SO_2R_{4c}, SO_2NHR_{4c}, SO_2-NR_{4c} R_{4d}, or NO_2;

R_{4b} is H, alkyl, OR_{4c}, SR_{4c}, amino, NHR_{4c}, $NR_{4c}R_{4d}$, (C1-C8), alkylaryl or mono-, di-, tri-, and per-halo(C1-C8) alkyl;

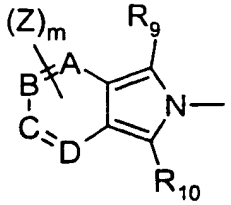
R_{4c} and R_{4d} are independently selected from H, alkyl, aryl, or in the case of any $NR_{4c}R_{4d}$ group R_{4c} and R_{4d} taken together with the nitrogen atom to which they are attached form a unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl group;

X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-C_{1-8}-alkyl, C_{1-8} alkoxy, thio-C_{1-8}-alkyl, C_{1-8} alkyl-amino, di(C_{1-8}-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8} alkyl-CO-O-, C_{1-8} alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, amine, C_{3-6} cycloalkyl, C_{1-8} alkyl optionally substituted with one or more members selected from the group consisting of F, Cl, OH, C_{1-8} alkoxyl and C_{1-8} acyloxy; and

Y is a radical of Formulae II or III:



Formula II



Formula III

wherein

R_5, R_6, R_7, and R_8 are each independently H, alkyl, CN, nitro, C_{1-8} alkyl, halo-C_{1-8}-alkyl, formyl, carboxy, alkoxycarbonyl, carboxamide, aryl, substituted-aryl, heteroaryl, or substituted-heteroaryl, or R_5 and R_6 and/or R_7 and R_8 together form an oxo group;

R_9, and R_{10} are each independently H, halogen, alkyl, OH, CN, mercapto, nitro, C_{1-8} alkyl, halo-C_{1-8}-alkyl, C_{1-8} alkoxyl, thio-C_{1-8}-alkyl, amino, C_{1-8}-alkyl-amino, di(C_{1-8}-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8}-alkyl-CO-O-, C_{1-8}-alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, alkoxy, heteroaryl, substituted-heteroaryl, or amine ;

A, B, C, and D are selected from C, S, O, and N to form any five to ten membered aromatic or heteroaromatic ring, said heteroaromatic ring having one to four members selected from the group consisting of S, O, and N;

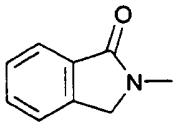
Z is selected from halogen, alkyl, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, CHO, COalkyl, amine, (dialkylamino)alkyl where dialkylamino is selected from dimethylamine, diethylamine,

morpholinyl, thiomorpholinyl, pyrroidinyl, or piperidinyl, or, alkoxy, or NHCO-(C_1-C_8-alkyl); and

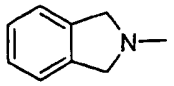
m is 0 or 1,

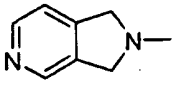
and the pharmaceutically acceptable salts and esters thereof.

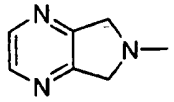
2. The compound of claim 1 wherein Y is selected from the group consisting of

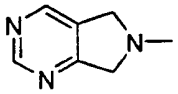


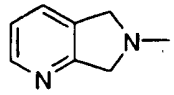
isoindolone-;

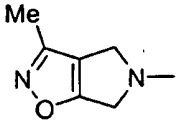

(1,3-dihydro-2H-isoindol-2-yl)-;

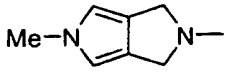

(6,7-dihydro-5H-pyrrolo[3,4-*c*]pyridin-6-yl)-;

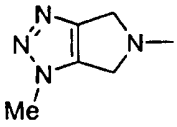

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyrazin-6-yl)-;

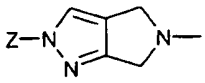

(6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidin-6-yl)-;

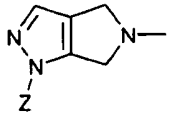

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)-;


(4,6-dihydro-3-methyl-5H-pyrrolo[3,4-*d*]isoxazol-5-yl)-;

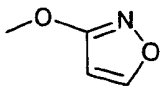

(3,5-dihydro-5-methylpyrrolo[3,4-*c*]pyrrol-2(1H)-yl)-; and

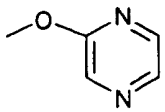

(4,6-dihydro-1-methylpyrrolo[3,4-*d*]-1,2,3-triazol-5(1H)-yl)-.

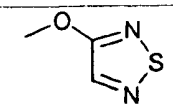


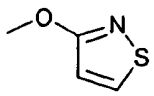


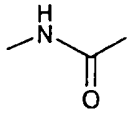
3. The compound of claim 1 wherein R is -NHCOCH$_3$ or is selected from the group consisting of

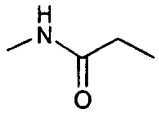


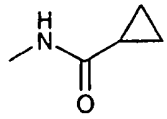


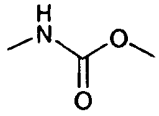


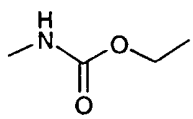


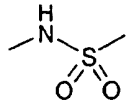


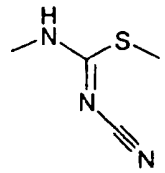


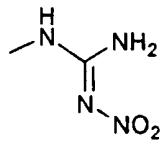






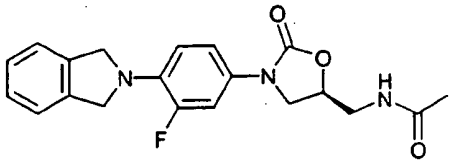




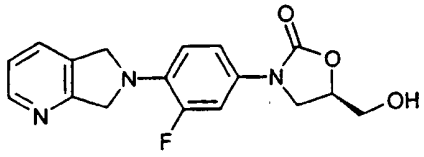


5

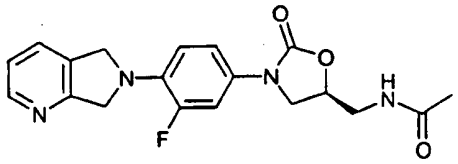
4. A compound of Claim 1 having the formula:



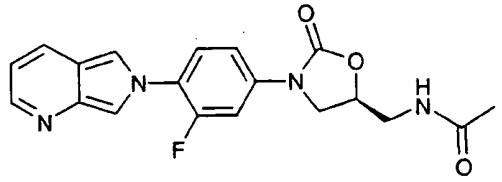
5. A compound of Claim 1 having the formula:



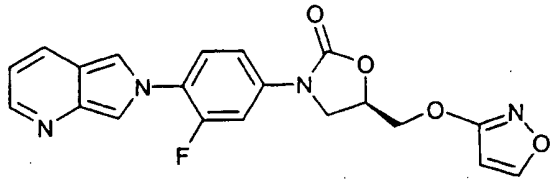
6. A compound of Claim 1 having the formula:



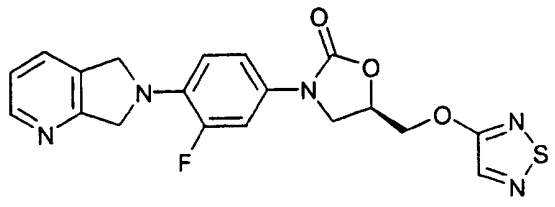
7. A compound of Claim 1 having the formula:



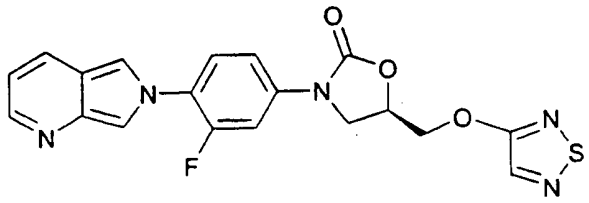
8. A compound of Claim 1 having the formula:



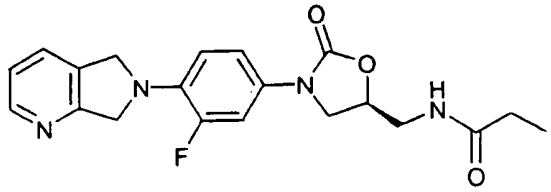
9. A compound of Claim 1 having the formula:\



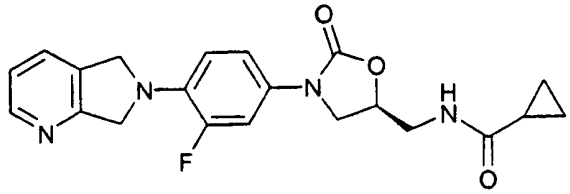
10. A compound of Claim 1 having the formula:



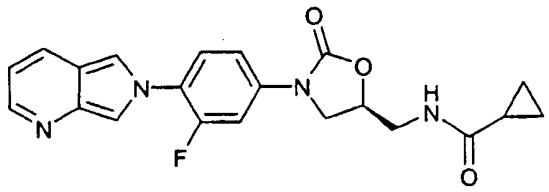
11. A compound of Claim 1 having the formula:



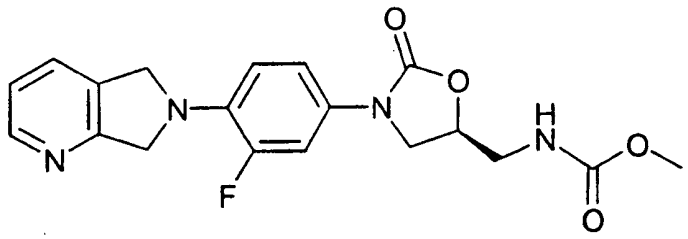
12. A compound of Claim 1 having the formula:



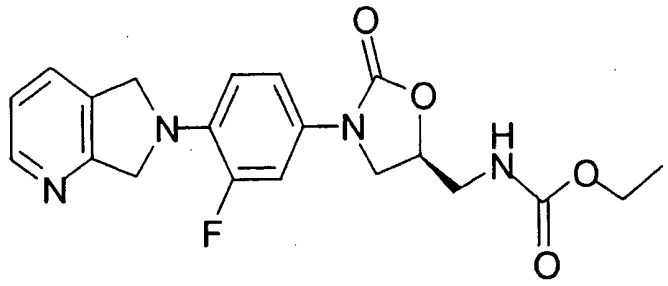
13. A compound of Claim 1 having the formula:



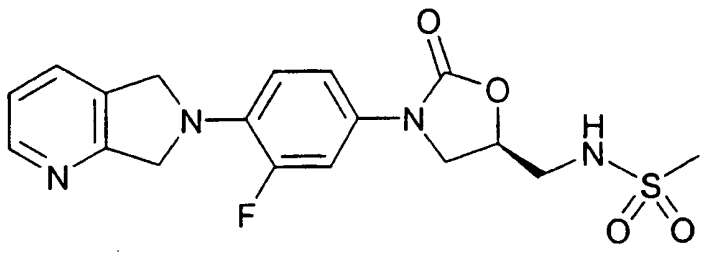
14. A compound of Claim 1 having the formula:



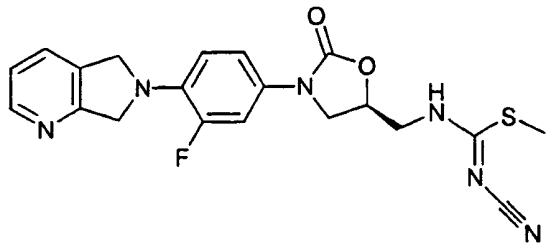
15. A compound of Claim 1 having the formula:



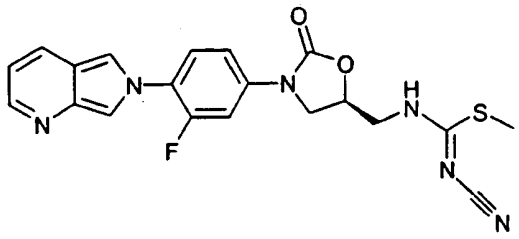
16. A compound of Claim 1 having the formula:



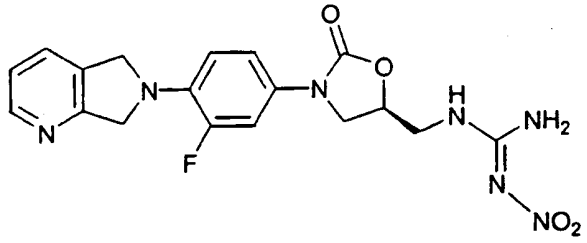
17. A compound of Claim 1 having the formula:



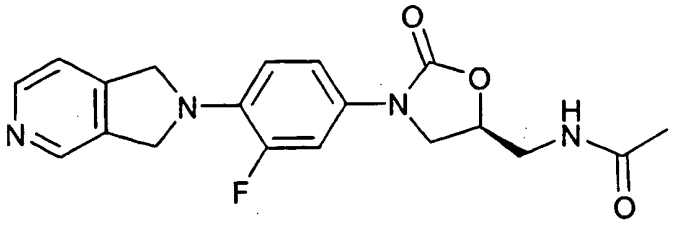
18. A compound of Claim 1 having the formula:



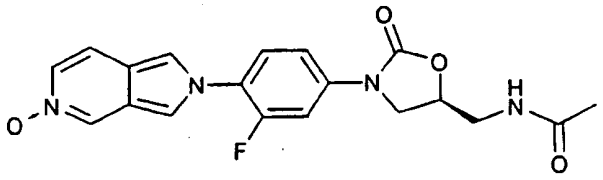
19. A compound of Claim 1 having the formula:



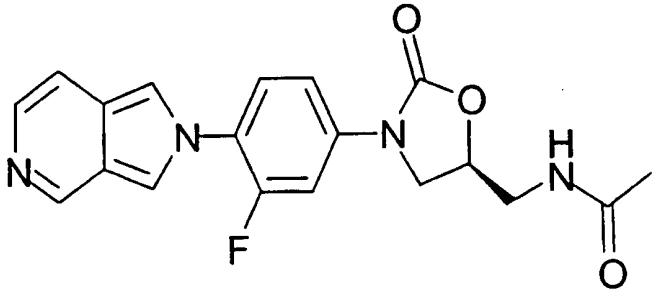
20. A compound of Claim 1 having the formula:



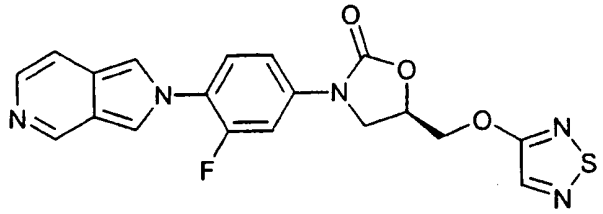
21. A compound of Claim 1 having the formula:



22. A compound of Claim 1 having the formula:

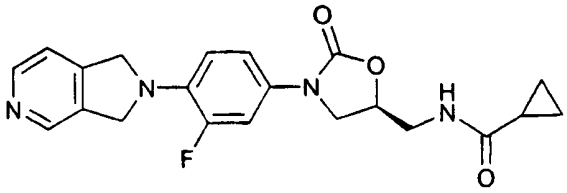


23. A compound of Claim 1 having the formula:

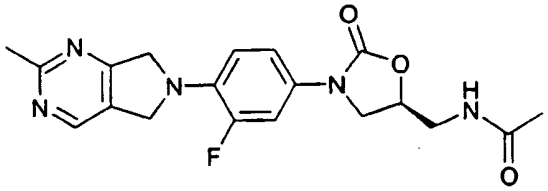


65

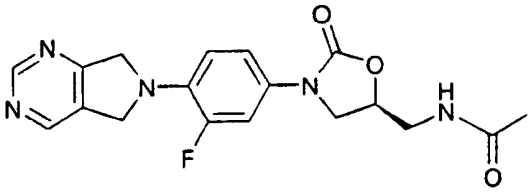
24. A compound of Claim 1 having the formula:



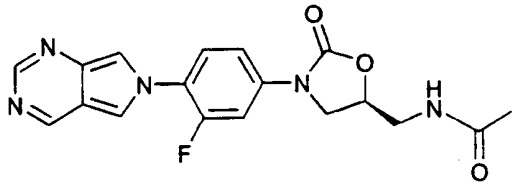
25. A compound of Claim 1 having the formula:



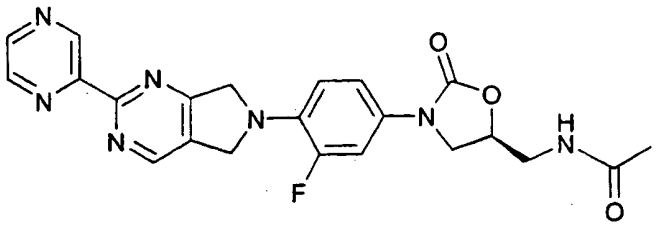
26. A compound of Claim 1 having the formula:



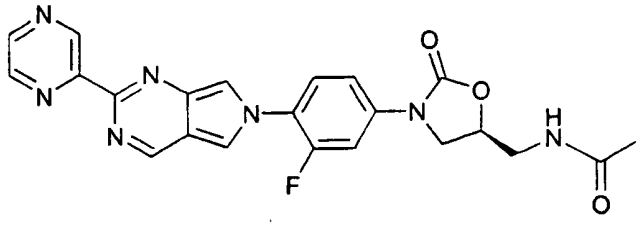
27. A compound of Claim 1 having the formula:



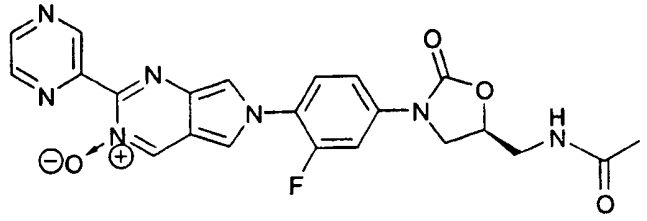
28. A compound of Claim 1 having the formula:



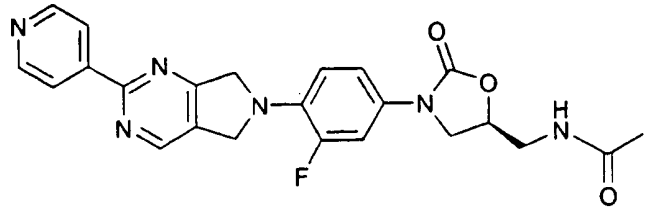
29. A compound of Claim 1 having the formula:



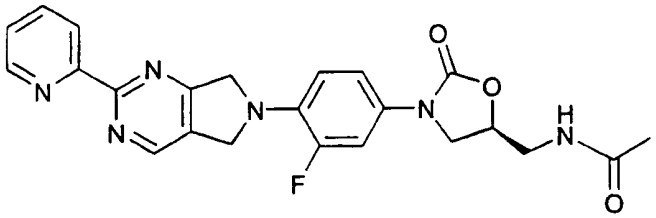
30. A compound of Claim 1 having the formula:



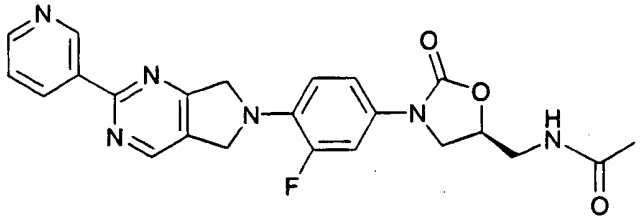
31. A compound of Claim 1 having the formula:



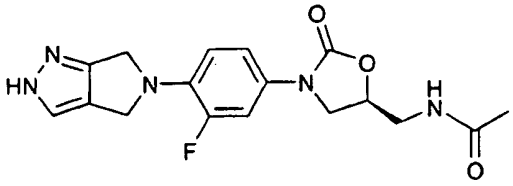
32. A compound of Claim 1 having the formula:



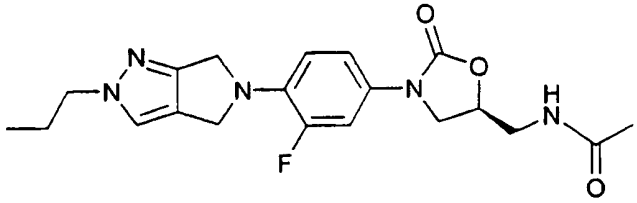
33. A compound of Claim 1 having the formula:



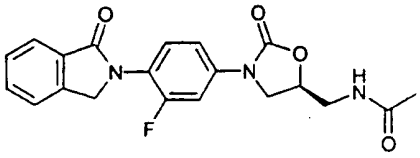
34. A compound of Claim 1 having the formula:



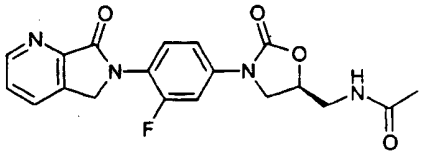
35. A compound of Claim 1 having the formula:



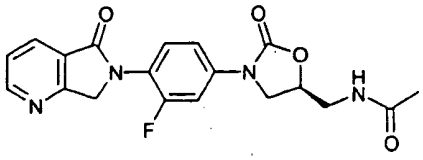
36. A compound of Claim 1 having the formula:



37. A compound of Claim 1 having the formula:



38. A compound of Claim 1 having the formula:



39. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

40. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound according to Claim 1.

41. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective dose of the pharmaceutical composition of a compound according to Claim 1.

42. The method of Claim 40 or 41 wherein said condition is selected from the group consisting of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, bone and joint infections and hospital-acquired lung infections.

43. The method of Claim 40 or 41 wherein said bacterium is selected from the group consisting of *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus spp., Moraxella catarrhalis* and *H. influenzae*.

44. The method of Claim 40 or 41 wherein said bacterium is a Gram-positive coccus.

45. The method of Claim 44 wherein said Gram-positive coccus is drug-resistant.

INTERNATIONAL SEARCH REPORT

Interl. ›nal Application No
PCT/US 00/21093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/10 C07D471/04 C07D487/04 C07D498/04 A61K31/422
A61K31/437 A61K31/4985 A61K31/519 A61K31/424 A61P31/04
//(C07D471/04,221:00,209:00),(C07D487/04,231:00,209:00),

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 7 C07D A61K A61P

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)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	DATABASE WPI Section Ch, Week 200006 Derwent Publications Ltd., London, GB; Class B03, AN 2000-069004 XP002154332 -& JP 11 322729 A (HOKURIKU PHARM CO LTD), 24 November 1999 (1999-11-24) abstract; particularly page 43, no 130, page 51, no 170, page 60, no 212, page 75, no 278 and page 88, no 56 of the original document ---	1-45
Y	WO 96 23788 A (PHARMACIA + UPJOHN COMPANY) 8 August 1996 (1996-08-08) cited in the application the whole document --- -/--	1-45

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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	Date of mailing of the international search report
1 December 2000	14/12/2000

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

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Form PCT/ISA/210 (second sheet) (July 1992)

3411

INTERNATIONAL SEARCH REPORT

Interl. ...nal Application No
PCT/US 00/21093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D487/04,241:00,209:00),(C07D498/04,261:00,209:00), (C07D487/04,209:00,209:00),(C07D487/04,249:00,209:00), (C07D487/04,239:00,209:00)

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)

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 99 10342 A (ZENECA LIMITED) 4 March 1999 (1999-03-04) the whole document	1,39-45
A	WO 96 35691 A (PHARMACIA & UPJOHN COMPANY) 14 November 1996 (1996-11-14) the whole document	1,39-45
A	WO 96 15130 A (THE UPJOHN COMPANY) 23 May 1996 (1996-05-23) the whole document	1,39-45

☐ 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	Date of mailing of the international search report
1 December 2000	

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

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Form PCT/ISA/210 (second sheet) (July 1992)

3412

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ...nal Application No
PCT/US 00/21093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 11322729 A	24-11-1999	NONE	
WO 9623788 A	08-08-1996	AU 703465 B	25-03-1999
		AU 4899896 A	21-08-1996
		BR 9607017 A	28-10-1997
		CA 2208603 A	08-08-1996
		CN 1172484 A	04-02-1998
		CZ 9702314 A	12-08-1998
		EP 0807112 A	19-11-1997
		FI 973217 A	04-08-1997
		JP 10513446 T	22-12-1998
		NO 973550 A	03-10-1997
		NZ 302844 A	29-06-1999
		PL 321663 A	22-12-1997
		US 6124334 A	26-09-2000
		US 5910504 A	08-06-1999
WO 9910342 A	04-03-1999	EP 1005468 A	07-06-2000
WO 9635691 A	14-11-1996	AU 702752 B	04-03-1999
		AU 5484996 A	29-11-1996
		CA 2218088 A	14-11-1996
		CN 1184481 A	10-06-1998
		EP 0828741 A	18-03-1998
		FI 974180 A	10-11-1997
		JP 11506430 T	08-06-1999
		NO 975158 A	09-01-1998
		US 6090820 A	18-07-2000
WO 9615130 A	23-05-1996	AU 702733 B	04-03-1999
		AU 3889095 A	06-06-1996
		BR 9509673 A	30-09-1997
		CN 1163615 A,B	29-10-1997
		EP 0792273 A	03-09-1997
		JP 10508844 T	02-09-1998
		NO 972222 A	14-05-1997
		NZ 295528 A	29-03-1999
		RU 2128660 C	10-04-1999
		US 5952324 A	14-09-1999

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 10/181051

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	21 minus 20=	* 1
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☑

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	890
X$ 9=		OR	X$18=	18
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	1188

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 30	Minus	** 21	=
Independent	* 3	Minus	*** 2	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 51	Minus	** 21	= 30
Independent	* 3	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

		OR		
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	540
X42=		OR	X84=	—
+140=		OR	+280=	—
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	540

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

		OR		
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

ORIGINAL

PTO/SB/22 (05-03)
Approved for use through 4/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional) **Le A 34 122**

In re Application of **Straub, et al.**

Application Number **10/181, 051** Filed **June 24, 2002**

For **Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation.**

Art Unit **1626** Examiner **Anderson, Rebecca L.**

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $ _____
- ☐ Two months (37 CFR 1.17(a)(2)) $ _____
- ☒ Three months (37 CFR 1.17(a)(3)) $ **980.00**
- ☐ Four months (37 CFR 1.17(a)(4)) $ _____
- ☐ Five months (37 CFR 1.17(a)(5)) $ _____

CERTIFICATION OF MAILING UNDER 37 C.F.R. 1.8(a): I hereby certify that this correspondence and any papers referred to as attached are being deposited, on the date shown below, with the United States Postal Service, with sufficient postage, as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: 19 October 2004

Typed or printed name: William F. Gray

Signature: William F. Gray

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $_____.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to change fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number **13-3372**.

I have enclosed a duplicate copy of this sheet.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

19 October 2004	William F. Gray
Date	Signature
(203) 812-2712	**William F. Gray**
Telephone Number	Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

10/21/2004 RFEKADU1 00000003 133372 10181051
01 FC:1253 980.00 DA

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	06/24/2002	Alexander Straub	Le A 34122	5850

35969 7590 04/19/2004

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
ANDERSON, REBECCA L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20* is/are pending in the application.

4a) Of the above claim(s) *8,10-16 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24, 12/9/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-20 are currently pending in the instant application. Claim 1 was cancelled in the amendment filed 7 January 2004. Claims 2-7, 9 and newly added claim 17 are rejected and claims 8, 10 and newly added claims 16 and 18-20 are withdrawn from consideration as being for non-elected subject matter.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7 and 9 in the response filed 7 January 2004 is acknowledged. The traversal is on the ground(s) that the claims have been amended to narrow the scope and the remaining claims now deal with the compounds, pharmaceutical compositions, method of making and method of treatment using the compounds of claim 2. However, this is not found persuasive because as stated in the previous restriction requirement, the claims lack unity of invention since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art. The compounds claimed contain 5-carbonylaminomethyl oxazol-2-one, which does not define a contribution over the prior art (as can be seen by formula (I) in WO-A-99/31092). The variables on the 5-carbonylaminomethyl oxazol-2-one vary extensively and when taken as a whole result in vastly different compounds. Accordingly, unity of invention is considered to be proper. The requirement is still deemed proper.

Applicant asks that the restricted group I be expanded to include substituents on the phenyl ring of R2 in recognition of the fact that a number of examples bearing the elected R2 group have the phenyl ring variously substituted. The elected invention of

Group I is therefore expanded to include the definition of R2 as found in claim 2 wherein the phenyl ring of substituent R2, radical A, is optionally substituted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7, 9 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims contain the subject matter of compounds of the formula (I) wherein R1 is an unsubstituted 2-thiophene radical, R2 is a mono- or polysubstituted phenyl radical and R3-R8 are each hydrogen. This subject matter is considered new matter since the specification and the originally filed claims excluded this subject matter from the chemical product as can be seen by original claim 1 and the specification pages 4- 7 which state that the present invention is the substituted oxazolidinones of the general formula (I) except for compounds of the general formula (I) in which the radical R1 is an unsubstituted 2-thiophene radical and the radical R2 is simultaneously a mono or polysubstituted phenyl radical and the radicals R3, R4, R5, R6, R7 and R8 are each simultaneously hydrogen. Therefore, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. This rejection can be overcome by deleting the new matter from the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (571) 272-0699.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier number for accessing the facsimile machine is (703) 872-9306

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

for

Joseph McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Serial No. 10/181,051	Group Art Unit ~~1646~~ 1626	Filing Date 06/24/02	Atty. Docket No. Le A 34 122
SUPPLEMENTAL INFORMATION DISCLOSURE CITATION		Applicant(s) Alexander Straub, et al.			

U.S. PATENT DOCUMENTS							
*		DOCUMENT NO.	DATE MM/DD/YY	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS														
		DOCUMENT NO.							DATE DD/MM/YY	COUNTRY	PRIMARY CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
RA	F3	9	9	0	6	3	7	1	11/02/99	WO	—	—		
RA	F4	9	9	3	7	3	0	4	29/07/99	WO	—	—		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, etc.)		
RA	R2	Ullmann's Encyclopedia of Industrial Chemistry, Fifth Revised Ed., Editors.: Elvers, B., Hawkins, S., VCH Verlagsgesellschaft mbH, Weinheim,1985-1996, ch. 5, 488-506
RA	R3	Zhu, B., Scarborough, R., "Recent Advances in Inhibitors of Factor Xa in the Prothrombinase Complex", Cur. Opinions Card. Pulm. Ren. Inv. Drugs, 1: 63-87 (1999)
RA	R4	Uzan, A., "Antithrombotic Agents", Emerging Drugs: The Prospect for Improved Medicines, 3: 189-208, (1998)
RA	R5	Kaiser, B., "Thrombin and Factor Xa Inhibitors", Drugs of the Future, 23: 423-436 (1998)
RA	R6	Al-Obeidi, F., Ostrem, J., "Factor Xa Inhibitors", Expert Opin. Therapeutic Patents, 9: 931-953 (1999)
RA	R7	Al-Obeidi, F., Ostrem, J., "Factor Xa Inhibitors by Classical and Combinatorial Chemistry", DDT, 3: 223-231 (May 1998)
RA	R8	Hauptmann, J., Sturzebecher, J., "Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside", Thrombosis Research, 93: 203-241 (1999)
RA	R9	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, pg. 199-200, Stichwort "Blutgerinnung"
RA	R10	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerinnung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, pg.259
RA	R11	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, pg. 610, Stichwort "Heparin"
RA	R12	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin"
RA	R13	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, pg. 292, Stichwort "Cumarinderivate"

EXAMINER	DATE CONSIDERED
Lebron Andrews	4/16/04

* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

10/181051
528 Rec'd PCT/PTC 24 JUN 2002

Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Serial No.	Group Art Unit	Filing Date	Atty. Docket No.
		10/181051	1626	JUN 24 2002	Le A 34 122

INFORMATION DISCLOSURE CITATION

Applicant(s) **Alexander STRAUB, et al.**

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE MM/DD/YY	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
RA	U_1	5561148	10/01/96	Gante et al.	514	376	09/22/94

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE DD/MM/YY	COUNTRY	PRIMARY CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
RA	F_1	744002	05/07/99	AU	—	—		
RA	F_2	0645376	29/03/95	EP	—	—		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, etc.)

RA	R_1	Becker, M. R., Ewing, W. R., Davis, R. S., Pauls, H. W., Ly, C., Li, A., Mason, H. J., Choi-Sledeski, Y. M., Spada, A. P., Chu, V., Brown, K. D., Colussi, D. J., Leadley, R. J., Bentley, R., Bostwick, J., Kasiewski, C., and Morgan, S., "Synthesis, Sar and in Vivo Activity of Novel Thienopyridine Sulfonamide Pyrrolidinones as Factor Xa Inhibitors", Bioorganic & Medicinal Chemistry Letters, 9: 2753-2758 (1999)

EXAMINER	DATE CONSIDERED
Rebecca Anderson	4/16/04

* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

submitted on JUN 24 2002

Notice of References Cited	Application/Control No. 10/181,051	Applicant(s)/Patent Under Reexamination STRAUB ET AL.	
	Examiner Rebecca L Anderson	Art Unit 1626	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,565,571	10-1996	Barbachyn et al.	546/144
*	B	US-5,654,428	08-1997	Barbachyn et al.	544/235
*	C	US-5,654,435	08-1997	Barbachyn et al.	546/271.4
*	D	US-5,756,732	05-1998	Barbachyn et al.	544/112
*	E	US-5,801,246	09-1998	Barbachyn et al.	548/152
*	F	US-5,929,248	07-1999	Barbachyn et al.	548/184
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

SEARCHED			
Class	Subclass	Date	Examiner
544	139	4/16/2004	RA

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor Name Search	4/16/2004	RA
STN structure search (enclosed)	4/16/2004	RA

Index of Claims

Application No.	Applicant(s)	
10/181,051	STRAUB ET AL.	
Examiner	**Art Unit**	
Rebecca L Anderson	1626	

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	4/16/04
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	3	√
	4	√
	5	√
	6	√
	7	√
	8	N
	9	√
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	11	N
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NEWS	4	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS	5	FEB 05	German (DE) application and patent publication number format changes
NEWS	6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 03	FRANCEPAT now available on STN
NEWS	9	MAR 29	Pharmaceutical Substances (PS) now available on STN
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NEWS	12	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
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NEWS LOGIN	Welcome Banner and News Items
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FILE 'HOME' ENTERED AT 13:53:35 ON 15 APR 2004

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 13:54:07 ON 15 APR 2004

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 APR 2004 HIGHEST RN 675571-70-7
DICTIONARY FILE UPDATES: 14 APR 2004 HIGHEST RN 675571-70-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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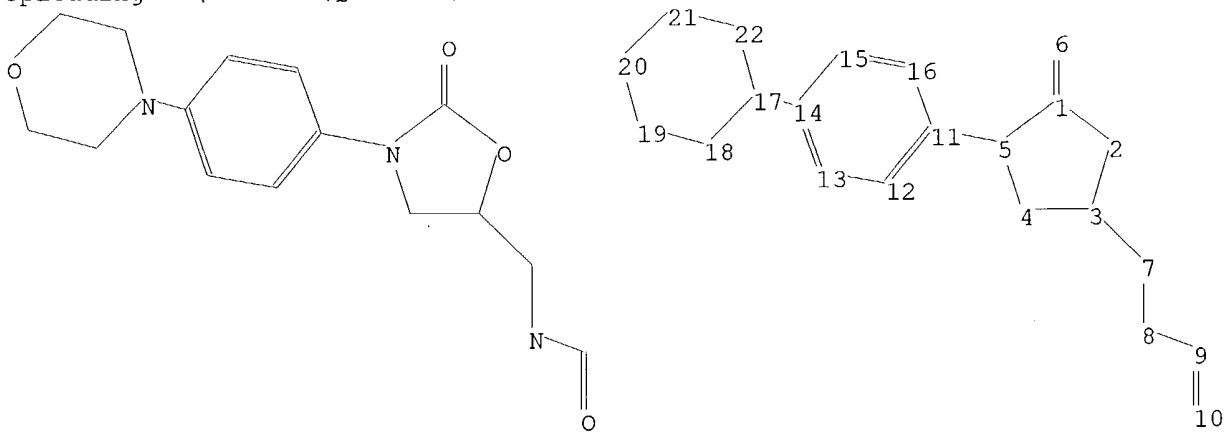

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exact bonds :
3-7

normalized bonds :
11-12 11-16 12-13 13-14 14-15 15-16

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom
19:Atom 20:Atom 21:Atom 22:Atom

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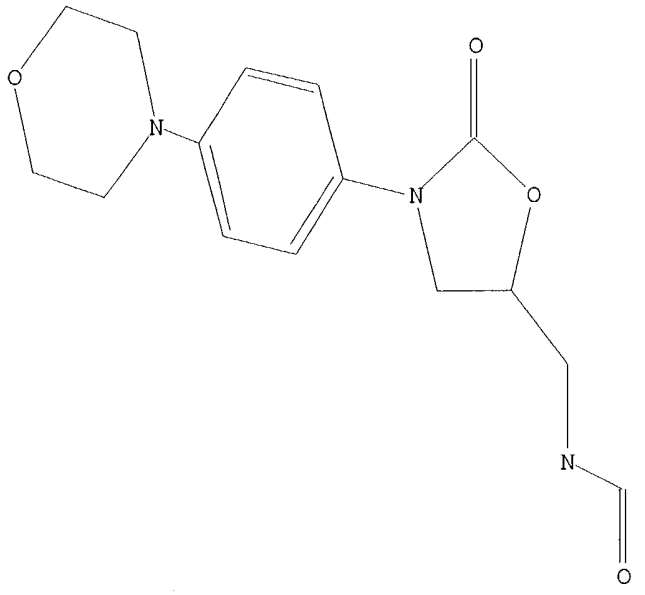
L1 HAS NO ANSWERS
L1 STR



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100.0% PROCESSED 130 ITERATIONS 5 ANSWERS
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FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
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PROJECTED ANSWERS: 5 TO 234

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35108500 CAPLUS/LC
L4 100 L3 AND CAPLUS/LC

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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FILE COVERS 1907 - 15 Apr 2004 VOL 140 ISS 16
FILE LAST UPDATED: 14 Apr 2004 (20040414/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L5 506 L4

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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STRUCTURE FILE UPDATES: 14 APR 2004 HIGHEST RN 675571-70-7
DICTIONARY FILE UPDATES: 14 APR 2004 HIGHEST RN 675571-70-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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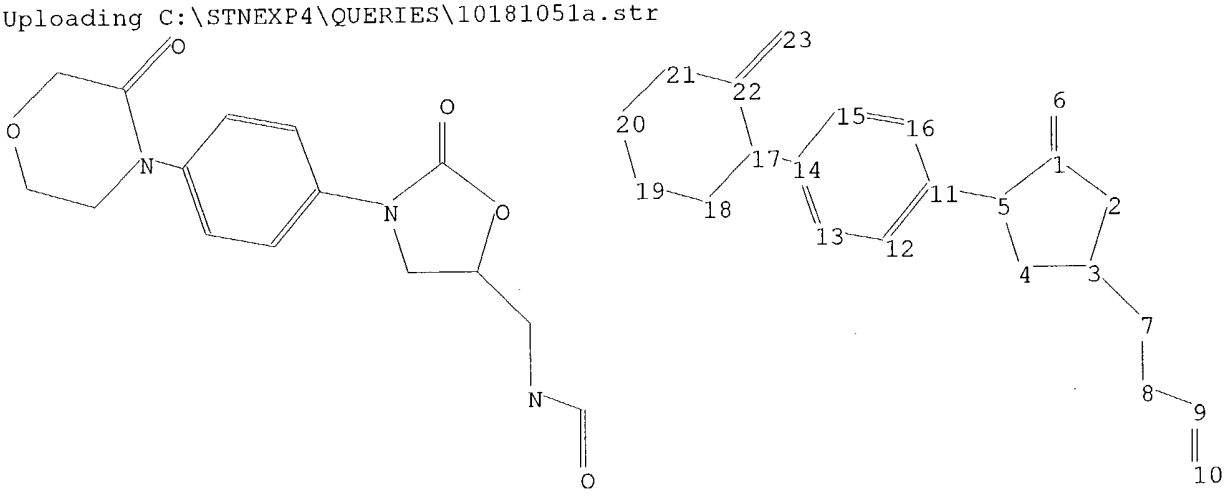

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ring nodes :
1 2 3 4 5 11 12 13 14 15 16 17 18 19 20 21 22
chain bonds :
1-6 3-7 5-11 7-8 8-9 9-10 14-17 22-23
ring bonds :
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exact/norm bonds :
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exact bonds :
1-2 2-3 3-4 3-7
normalized bonds :
11-12 11-16 12-13 13-14 14-15 15-16
isolated ring systems :
containing 1 : 11 : 17 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:CLASS

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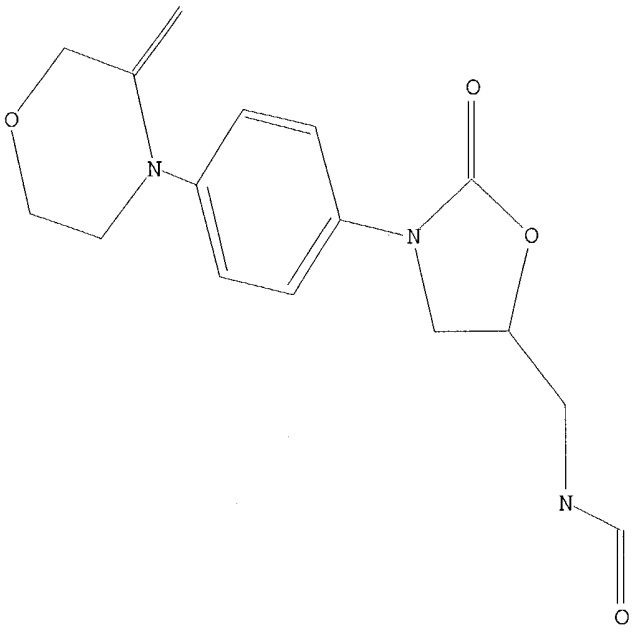

Structure attributes must be viewed using STN Express query preparation.

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L7 23 SEA SUB=L4 SSS FUL L6

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.84	316.34

FILE 'CAPLUS' ENTERED AT 13:56:19 ON 15 APR 2004
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FILE COVERS 1907 - 15 Apr 2004 VOL 140 ISS 16
FILE LAST UPDATED: 14 Apr 2004 (20040414/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l7
L8 3 L7

=> d ibib abs hitstr l8 1-3

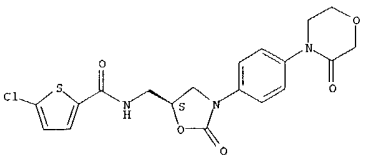
L8 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:334957 CAPLUS
DOCUMENT NUMBER: 138:343913
TITLE: Stents with oxazolidine derivatives for the prophylaxis and treatment of restenosis and thrombosis
INVENTOR(S): Perzborn, Elisabeth; Kalbe, Jochen; Ledwoch, Wolfram; Meulien, Didier
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035133	A1	20030501	WO 2002-EP11402	20021011
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10152460	A1	20030508	DE 2001-10152460	20011024

PRIORITY APPLN. INFO.: DE 2001-10152460 A 20011024
OTHER SOURCE(S): MARPAT 138:343913
AB The invention concerns stents containing oxazolidine derivs., methods for making the stents and their use in treatment of restenosis and thrombosis, especially after percutaneous transluminal coronary angioplasty, PTCA. Stents are coated with the oxazolidine derivative or the drug is incorporated into the stent material, e.g. polymer.
IT **366789-02-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stents with oxazolidine derivs. for prophylaxis and treatment of restenosis and thrombosis)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L8 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:5775 CAPLUS
DOCUMENT NUMBER: 138:89797
TITLE: Preparation of substituted oxazolidinones for combinational therapy in the treatment and/or prophylaxis of thromboembolic diseases
INVENTOR(S): Straub, Alexander; Lampe, Thomas; Pernerstorfer, Josef; Perzborn, Elisabeth; Pohlmann, Jens; Roehrig, Susanne; Schlemmer, Karl-Heinz
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 161 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

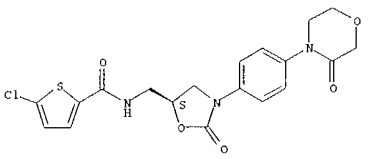
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000256	A1	20030103	WO 2002-EP6237	20020607
WO 2003000256	C2	20030206		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10129725	A1	20030102	DE 2001-10129725	20010620

PRIORITY APPLN. INFO.: DE 2001-10129725 A 20010620
OTHER SOURCE(S): MARPAT 138:89797
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

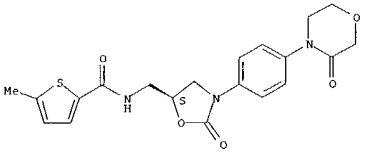
AB The invention relates to combinations of (A) oxazolidinones I [R1 = 5-X-2-thienyl (X = Cl, Br, Me, CF3); R2 = DA; A = phenylene; D = 5- or 6-membered heterocyclic ring containing S, N or O; R4 - R8 = H], or their pharmaceutically acceptable salts, hydrates, prodrugs or their mixts. and (B) other pharmaceutically active ingredients; to a method for producing said combinations; and to the use thereof as medicaments, in particular for the treatment and/or prophylaxis of thrombo-embolic diseases. Thus, the claimed oxazolone II was prepared from epoxide III via epoxide ring opening with aniline derivative IV, cyclization with carbonyldiimidazole, and N-acylation with 5-chlorothiophene-2-sulfonyl chloride. II was tested for antithrombotic activity in the arteriovenous shunt model (Rat) after [ED50 = 3 mg/kg (p.o.); IC50 = 0.7 nM]; II had a synergistic effect when used in combination with clopidogrel.
IT **366789-02-8P 482305-79-3P 482305-80-6P**
482306-30-9P 482306-32-1P 482306-49-0P
482306-50-3P 482306-58-1P 482306-63-8P
482308-00-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and pharmacol. activity of; prepn. of substituted oxazolidinones for combinational therapy in the treatment and/or prophylaxis of thromboembolic diseases)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



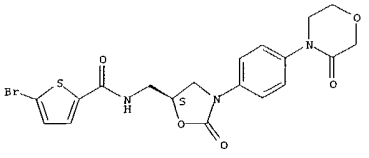
RN 482305-79-3 CAPLUS
CN 2-Thiophenecarboxamide, 5-methyl-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



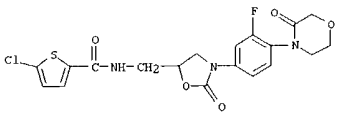
RN 482305-80-6 CAPLUS
CN 2-Thiophenecarboxamide, 5-bromo-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

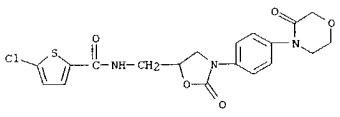


L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

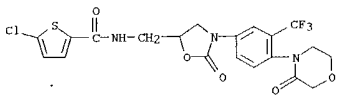
RN 482306-30-9 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)



RN 482306-32-1 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

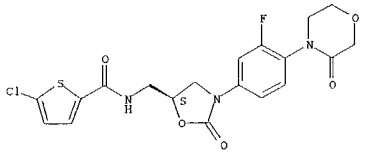


RN 482306-49-0 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[2-oxo-3-[4-(3-oxo-4-morpholinyl)-3-(trifluoromethyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)



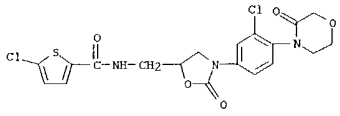
RN 482306-50-3 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3-methyl-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

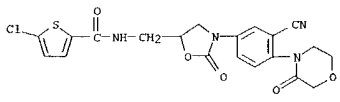


IT **482306-48-9P 482306-51-4P 482306-54-7P**
482306-59-2P 482306-60-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and pharmacol. activity of; preparation of substituted oxazolidinones for combinational therapy in the treatment and/or prophylaxis of thromboembolic diseases)

RN 482306-48-9 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3-chloro-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

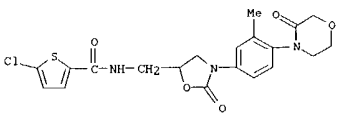


RN 482306-51-4 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3-cyano-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

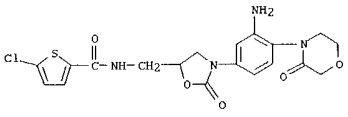


RN 482306-54-7 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3,5-dimethyl-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

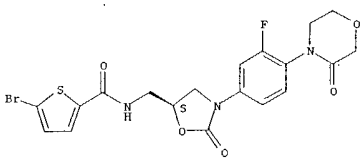


RN 482306-58-1 CAPLUS
CN 2-Thiophenecarboxamide, N-[[3-[3-amino-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-5-chloro- (9CI) (CA INDEX NAME)



RN 482306-63-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-bromo-N-[[(5S)-3-[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

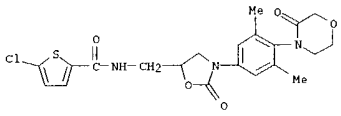
Absolute stereochemistry.



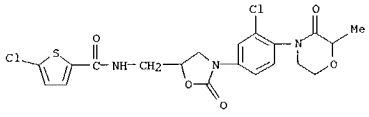
RN 482308-00-9 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-3-[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

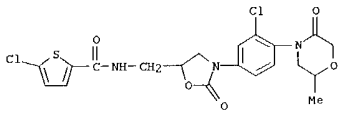
L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 482306-59-2 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3-chloro-4-(2-methyl-3-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)



RN 482306-60-5 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[3-[3-chloro-4-(2-methyl-5-oxo-4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)



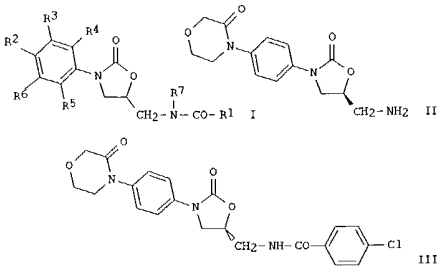
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:609543 CAPLUS
DOCUMENT NUMBER: 137:169507
TITLE: Preparation of oxazolidinones and their use as inhibitors of human blood-coagulation factor Xa
INVENTOR(S): Straub, Alexander; Lampe, Thomas; Pernerstorfer, Josef; Perzborn, Elisabeth; Pohlmann, Jens; Roehrig, Susanne; Schlemmer, Karl-Heinz
PATENT ASSIGNEE(S): Bayer Ag, Germany
SOURCE: Ger. Offen., 20 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10105989	A1	20020814	DE 2001-10105989	20010209
WO 2002064575	A1	20020822	WO 2002-EP857	20020128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1366029	A1	20031203	EP 2002-702317	20020128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: DE 2001-10105989 A 20010209
WO 2002-EP857 W 20020128
OTHER SOURCE(S): MARPAT 137:169507
GI

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



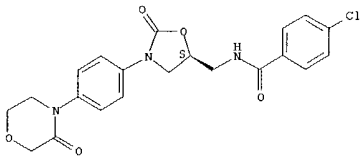
AB Title compds. I [R1 = (un)substituted aryl or heteroaryl with 1-2 heteroatoms, e.g. N, O, S; R2 = CONR8R9, NR10COR11, N(O)xR12R13; R3-R6 = H, halo, alkyl, etc.; R7 = H, alkyl; R8 = H, (un)substituted alkyl, e.g., halo, amino, OH, etc.; R9-R11 = (un)substituted alkyl, e.g., halo, amino, OH, etc.; R8 and R9 are bond together with N atom to form a heterocyclic ring; R10, R11 with N(CO) form a heterocyclic ring; R12 and R13 are bond together with N atom to form a heterocyclic ring; x = 0, 1] were prepared For example, coupling of II, e.g., prepared from 2-[(2S)-oxiranylmethyl]-1H-isoindole-1,3(2H)-dione in 3 steps, and 4-chlorobenzoyl chloride provide claimed oxazolidinone III in 89% yield. Oxazolidinone III inhibited human blood-coagulation factor Xa with an IC50 of 20 nM. Compds. I are useful in the area of blood coagulation.

IT **446291-85-6P 446291-91-4P 446291-93-6P 446291-94-7P 446291-96-9P 446291-98-1P 446292-00-8P 446292-02-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of oxazolidinones and their use as inhibitors of human blood-coagulation factor Xa)

RN 446291-85-6 CAPLUS
CN Benzamide, 4-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

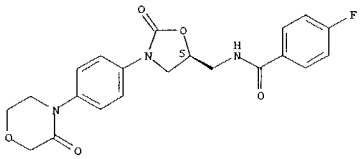
Absolute stereochemistry.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



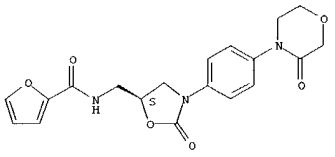
RN 446291-91-4 CAPLUS
CN Benzamide, 4-fluoro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 446291-93-6 CAPLUS
CN 2-Furancarboxamide, N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

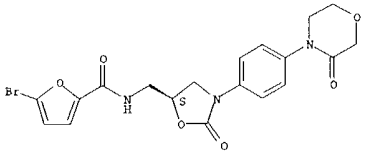
Absolute stereochemistry.



RN 446291-94-7 CAPLUS
CN 2-Furancarboxamide, 5-bromo-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

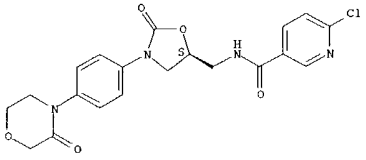
Absolute stereochemistry.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



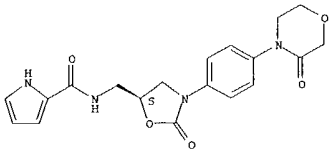
RN 446291-96-9 CAPLUS
CN 3-Pyridinecarboxamide, 6-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 446291-98-1 CAPLUS
CN 1H-Pyrrole-2-carboxamide, N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

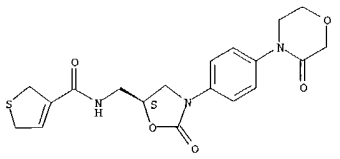
Absolute stereochemistry.



RN 446292-00-8 CAPLUS
CN 3-Thiophenecarboxamide, 2,5-dihydro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

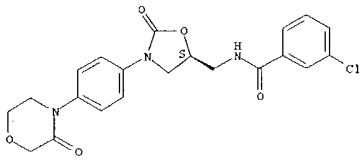
Absolute stereochemistry.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 446292-02-0 CAPLUS
CN Benzamide, 3-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	16.02	332.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.08	-2.08

STN INTERNATIONAL LOGOFF AT 13:58:48 ON 15 APR 2004

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

plication or Docket Number
10/181051

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	21 minus 20=	* 1
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☑

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐			OR	OTHER THAN SMALL ENTITY	
RATE	FEE			RATE	FEE
BASIC FEE			OR	BASIC FEE	890
X$ 9=			OR	X$18=	18
X42=			OR	X84=	
+140=			OR	+280=	280
TOTAL			OR	TOTAL	1188

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 20	Minus	** 21	=
Independent	* 3	Minus	*** 2	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY			OR	OTHER THAN SMALL ENTITY	
RATE	ADDI-TIONAL FEE			RATE	ADDI-TIONAL FEE
X$ 9=			OR	X$18=	
X42=			OR	X84=	
+140=			OR	+280=	
TOTAL ADDIT. FEE			OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDI-TIONAL FEE		RATE	ADDI-TIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDI-TIONAL FEE		RATE	ADDI-TIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPEND. . CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO.

FILING DATE

APPLICANT(S) 10/181051

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		—			
2		1	1			
3		1		1		
4		1		1		
5		1		1		
6		1		1		
7		1	1			
8		10		1		
9		7		1		
10	1	1	1			
11		1		1		
12		1		1		
13		1		1		
14		1		1		
15		1		1		
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17				2		
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TOTAL IND.	2	⬇	3	⬇		⬇
TOTAL DEP.	19		17			
TOTAL CLAIMS	21		20			

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
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99						
100						
TOTAL IND.		⬇		⬇		⬇
TOTAL DEP.						
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-1360 (REV. 3-78)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

In the United States Patent and Trademark Office

Appl. No.:	10/181,051	Confirmation No. 5850
Applicant(s):	Straub, et al.	
Filed:	June 24, 2002	
TC/A.U.:	1626	
Examiner:	Anderson, Rebecca L.	

Docket No.:	LeA 34 122
Customer No.:	35969

CERTIFICATION OF MAILING UNDER 37 C.F.R. 1.8(a)

I hereby certify that this correspondence and any papers referred to as attached are being deposited, on the date shown below, with the United States Postal Service, with sufficient postage, as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: 5 Jan 2004 William F. Gray

William F. Gray

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

AMENDMENT

Sir:

This is in response to the Official Action dated 10/03/2003. Please amend the above-identified application as follows:

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 24 of this paper.

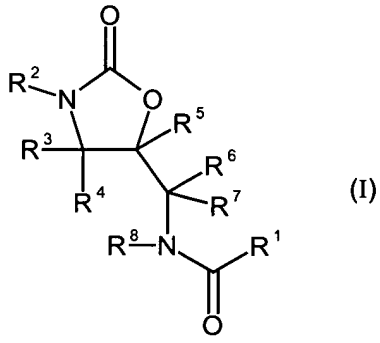
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Canceled)

2. (Currently amended) ~~Compounds~~ A compound of the general formula (I) ~~according to Claim 1~~[[,]]



(I)

characterized in that

R^1 represents an optionally benzo-fused thiophene ~~(thienyl)~~ group which may optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; cyano; nitro; amino; aminomethyl; $(C_1$-$C_8)$-alkyl which for its part may optionally be mono- or polysubstituted by halogen; $(C_3$-$C_7)$-cycloalkyl; $(C_1$-$C_8)$-alkoxy; imidazolinyl; $-C(=NH)NH_2$; carbamoyl; and mono- and di-$(C_1$-$C_4)$-alkyl-aminocarbonyl,

R^2 represents ~~one of the groups below~~[[:]]

[[A-,]]

[[A-M-,]]

D-M-A-,

[[B-M-A-,]]

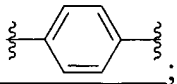
[[B-,]]

[[B-M-,]]

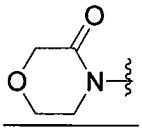
[[B-M-B-,]]

[[D-M-B-,]]

where:

the radical "A" represents ~~(C_6-C_{14}) aryl, preferably (C_6-C_{10}) aryl, in particular phenyl or naphthyl, very particularly preferably phenyl~~ optionally substituted  ;

~~the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O~~[[;]]

the radical "D" represents ~~a saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused 4- to 9-membered heterocycle which contains up to three heteroatoms and/or hetero chain members selected from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O~~  ;and

the radical "M" ~~represents NH-, $-CH_2-$, $-CH_2CH_2-$, -O-, $-NH-CH_2-$, $-CH_2-NH-$, $-OCH_2-$, $-CH_2O-$, -CONH-, -NHCO-, -COO-, -OOC-, -S-, $-SO_2-$ or~~ represents a covalent bond;

where

the ~~groups~~ group "A" [[,]] ~~"B" and "D"~~ defined above may ~~each~~ optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; ~~oxo~~[[;]] cyano; nitro; carbamoyl; ~~pyridyl~~[[;]] (C_1-C_6)-alkanoyl; ~~(C_3-C_7)-cycloalkanoyl; (C_6-C_{14})-arylcarbonyl; (C_5-C_{10})-heteroarylcarbonyl; (C_1-C_6)-alkanoyloxymethyloxy; (C_1-C_4)-hydroxyalkylcarbonyl; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$~~ [[;]] $-OR^{30}$; $-NR^{30}R^{31}$, and (C_1-C_6)-alkyl ~~and (C_3-C_7)-cycloalkyl~~ ,

~~where (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; OR^{27}; $NR^{28}R^{29}$; $CO(NH)_v(NR^{27}R^{28})$ and $C(NR^{27}R^{28})=NR^{29}$;~~

where [[:]]

~~v is either 0 or 1 and~~

~~R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_4)-alkanoyl, carbamoyl, trifluoromethyl, phenyl or pyridyl, and/or~~

~~R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S,~~ and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl, ~~$(C_3$-$C_7)$-cycloalkyl, $(C_1$-$C_4)$-alkylsulphonyl, $(C_1$-$C_4)$-hydroxyalkyl, $(C_1$-$C_4)$-aminoalkyl, di-$(C_1$-$C_4)$-alkylamino-$(C_1$-$C_4)$-alkyl, $-CH_2C(NR^{27}R^{28})=NR^{29}$ or $-COR^{33}$~~ or $C(O)R^{33}$,

where

R^{33} represents ~~$(C_1$-$C_6)$-alkoxy, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxycarbonyl-$(C_1$-$C_4)$-alkyl,~~ $(C_1$-$C_4)$-aminoalkyl, ~~$(C_1$-$C_4)$-alkoxycarbonyl, $(C_1$-$C_4)$-alkanoyl-$(C_1$-$C_4)$-alkyl, $(C_3$-$C_7)$-cycloalkyl, $(C_1$-$C_6)$-alkenyl,~~ or $(C_1$-$C_8)$-alkyl, ~~which may optionally be substituted by phenyl or acetyl, $(C_6$-$C_{14})$-aryl, $(C_5$-$C_{10})$-heteroaryl, trifluoromethyl, tetrahydrofuranyl or butyrolactone,~~

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents $(C_1$-$C_6)$-alkyl

~~and their pharmaceutically acceptable salts, hydrates and prodrugs~~ or a pharmaceutically acceptable salt, hydrate, or prodrug thereof[[,]]

~~except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen~~ .

3. (Currently amended) ~~Compounds~~ The compound of the general formula (I) according to Claim [[1]] 2, characterized in that

R^1 represents thiophene ~~(thienyl), in particular 2-thiophene~~[[,]] which may optionally be mono- or polysubstituted by halogen, ~~preferably chlorine or bromine, by~~ amino, aminomethyl or $(C_1$-$C_8)$-alkyl, ~~preferably methyl,~~ where the $(C_1$-$C_8)$-alkyl radical for its part may optionally be mono- or polysubstituted by halogen, ~~preferably fluorine~~ [[,]]

R^2 represents ~~one of the groups below~~[[:]]

[[A-,]]

[[A-M-,]]

D-M-A-,

[[B-M-A-,]]

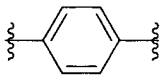
[[B-,]]

[[B-M-,]]

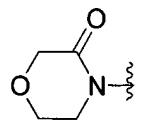
[[B-M-B-,]]

[[D-M-B-,]]

where:

the radical "A" represents optionally substituted  ~~$(C_6$-$C_{14})$-aryl, preferably $(C_6$-$C_{10})$-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl~~ ;

~~the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O~~ [[;]]

the radical "D" represents  ~~a saturated or partially unsaturated 4- to 7-membered heterocycle which contains up to three heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O~~ ; and

the radical "M" ~~represents NH, $-CH_2-$, $-CH_2CH_2-$, O, $-NH-CH_2-$, $-CH_2-NH-$, $-OCH_2-$, $-CH_2O-$, CONH, NHCO, COO, OOC, S or~~ represents a covalent bond;

where

the ~~groups~~ group "A" [[,]] ~~"B" and "D"~~ defined above may ~~in each case~~ optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; ~~oxo~~[[;]] cyano; nitro; carbamoyl; ~~pyridyl~~[[;]] (C_1-C_6)-alkanoyl; ~~(C_3-C_7)-cycloalkanoyl; (C_6-C_{14})-arylcarbonyl; (C_5-C_{10})-heteroarylcarbonyl; (C_1-C_6)-alkanoyloxymethyloxy; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$~~ [[;]]$-OR^{30}$; $-NR^{30}R^{31}$, and (C_1-C_6)-alkyl ~~and (C_3-C_7)-cycloalkyl~~ ,

~~where (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; $-OR^{27}$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ and $-C(NR^{27}R^{28})=NR^{29}$[[,]]~~

where[[:]]

~~v is either 0 or 1 and~~

~~R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl or $(C_3$-$C_7)$-cycloalkyl, and/or~~

~~R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S,~~ and

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl, ~~$(C_3$-$C_7)$-cycloalkyl, $(C_1$-$C_4)$-alkylsulphonyl, $(C_1$-$C_4)$-hydroxyalkyl, $(C_1$-$C_4)$-aminoalkyl, di-$(C_1$-$C_4)$-alkylamino-$(C_1$-$C_4)$-alkyl,~~ $(C_1$-$C_4)$-alkanoyl, ~~$(C_6$-$C_{14})$-arylcarbonyl, $(C_5$-$C_{10})$-heteroarylcarbonyl,~~ or $(C_1$-$C_4)$-alkylaminocarbonyl ~~or $-CH_2C(NR^{27}R^{28})=NR^{29}$~~ ,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and
each represents hydrogen or represents $(C_1$-$C_6)$-alkyl

~~and their pharmaceutically acceptable salts, hydrates and prodrugs~~ or a pharmaceutically acceptable salt, hydrate, or prodrug thereof [[,]]

~~except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen~~ .

4. (Currently amended) ~~Compounds~~ The compound of the general formula (I) according to Claim [[1]] 2, characterized in that

R^1 represents thiophene ~~(thienyl), in particular 2-thiophene~~[[,]] which may optionally be mono- or polysubstituted by halogen[[,]] ~~preferably chlorine or bromine~~[[,]] or by (C_1-C_8)-alkyl, ~~preferably methyl~~[[,]] where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen, ~~preferably fluorine~~[[,]]

R^2 represents ~~one of the groups below~~[[:]]

[[A-,]]

[[A-M-,]]

D-M-A-,

[[B-M-A-,]]

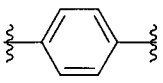
[[B-,]]

[[B-M-,]]

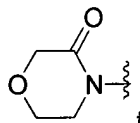
[[B-M-B-,]]

[[D-M-B-,]]

where:

the radical "A" represents optionally substituted  ~~phenyl or naphthyl, in particular phenyl~~ ;

~~the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 2 heteroatoms from the group consisting of S, N, NO (N-oxide) and O~~ [[;]]

the radical "D" represents  ~~a saturated or partially unsaturated 5- or 6-membered heterocycle which contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O~~ ; and

the radical "M" ~~represents NH, O, NH CH_2, CH_2 NH, OCH_2, CH_2O, CONH, NHCO or~~ represents a covalent bond;

where

the ~~groups~~ group "A" [[,]] ~~"B" and "D"~~ defined above may ~~in each case~~ optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; ~~oxo~~[[;]] cyano; ~~pyridyl~~[[;]] (C_1-C_3)-alkanoyl; ~~(C_6-C_{10})-arylcarbonyl; (C_5-C_6)-heteroarylcarbonyl; (C_1-C_3)-alkanoyloxymethyloxy; $C(NR^{27}R^{28})=NR^{29}$; $CONR^{28}R^{29}$; $SO_2NR^{28}R^{29}$~~ [[;]] -OH; $-NR^{30}R^{31}$; and (C_1-C_4)-alkyl; ~~and cyclopropyl, cyclopentyl or cyclohexyl~~[[,]]

~~where (C_1-C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl for their part may optionally be substituted by a radical from the group consisting of cyano; -OH; OCH_3; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ and $C(NR^{27}R^{28})=NR^{29}$;~~

where[[:]]

~~v is either 0 or 1, preferably 0, and~~

~~R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl~~

~~and/or~~

~~R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached may form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to two identical or different heteroatoms from the group consisting of N, O and S, and~~

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl, ~~cyclopropyl, cyclopentyl, cyclohexyl, $(C_1$-$C_4)$-alkylsulphonyl, $(C_1$-$C_4)$-hydroxyalkyl, $(C_1$-$C_4)$-aminoalkyl, di-$(C_1$-$C_4)$-alkylamino-$(C_1$-$C_4)$-alkyl~~[[,]] or $(C_1$-$C_3)$-alkanoyl ~~or phenylcarbonyl~~,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and
each represents hydrogen or represents $(C_1$-$C_6)$-alkyl

~~and their pharmaceutically acceptable salts, hydrates and prodrugs~~ or a pharmaceutically acceptable salt, hydrate, or prodrug thereof[[,]]

~~except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen~~ .

5. (Currently amended) ~~Compounds~~ The compound of the general formula (I) according to Claim [[1]] 2, characterized in that

R^1 represents 2-thiophene which may optionally be substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl ~~or~~ and trifluoromethyl,

R^2 represents ~~one of the groups below~~[[:]]

[[A-,]]

[[A-M-,]]

D-M-A-,

[[B-M-A-,]]

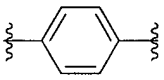
[[B-,]]

[[B-M-,]]

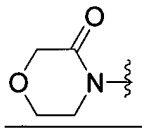
[[B-M-B-,]]

[[D-M-B-,]]

where:

the radical "A" represents optionally substituted  ~~phenyl or naphthyl, in particular phenyl~~ ;

~~the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 2 heteroatoms from the group consisting of S, N, NO (N-oxide) and O;~~

the radical "D" represents  ~~a saturated or partially unsaturated 5- or 6-membered heterocycle which contains a nitrogen atom and optionally a further heteroatom and/or hetero chain member from the group consisting of S, SO, SO_2 and O; or contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2 and O~~ ; and

the radical "M" ~~represents -NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or~~ represents a covalent bond;

where

the ~~groups~~ group "A" [[,]] ~~"B" and "D"~~ defined above may ~~in each case~~ optionally be mono- or polysubstituted by a radical selected from the group consisting of halogen; trifluoromethyl; ~~oxo~~[[;]] cyano; ~~pyridyl~~[[;]] (C_1-C_3)-alkanoyl; ~~(C_6-C_{10})-arylcarbonyl; (C_5-C_6)-heteroarylcarbonyl; (C_1-C_3)-alkanoyloxymethyloxy; $CONR^{28}R^{29}$; $SO_2NR^{28}R^{29}$~~ [[;]] -OH; -$NR^{30}R^{31}$; and (C_1-C_4)-alkyl; ~~and cyclopropyl, cyclopentyl or cyclohexyl~~[[,]]

~~where (C_1-C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl for their part may optionally be substituted by a radical from the group consisting of cyano; -OH; $-OCH_3$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ and $-C(NR^{27}R^{28})=NR^{29}$;~~

where:

~~v is either 0 or 1, preferably 0, and~~

~~R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl~~

~~and/or~~

~~R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached may form a saturated or partially unsaturated 5- to 7-~~

~~membered heterocycle having up to two identical or different heteroatoms from the group consisting of N, O and S, and~~

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, ~~cyclopropyl, cyclopentyl, cyclohexyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl~~ , or (C_1-C_3)-alkanoyl ~~or phenylcarbonyl~~ ,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_4)-alkyl

~~and their pharmaceutically acceptable salts, hydrates and prodrugs~~[[,]] or a pharmaceutically acceptable salt, hydrate, or prodrug thereof[[,]]

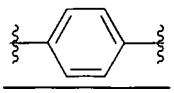
~~except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen~~ .

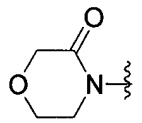
6. (Currently amended) ~~Compounds~~ The compound of the general formula (I) according to Claim [[1]] 2, characterized in that

R^1 represents 2-thiophene which is substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl,

R^2 represents D-A-:

where:

the radical "A" represents  ~~phenylene~~ ;

the radical "D" represents  ~~a saturated 5- or 6-membered heterocycle~~,

~~which is attached to "A" via a nitrogen atom,~~

~~which has a carbonyl group directly adjacent to the linking nitrogen atom and~~

~~in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;~~

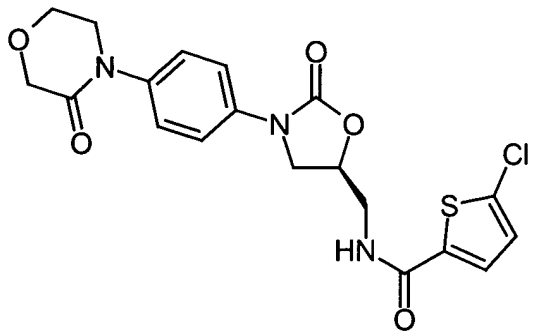
where

the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical selected from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen

~~and their pharmaceutically acceptable salts, hydrates and prodrugs~~ or a pharmaceutically acceptable salt, hydrate, or prodrug thereof .

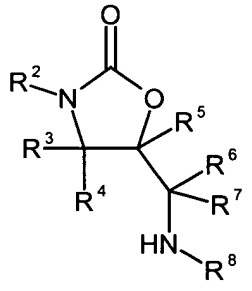
7. (Currently amended) ~~Compound~~ The compound ~~according to Claim 1~~ having the following formula



~~and its pharmaceutically acceptable salts, hydrates and prodrugs~~ or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

8. Currently amended) Process for preparing the substituted oxazolidinone[[s]] ~~according to Claims 1 to 7~~ of claim 2, where
either according to a process alternative

[A] ~~compounds~~ a compound of the general formula (II)



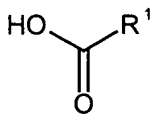
(II),

[[ ]]

in which

the radicals R^2, R^3, R^4, R^5, R^6 and R^7 are each as defined in Claim [[1]] 2

~~are~~ is reacted with a carboxylic ~~acids~~ acid of the general formula (III)

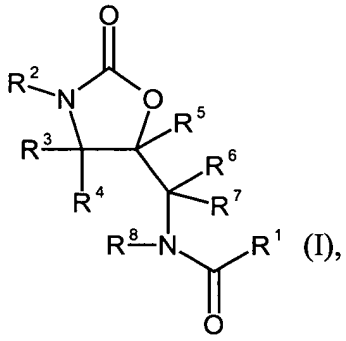

(III),

in which

the radical R^1 is as defined in Claim [[1]] 2,

or else with ~~the~~ a corresponding carbonyl ~~halides~~ halide, ~~preferably carbonyl chlorides,~~ or else with ~~the~~ a corresponding symmetric or mixed carboxylic ~~anhydrides~~ anhydride of the carboxylic ~~acids~~ acid of the general formula (III) defined above

in an inert ~~solvents~~ solvent, if appropriate in the presence of an activating or coupling agent and/or a base, to give a ~~compounds~~ compound of the general formula (I)

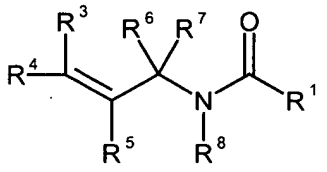

(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim [[1]] 2,

or else according to a process alternative

[B] ~~compounds~~ a compound of the general formula (IV)



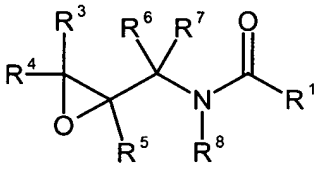
(IV),

[[ ]]

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim [[1]] 2,

~~are~~ is converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the general formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim [[1]] 2,

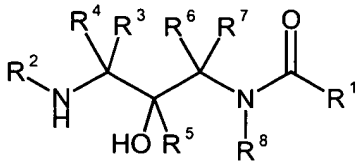
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the general formula (VI)

$$R^2\text{-}NH_2 \qquad \text{(VI)},$$

in which

the radical R^2 is as defined in Claim [[1]] 2,

~~the compounds~~ a compound of the general formula (VII)



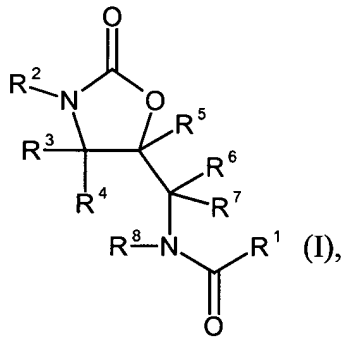
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim [[1]] 2,

~~are~~ is initially prepared and,

subsequently, in an inert solvent in the presence of phosgene or a phosgene equivalent[[s]], ~~such as, for example, carbonyldiimidazole (CDI),~~ cyclized to give the ~~compounds~~ a compound of the general formula (I)



(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim [[1]] 2,

where - both for process alternative [A] and for process alternative [B] - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a BOC amino protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

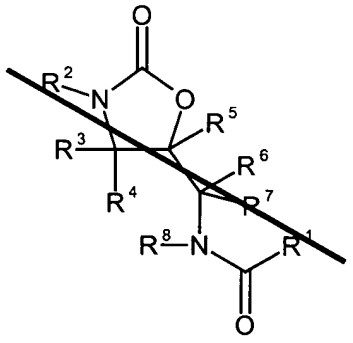
where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with ~~various reagents such as~~ a carboxylic ~~acids~~ acid, carboxylic ~~anhydrides~~ anhydride, carbonyl ~~chlorides~~ chloride, ~~isocyanates~~ isocyanate, sulphonyl ~~chlorides~~ chloride or alkyl ~~halides~~ halide to give the corresponding ~~derivatives~~ derivative may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with ~~amines~~ an amine to give the corresponding ~~sulphonamides~~ sulfonamide may follow.

9. (Currently amended) ~~Medicaments~~[[,]] A pharmaceutical composition comprising at least one compound of the general formula (I) according to ~~Claims 1 to 7~~ claim 2 and one or more pharmacologically acceptable auxiliaries or excipients.

10. (Currently amended) ~~Use of compounds of the general formula (I)~~



~~(I),~~

~~in which:~~

~~R^1 represents optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted;~~

~~R^2 represents any organic radical;~~

~~R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6) alkyl~~

~~and their pharmaceutically acceptable salts, hydrates and prodrugs,~~

~~for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or~~ A method for treatment of a thromboembolic disorder[[s]], ~~in particular myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses~~ comprising administering an effective amount of a compound of claim 2.

11. (Currently amended) ~~Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or~~ A method for treatment of disorders which are influenced positively by inhibition of factor Xa comprising administering an effective amount of a compound of claim 2.

12. (Currently amended) ~~Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions for the~~ A method for treatment of disseminated intravascular coagulation (DIC) comprising administering an effective amount of a compound of claim 2.

13. (Currently amended) ~~Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or~~ A method for treatment of ~~disorders such as~~ atherosclerosis[[;]] , arthritis[[;]] , Alzheimer's disease or cancer comprising administering an effective amount of a compound of claim 2.

14. (Currently amended) ~~Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions~~ A method for the inhibition of factor Xa comprising administering an effective amount of a compound of claim 2.

15. (Currently amended) Method for preventing the coagulation of blood in vitro, comprising adding to said blood a compound of claim 2 ~~in particular in the case of banked blood or biological samples containing factor Xa, characterized in that compounds of the general formula (I) according to Claim 10 are added~~.

16. (New) The method of claim 15 wherein said blood is banked blood or a biological sample containing factor Xa.

17. (New) The compound of claim 3 or 4 wherein R^1 represents an optionally substituted 2-thiophene group, and wherein said halogen substituent is chlorine or bromine, and said (C_1-C_8)-alkyl substituent is methyl, where the methyl radical for its part optionally may be mono- or polysubstituted by fluorine.

18. (New) The process of claim 8 wherein in process alternative "A", the corresponding carbonyl halide of carboxylic acid (III) is a carbonyl chloride.

19. (New) The process of claim 8 wherein in process alternative "B", the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldiimidazole (CDI).

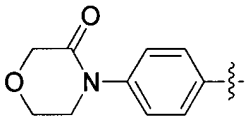
20. (New) The method of claim 10 wherein the thromboembolic disorder is myocardial infarct, angina pectoris (including unstable angina), reocclusion or restenosis after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attack, peripheral arterial occlusive disease, pulmonary embolism or deep venous thrombosis.

Remarks / Arguments

Claims 2-20 are pending in this application. Claim 1 has been canceled. Claims 2-15 have been amended. New claims 16-20 have been added. No new matter has been added.

Election/Restrection

In response to the restriction requirement, applicants elect to proceed with prosecution of the claims of restriction group I.

In the official action, the examiner defined restriction group I as claims 1-7 and 9, drawn to a product wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are as found in claim 1 and R^2 is  . The examiner would appear to have based this definition of R^2 on the disclosed exemplary compounds, but has not allowed for the fact that in a number of the examples bearing this R^2 group, the phenyl ring is variously substituted. Applicants request that restriction group (I) be expanded to include substituents on the phenyl ring of R^2 in recognition of this fact.

In the present amendment, applicants have elected to proceed with prosecution of restriction group I, but have included a limited listing of substituents on the phenyl ring. Most (but not all) of the presently-listed substituents find express support in the exemplary compounds. Applicants note for the record that R^2 substituents being deleted from the original listing are deleted in response to the restriction requirement, and that R^2 substituents being retained in the present amendment are being suggested to the examiner for consideration of a possible expansion of the restriction requirement.

Claim 1 has been canceled.

Claim 2 has been converted into an independent claim, and has been further amended to delete non-elected subject matter, but still includes a suggested listing of substituents on the phenyl group of R^2 as discussed above.

In the amendment to claim 2, the group COR^{33} in the definition of groups R^{30} and R^{31} has been corrected to read " $C(O)R^{33}$ " . The recitations of the groups constituting R^{30} and R^{31} as given on pages 9,11, 13, 23, and 25 confirm the appropriateness of this correction.

Claims 3-6 have been amended for consistency with amended claim 2.

Claim 7 has been converted into an independent claim specifically claiming a compound within the scope of claim 2.

Process claim 8 has been amended to recite the synthesis of compounds of claim 2.

Medicament claim 9 has been amended to recite a pharmaceutical composition comprising a compound of claim 2.

Claims 10-15 have each been amended to recite a method of using the compound of claim 2.

New claims 16-20 recite subject matter removed from previous claims.

Unity of Invention

The examiner has indicated that the claims as originally presented lack unity of invention. Reconsideration is requested in light of the present amendment, in which claim 2 has been narrowed in response to the restriction requirement, and the remaining claims now deal with the compounds, pharmaceutical compositions, method of making, and method of treatment using the compounds of claim 2.

In view of the above amendments, the claims of this application are deemed to be of a form which is amenable to further prosecution. Examination is accordingly requested.

Respectfully submitted,

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Phone: (203) 812-2712
Date: 5 Jan. 2004

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PTO/SB/122 (05-03)
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Application Number	10/181,051
Filing Date	06/24/2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	Rebecca L. Anderson
Attorney Docket Number	Le A 34 122

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[X] Attorney or Agent of record.

[ ] Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number_____

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Signature	William F. Gray
Date: 5 Jan '04	Telephone **(203) 812-2712**

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In re Application of **Alexander Straub, et al.**

Application Number **10/181,051** | Filed **June 24, 2002**

For **Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation**

Art Unit **1626** | Examiner **Rebecca L. Anderson**

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $ _____
- ☒ Two months (37 CFR 1.17(a)(2)) $ **420.00**
- ☐ Three months (37 CFR 1.17(a)(3)) $ _____
- ☐ Four months (37 CFR 1.17(a)(4)) $ _____
- ☐ Five months (37 CFR 1.17(a)(5)) $ _____

CERTIFICATION OF MAILING UNDER 37 C.F.R. 1.8(a): I hereby certify that this correspondence and any papers referred to as attached are being deposited, on the date shown below, with the United States Postal Service, with sufficient postage, as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: 5 Jan 2004

Typed or printed name: WILLIAM F. GRAY

Signature: William F. Gray

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $_____.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to change fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number **13-3372**.

I have enclosed a duplicate copy of this sheet.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

5 Jan. 2004
Date

William F. Gray
Signature

(203) 812-2712
Telephone Number

William F. Gray
Reg. No.: 31,018
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of **1** forms are submitted.

01/09/2004 CCHAU1 00000073 133372 10181051

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1626

PTO/SB/21 (05-03)
Approved for use through 04/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Image

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/181,051
Filing Date	June 24, 2002
First Named Inventor	Alexander Straub
Art Unit	1626
Examiner Name	Rebecca L. Anderson
Total Number of Pages in This Submission: 29	Attorney Docket Number: Le A 34 122

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☐ Fee Attached
- ☒ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):

1) Change of Correspondence Address; and
2) Return Receipt Postcard.

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	**William F. Gray** **Reg. No.: 31,018** **Customer No.: 35969**
Signature	William F. Gray
Date	5 Jan 2004

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	**William F. Gray**		
Signature	William F. Gray	Date	

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/181,051	06/24/2002	Alexander Straub	Le A 34122	5850

27941 7590 10/03/2003

JEFFREY M. GREENMAN
VICE PRESIDENT, PATENTS AND LICENSING
BAYER CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication app ars on th cover sh t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-15 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-15 are currently pending in the instant application. It is noted that claims 10-14 are improper "use" claims and for the purpose of a lack of unity requirement are interpreted as process claims for the preparation of a medicament or pharmaceutical composition of the compound of the formula (I).

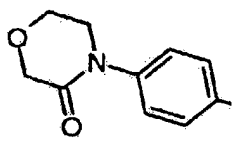
Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

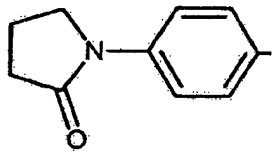
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Due to the numerous and widely divergent variables in substituent R2, a precise listing of inventive groups cannot be made. The following groups are exemplary:

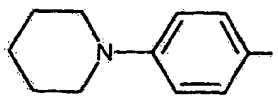
Group I, claims 1-7 and 9, drawn to a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



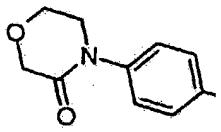
Group II, claims 1-7 and 9, drawn to a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



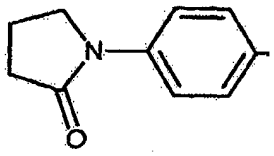
Group III, claims 1-7 and 9, drawn to a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



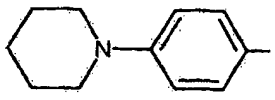
Group IV, claim 8, drawn to a process for the preparation of a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



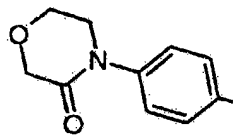
Group V, claim 8, drawn to a process for the preparation of a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



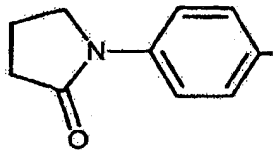
Group VI, claim 8, drawn to a process for the preparation of a compound of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



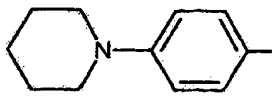
Group VII, claims 10-14, drawn to a process for the preparation of a compound of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and

R2 is  .

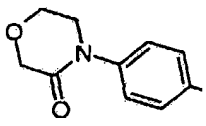
Group VIII, claims 10-14, drawn to a process for the preparation of a compound of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and

R2 is  .

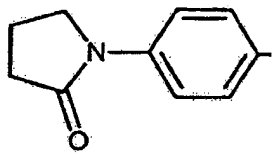
Group IX, claims 10-14, drawn to a process for the preparation of a compound of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2

is  .

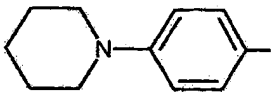
Group X, claim 15, drawn to a method of use for a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is

 .

Group XI, claim 15, drawn to a method of use for a product of the formula (I) wherein R1, R3, R4, R5, R6, R7 and R8 are as found in claim 1 and R2 is



Group XII, claim 15, drawn to a method of use for a product of the formula (I) wherein R1, R3, R4, R5, R6, R7, and R8 are as found in claim1 and R2 is



In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted. Again, this list is not exhaustive as it would be impossible under the time constraints due to the sheer volume of subject matter instantly claimed. Therefore, applicant may choose to elect a single invention (a product, a method of preparation or a method of use) by identifying another specific embodiment not listed in the exemplary groups of the invention and examiner will endeavor to group the same. The applicant may also choose to elect a single disclosed species and the examiner will endeavor to create a group comprising the elected species.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a) the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the

prior art. The compounds claimed contain 5-carbonylaminomethyl oxazol-2-one, which does not define a contribution over the prior art (as can be seen by formula (I) in WO – A-99/31092, page 1-19). The variables on contain 5-carbonylaminomethyl oxazol-2-one vary extensively and when taken as a whole result in vastly different compounds. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Additionally, the vastness of the claimed subject matter, and the complications in understanding the claimed subject matter imposes a serious burden on any examination of the claimed subject matter.

Furthermore, even if unity of invention under 37 CFR 1.475(a) is not lacking, under 37 CFR 1.475(b) a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations:

(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and a process of use of said product; or
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

And, according to 37 CFR 1.475(c)

if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b), unity of invention might not be present.

Therefore, since the claims are drawn to more than a product, more than a process for the preparation and more than a method of use, and according to 37 CFR 1.475 (e)

> the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The claims lack unity of invention and should be limited to only a product, a process for the manufacture of the said product, or a use of the said product.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (703) 605-1157. Mrs. Anderson can normally be reached Monday through Friday 7:00AM to 3:30PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Joseph McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Notice of References Cited	Application/Control No. 10/181,051	Applicant(s)/Patent Under Reexamination STRAUB ET AL.	
	Examiner Rebecca L Anderson	Art Unit 1626	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
*	N	WO-99-31092	06-1999	WO	DORSCH et al.	----
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
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	W	
	X	* This reference is not being furnished since it was cited in the International Search Report for PCT/EP 00/12492.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims

Application No.	Applicant(s)
10/181,051	STRAUB ET AL.
Examiner	**Art Unit**
Rebecca L Anderson	1626

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	9/26/03
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Search Notes	Application No.	Applicant(s)	
	10/181,051	STRAUB ET AL.	
	Examin r	Art Unit	
	Rebecca L Anderson	1626	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Lack Of Unity Requirement	9/26/2003	RA

1646

Attorney Docket No. Le A 34 122

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Alexander Straub, et al.

Group No.: 1646

Serial No.: 10/181,051

Examiner:

Filed: 06/24/02

For: "Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation"

CERTIFICATION OF MAILING UNDER 37 C.F.R. 1.8(a)

I hereby certify that this correspondence and any papers referred to as attached are being deposited, on the date shown below, with the United States Postal Service, with sufficient postage, as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: 12/06/02

Signature of Person Certifying

ASSISTANT COMMISSIONER FOR PATENTS
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TRANSMITTAL OF SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BEFORE MAILING OF FIRST OFFICE ACTION (37 C.F.R. 1.97(b))

Dear Sir:

Applicants wish to cite for the record in the above-identified application the references shown on the accompanying copy of PTO form 1449.

IDENTIFICATION OF TIME OF FILING THE ACCOMPANYING INFORMATION DISCLOSURE STATEMENT

The information disclosure statement transmitted herewith is being filed ***before*** the mailing date of the first Office action on the merits.

FEE PAYMENT

Applicants believe that no fees are due with this submission. However, the Commissioner is hereby authorized to charge any fees that may have been overlooked but that are required to Deposit Account 13-3372. Additionally, please credit any overpayment to the same account.

Respectfully submitted,

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Date: 12/6/02

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Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Serial No. 10/181,051	Group Art Unit 1646	Filing Date 06/24/02	Atty. Docket No. Le A 34 122
SUPPLEMENTAL INFORMATION DISCLOSURE CITATION		Applicant(s) Alexander Straub, et al.			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE MM/DD/YY	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE DD/MM/YY	COUNTRY	PRIMARY CLASS	SUB-CLASS	TRANSLATION	
							YES	NO
	F3	99 06 37 1	11/02/99	WO				
	F4	99 37 30 4	29/07/99	WO				

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, etc.)

	R2	Ullmann's Encyclopedia of Industrial Chemistry, Fifth Revised Ed., Editors.: Elvers, B., Hawkins, S., VCH Verlagsgesellschaft mbH, Weinheim,1985-1996, ch. 5, 488-506
	R3	Zhu, B., Scarborough, R., "Recent Advances in Inhibitors of Factor Xa in the Prothrombinase Complex", Cur. Opinions Card. Pulm. Ren. Inv. Drugs, 1: 63-87 (1999)
	R4	Uzan, A., "Antithrombotic Agents", Emerging Drugs: The Prospect for Improved Medicines, 3: 189-208, (1998)
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	R7	Al-Obeidi, F., Ostrem, J., "Factor Xa Inhibitors by Classical and Combinatorial Chemistry", DDT, 3: 223-231 (May 1998)
	R8	Hauptmann, J., Sturzebecher, J., "Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside", Thrombosis Research, 93: 203-241 (1999)
	R9	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, pg. 199-200, Stichwort "Blutgerinnung"
	R10	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerinnung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, pg.259
	R11	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, pg. 610, Stichwort "Heparin"
	R12	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin"
	R13	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, pg. 292, Stichwort "Cumarinderivate"

EXAMINER	DATE CONSIDERED

* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 213/82, A61K 31/455 — A1

(11) International Publication Number: **WO 99/06371**

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(30) Priority Data:
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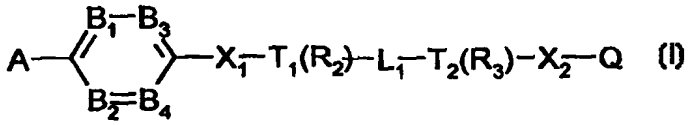
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, 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).

Published
With international search report.

(54) Title: HETEROCYCLIC DERIVATIVES WHICH INHIBIT FACTOR XA

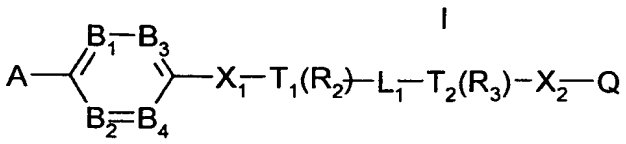
(57) Abstract

The invention relates to heterocyclic derivatives, or pharmaceutically–acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect, formula (I).



CLAIMS

1. A compound of the formula I



wherein:

A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur atoms;

B_1, B_2, B_3 and B_4 are independently CH or a nitrogen atom, wherein the ring formed from B_1, B_2, B_3 and B_4 may optionally be substituted; with the proviso that at least one of B_1, B_2, B_3 and B_4 is nitrogen;

T_1 is CH or N;

T_2 is CH or N;

with the proviso that at least one of T_1 and T_2 is N;

X_1 is SO, SO_2, $C(R_4)_2$ or CO when T_1 is CH or N; or in addition X_1 is O or S when T_1 is CH; and wherein each R_4 is independently hydrogen or (1-4C)alkyl;

L_1 is (1-4C)alkylene or (1-3C)alkylenecarbonyl;

R_2 is hydrogen or (1-4C)alkyl;

R_3 is hydrogen or (1-4C)alkyl;

or R_2 and R_3 are joined to form a C_{1-4}alkylene or $-CH_2CO-$ group; wherein the ring formed by T_1, R_2, R_3, T_2 and L_1 is optionally substituted;

X_2 is $S(O)_y$ wherein y is one or two, $C(R^5)_2$ or CO; and each R^5 is hydrogen or C_{1-4}alkyl;

Q is phenyl, naphthyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl or a heterocyclic moiety containing up to 4 ring heteroatoms selected from nitrogen, oxygen and sulphur and Q is optionally substituted;

and pharmaceutically acceptable salts thereof.

2. A compound of formula I as claimed in claim 1 wherein Q is eiter unsubstituted or substituted by by one, two or three substituents selected from halo, trifluromethyl,

trifluoromethoxy, cyano, hydroxy, amino, nitro, trifluoromethanesulphonyl, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl, (2-4C)alkanoyl, (2-4C)alkanoylamino, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-(1-4C)alkylcarbamoyl-(1-4C)alkyl, phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl, benzoyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl and heteroarylsulphonyl, and wherein said heteroaryl substituent or the heteroaryl group in a heteroaryl-containing substituent comprises a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from nitrogen, oxygen and sulphur, and wherein said phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl, heteroarylsulphonyl, benzyl or benzoyl substituent optionally bears 1, 2 or 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl and (2-4C)alkanoylamino.

3. A compound of formula I as claimed in either claim 1 or 2 wherein any ring formed by T_1, R_2, R_3, T_2 is either unsubstituted or substituted by one or two substituents selected from hydroxy, oxo, carboxy, (1-4C)alkoxycarbonyl or one of the following;

$-(CH_2)_n-R$, $-(CH_2)_n-NRR_1$, $-CO-R$, $-CO-NRR_1$, $-(CH_2)_n-CO-R$ and $-(CH_2)_n-CO-NRR_1$;

wherein n is 1 or 2;

R and R_1 are independently selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy(1-4C)alkyl, carboxy(1-4C)alkyl and (1-4C)alkoxycarbonyl(1-4C)alkyl or where possible R and R_1 may together form a

5- or 6-membered optionally substituted heterocyclic ring which may include in addition to the nitrogen atom to which R and R_1 are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur.

4. A compound of formula I as claimed in any of the preceding claims wherein X_1 is CO.

5. A compound of formula I as claimed in any of the preceding claims wherein X_2 is SO_2.

6. A compound of formula I as claimed in any of the preceding claims for use in medical therapy.

7. Use of a compound of formula I, as defined in any one of the claims 1 to 5, in the production of a medicament for treating a Factor Xa mediated disease or medical condition.

8. A pharmaceutical composition comprising a compound of formula I, as defined in any one of claims 1 to 5.

9. A method of treating a Factor Xa mediated disease or medical condition which comprises administering to a warm-blooded animal requiring such treatment an effective amount of a compound of formual I, as claimed in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/GB 98/02210

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/82 A61K31/455

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 96 10022 A (ZENECA LTD ;FAULL ALAN WELLINGTON (GB); MAYO COLETTE MARIE (GB); P) 4 April 1996 see page 111; table IV ---	1-9
Y	KUNITADA S ET AL: "FACTOR XA INHIBITORS" CURRENT PHARMACEUTICAL DESIGN, vol. 2, no. 5, October 1996, pages 531-542, XP002057653 see page 539 ---	1-9
P,Y	WO 98 21188 A (TURNER PAUL ;PRESTON JOHN (GB); STOCKER ANDREW (GB); ZENECA LTD (G) 22 May 1998 see page 19-23; claim 1 ---	1-9

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate 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 theinternational search	Date of mailing of the international search report
23 October 1998	30/10/1998

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

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INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 98/02210

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	WO 97 28129 A (ZENECA LTD ;SMITHERS MICHAEL JAMES (GB); PRESTON JOHN (GB); STOCKE) 7 August 1997 see page 31-34; claim 1	1-9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ial Application No
PCT/GB 98/02210

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		CA 2197471 A	04-04-1996
		CZ 9700893 A	16-07-1997
		DE 69503647 D	27-08-1998
		EP 0783500 A	16-07-1997
		ES 2119472 T	01-10-1998
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WO 9728129 A	07-08-1997	AU 1608597 A	22-08-1997

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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(30) Priority Data:
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(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)

(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).

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(74) Agents: NEWMAN, Irving et al.; Rhône-Poulenc Rorer Pharmaceuticals Inc., 500 Arcola Road, P.O. Box 5093, Collegeville, PA 19426-0997 (US).

(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).

Published
With international search report.

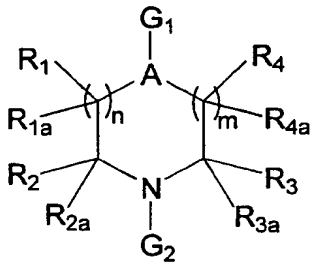
(54) Title: SUBSTITUTED OXOAZAHETEROCYCLYL FACTOR Xa INHIBITORS

(57) Abstract

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.

We Claim

1. A compound of formula



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 heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and 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 optionally substituted alkynylene;

L_4 is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene;

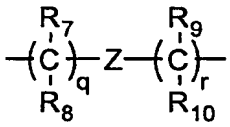
Q and Q' are independently absent, O, S, NR_5, $-S(O)_p-$, $-S(O)_pNR_5-$ or -C(X)Y-;

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, 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 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



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_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} 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_7 and R_8 or one of R_9 and R_{10} is hydroxy

or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α substituted to a N, O or S in Z;

X is O or S;

Y is absent or is selected from O, S and NR_5;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, $S(O)_p$, NR_5, $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4;

v is 2, 3 or 4;

p is 1 or 2; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0;

2. A compound according to claim 1 wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

3. A compound according to claim 1 wherein Z is absent or is selected from O, $S(O)_p$ and NR_5;

4. A compound according to claim 3 wherein m is 1; and n is 1.

5. A compound according to claim 4 wherein A is N.

6. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

7. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2, R_{2a} and R_4 are hydrogen; and R_{4a} is optionally substituted alkyl.

8. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2 and R_4 are hydrogen; and R_{2a} and R_{4a} are optionally substituted alkyl.

9. A compound according to claim 5 wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a} and R_4 are hydrogen; and R_{1a} and R_{4a} are optionally substituted alkyl.

10. A compound according to claim 5 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, alkoxycarbonyl, Y^1Y^2NCO or optionally substituted alkyl.

11. A compound according to claim 5 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, alkoxycarbonyl, Y^1Y^2NCO or optionally substituted alkyl.

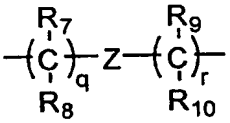
12. A compound according to claim 5 wherein L_1 is $-S(O)_p-$, -C(X)Y- or -L3-Q-L4-Q'-L5-.

13. A compound according to claim 5 wherein Cy_1 is optionally substituted aryl or optionally substituted heteroaryl.

14. A compound according to claim 5 wherein L_2 is alkylene of one to three carbon atoms.

15. A compound according to claim 14 wherein L_2 is $-CH_2-$.

16. A compound according to claim 5 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.

17. A compound according to claim 16 wherein R_5 is hydrogen.

18. A compound according to claim 5 wherein Cy_2 is optionally substituted aryl or optionally substituted heteroaryl.

19. A compound according to claim 5 wherein L_1 is $-S(O)_2-$.

20. A compound according to claim 5 wherein L_1 is -C(X)Y-; X is O; and Y is NH.

21. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; Q is $-S(O)_2-$ or -C(O)-; and L_4 is optionally substituted alkenylene.

22. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; and L_4 is optionally substituted alkylene.

23. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; Q is -C(O)-; Q' is O; and L_4 is optionally substituted alkylene.

24. A compound according to claim 5 wherein L_1 is -L3-Q-L4-Q'-L5-; L_3 is optionally substituted alkylene; and L_4 is optionally substituted alkenylene.

25. A compound according to claim 5 wherein Cy_1 is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl, optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

26. A compound according to claim 5 wherein Cy_2 is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

27. A compound according to claim 1 wherein Z is $-NR_5C(O)-$ and $-C(O)NR_5-$.

28. A compound according to claim 27 wherein m is 1; and n is 1.

29. A compound according to claim 28 wherein A is N.

30. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

31. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2, R_{2a} and R_4 are hydrogen; and R_{4a} is optionally substituted alkyl.

32. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2 and R_4 are hydrogen; and R_{2a} and R_{4a} are optionally substituted alkyl.

33. A compound according to claim 29 wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a} and R_4 are hydrogen; and R_{1a} and R_{4a} are optionally substituted alkyl.

34. A compound according to claim 29 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, alkoxycarbonyl or optionally substituted alkyl.

35. A compound according to claim 29 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, alkoxycarbonyl or optionally substituted alkyl.

36. A compound according to claim 29 wherein L_1 is $-S(O)_p-$, -C(X)Y- or-L3-Q-L4-Q'-L5-.

37. A compound according to claim 29 wherein Cy_1 is optionally substituted aryl or optionally substituted heteroaryl.

38. A compound according to claim 29 wherein R_5, R_7, R_8, R_9 and R_{10} are hydrogen.

39. A compound according to claim 29 wherein Cy_2 is optionally substituted aryl or optionally substituted heteroaryl.

40. A compound according to claim 29 wherein L_1 is $-S(O)_2-$.

41. A compound according to claim 29 wherein L_1 is -C(X)Y-; X is O; and Y is NH.

42. A compound according to claim 29 wherein L_1 is -L3-Q-L4-Q'-L5-; Q is $-S(O)_2-$ or -C(O)-; and L_4 is optionally substituted alkenylene.

43. A compound according to claim 29 wherein L_1 is-L3-Q-L4-Q'-L5-; and L_4 is optionally substituted alkylene.

44. A compound according to claim 29 wherein L_1 is-L3-Q-L4-Q'-L5-; Q is -C(O)-; Q' is O; and L_4 is optionally substituted alkylene.

45. A compound according to claim 29 wherein L_1 is-L3-Q-L4-Q'-L5-; L_3 is optionally substituted alkylene; and L_4 is optionally substituted alkenylene.

46. A compound according to claim 29 wherein Cy_1 is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl, optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

47. A compound according to claim 29 wherein Cy_2 is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

48. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

49. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of the compound according to claim 1.

50. A compound selected from

4-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxo-piperazine-1-ylmethyl]benzamidine,
4-[4-(4-Methoxy-benzenesulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(5-Chloro-thieno[3,2-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[2-Oxo-4-(thieno[2,3-c]pyridine-2-sulfonyl)-piperazin-1-ylmethyl]-benzamidine,
4-[4-(7-Chloro-thieno[2,3-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[4-(4-Chloro-thieno[3,2-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine,
4-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,
4-Amino-3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

3-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine,

3-[4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

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,

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-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine,

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-benzoimidazol-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,

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,

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-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,

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,

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,

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,

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,

(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,

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,

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,

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,

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,

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,

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,

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,

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,

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-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,

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-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,

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,

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-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,

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,

{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,

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-methoxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one,

4-(6-Chlorothieno[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,

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,

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-benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(1H-Benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

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,

4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2-(5-Chloro-4-methoxy-thiophen-2-yl)-ethenesulfonyl]-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,

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,

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)-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,

(±)-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)-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,

(±)-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)-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,

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,

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-benzoimidazol-2-ylmethyl)piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzothioazol-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-benzothioazol-2-ylmethyl)-piperazin-2-one,

3-[4-(4-Aminoquinazoline-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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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-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,

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-Aminoquinazoline-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,

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,

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,

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,

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,

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-benzoimidazol-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,

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,

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-benzoimidazol-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,

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-benzoimidazol-2-ylmethyl)-piperazin-2-one,

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-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-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-benzoimidazol-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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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-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-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,

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-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,

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,

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,

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,

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,

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,

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,

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]-(S)-3-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(S)-3-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-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,

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]-(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 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,

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-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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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,

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-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)-,

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-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,

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-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,

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-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,

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,

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-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,

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,

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,

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,

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,

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,

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,

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,

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-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,

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]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-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,

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-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,

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-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,

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,

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-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,

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-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,

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-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,

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,

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,

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-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,

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-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,

(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-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,

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,

(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-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,

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,

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,

(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-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,

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,

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-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,

(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,

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-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,

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)-acryloyl]-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)-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,

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,

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,

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,

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,

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.

. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-1H-benzoimidazol-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,

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,

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,

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,

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,

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,

(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,

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,

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,

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,

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,

(±)-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-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,

(+/-)-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-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,

(+/-)-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-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,

(+/-)-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-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,

(±)-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-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.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile,

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-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,

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,

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,

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]-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,

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]-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,

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)-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,

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]-benzamidine,

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(R)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine,

3-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine, and

4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine, or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

51. A compound selected from

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-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,

(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,

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,

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,

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,

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,

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,

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,

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,

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,

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-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-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,

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,

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-carboxamidine,

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-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,

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,

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,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-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)-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,

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-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,

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)-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,

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-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-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,

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,

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-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-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,

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,

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-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,

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,

(3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3, 5-dimethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid,

1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-(S)-carboxylic acid methyl ester,

(+/-)-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-(1H-5 3-chloro-1-aza-inden-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,

(+/-)-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-carboxylic acid (2-hydroxy-ethyl)-amide,

(+/-)-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-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid,

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,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-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,

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

52. A compound which is

2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-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-(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,
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,
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,
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,
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,
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,

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

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.

53. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

54. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

55. A compound which is 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

56. A compound which is 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

57. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one, or

a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

58. A compound which is 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one, or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

59. A compound which is 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one, or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

60. A compound which is 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one, or
a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

61. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

62. A method of inhibiting Factor Xa comprising contacting a Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

63. A method of inhibiting the formation of thrombin comprising contacting Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

64. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of the compound according to claim 1.

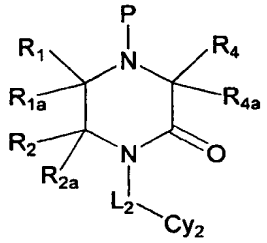
65. The method according to claim 63 wherein the physiological condition is venous vasculature, arterial vasculature, abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip

surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

66. The method according to claim 63 wherein the physiological condition is abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, transient ischemic attacks, intermittent claudication or bypass grafting of the coronary or peripheral arteries, restenosis post coronary or venous angioplasty, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery or a risk of pulmonary thromboembolism.

67. The method according to claim 63 wherein the physiological condition is stroke, vessel luminal narrowing, maintenance of vascular access patency in long-term hemodialysis patients, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

68. A compound of formula

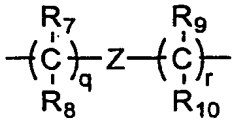


wherein

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;

L_2 is a group of formula



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 heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

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_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} 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_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α substituted to a N, O or S in Z;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, $S(O)_p$, NR_5, $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4;

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.

69. A compound according to claim 68 wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

70. A compound according to claim 67 wherein Z is absent.

71. A compound according to claim 68 wherein R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

72. A compound according to claim 67 which is

(2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

(2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,

(3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,

4-(2-Oxopiperazin-1-ylmethyl)benzamidine,

1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one,

1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one,

2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester,

2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one,

1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one,

4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one,

1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) l-piperazine-2-one,

1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one,

(3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,

1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one,

1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one,

1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one,

1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one,

1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one trifluroacetate,

1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one,

1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one,

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester,

4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,

(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester, or

(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.