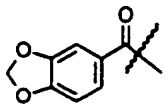
f) $H_3C$-C(O)-$(CH_2)_2$-C(O)-,

g) $R^9$-$SO_2$-,

h)  VIII , or

i) $R^{12}$-NH-C(O)-;

wherein $R^9$ is

a) $-CH_3$,

b) $-CH_2Cl$

c) $-CH_2CH=CH_2$,

d) aryl, or

e) $-CH_2CN$;

wherein $R^{10}$ and $R^{11}$ are independently

a) H-,

b) $CH_3$-; or

$R^{10}$ and $R^{11}$ taken together are $-CH_2-CH_2-$;

wherein $R^{12}$ is $-(CH_2)_p$-aryl;

wherein $R^{13}$ is

a) $R^2O$-C($R_{10}$)($R_{11}$)-C(O)-,

b) $R^3O$-C(O)-,

c) $R^4$-C(O)-,

d) $R^9$-$SO_2$-, or

e) $R^{12}$-NH-C(O)-;

wherein m is zero (0) or one (1);

wherein n is one (1) to three (3), inclusive;

wherein p is zero (0) or one (1);

wherein aryl is phenyl substituted with zero (0) or one (1) of the following:

a) -F,

b) -Cl,

c) $-OCH_3$,

d) -OH,

e) $-NH_2$,

f) $-(C_1-C_4)$alkyl,

g) $-O-C(O)-OCH_3$,

h) $-NO_2$, or

i) -CN;

with the following provisos:

1) in the moiety of formula II, $Z^1$ is -CH($R^5$)-$CH_2$- wherein $R^5$ is ($C_1$-$C_3$)alkyl, only when n is one (1), $A^1$ is H and $A^2$ is $R^2$O-$CH_2$-C(O)-NH-, $R^3$O-C(O)-NH-, or $R^4$-C(O)-NH-; and

2) in the moiety of formula II, when $Z^1$ is -$CH_2$-, n is one (1).

The present invention more particularly provides:

The compound of claim 1 wherein $Q^1$ is the moiety of formula II;

The compound of claim 1 wherein $Q^1$ is the moiety of formula III;

The compound of claim 1 wherein $Q^1$ is the moiety of formula IV;

The compound of claim 1 wherein $Q^1$ is the moiety of formula V;

The compound of claim 1 wherein one of $X^1$ and $X^2$ is -H and the other is -F or wherein $X^1$ is -F and $X^2$ is -F; and

The compound of claim 1 wherein $R^1$ is acetyl.

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

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix $C_i$-$C_j$ indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, ($C_1$-$C_3$)alkyl refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl and isopropyl, straight and branched forms thereof.

Throughout this application, abbreviations which are well known to one of ordinary skill in the art may be used, such as "Ph" for phenyl, "Me" for methyl, and "Et" for ethyl.

The following Charts I-IX describe the preparation of the parent amine compounds, which are the starting compounds from which the N-oxide compounds of the present invention are prepared. All of the starting compounds are prepared by procedures described in these charts or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. The following applications and publications which further describe and exemplify these procedures are hereby incorporated by reference herein: WO 95/07271, published 16 March 1995; WO96/15130, published 23 May 1996; WO 95/25106, published 21 September 1995; WO96/13502, published 9 May 1996; WO 93/23384, published 25 November 1993; WO 95/4684, published 1 June 1995; and PCT/US96/05202, filed 18 April 1996.

In the text below corresponding to these charts, the formula at the left margin corresponds to a specific $Q^2$ moiety in the charts and the other variables are as defined with $X^1$ and $X^2$ most often being hydrogen or fluorine and $R^1$ most often being -$COCH_3$, for purposes of example only.

CHART I

I-A Using the procedures from WO 95/07271, published 16 March 1995, page 21, line 33, thru page 23, line 32 for preparation of the intermediate sulfide and then oxidation to the sulfone using the general procedures from WO 95/07271, published 16 March 1995, page 15, line 32 thru page 16, line 14.

I-B Using the procedures described in WO 95/07271, published 16 March 1995, page 21, line 33, thru page 23, line 32, but substituting oxazolidine for thiazolidine.

CHART II

II-A Using the general procedures from WO 95/07271, published 16 March 1995, page 12, line 31, thru page 16, line 14.

II-B Using the general procedures from WO 95/07271, published 16 March 1995, page 12, line 31 thru page 16, line 14, but substituting 2-methylthiomorpholine for thiomorpholine. 2-Methylthiomorpholine is prepared according to the procedure of Gallego, *et al, J. Org. Chem.*, 1993, *58*, 3905-11.

II-C Using the general procedures from WO96/15130, published 23 May 1996, Examples 2 and 3 at page 14, line 24, thru page 17, line 21.

CHART III

III-A Using the general procedures from WO 95/07271, published 16 March 1995, page 19, line 6, thru page 21, line 13; and page 23, line 33, thru page 24, line 35.

III-B Using the general procedures from WO96/15130, published 23 May 1996, Example 1 at page 12, line 1, thru page 14, line 22.

CHART IV

IV-A Using the general procedures from WO 95/25106, published 21 September 1995, page 20, line 27 thru page 22, line 5 but substituting azetidine for piperidine.

IV-B Using the general procedures of WO96/13502, published 9 May 1996, Example 11 at page 53, line 32 through page 56, line 3, but substituting 1-(diphenylmethyl)-3-azetidinone in place of 1-benzyl-3-pyrrolidinone. 1-(Diphenylmethyl)-3-azetidinone can be prepared by the procedure of

Chatterjee, et al, *Synthesis*, 1973, 153-4.

IV-C From IV-B using the general procedure from WO96/13502, published 9 May 1996, page 56, line 4 through line 17.

IV-D From IV-C using the general procedure from WO 95/25106, published 21 September 1995, page 28, line 26 through page 29, line 5.

IV-E Using the general procedures from WO96/13502, published 9 May 1996, Example 2 at page 33, line 4, thru page 36, line 22.

IV-F Starting with IV-E, and using procedures well known for acetylation; e.g., acetic anhydride and triethylamine in a suitable solvent.

IV-G Using the general procedures from WO96/13502, published 9 May 1996, Example 7 at page 43, line 36, thru page 47, line 28.

IV-H Using the general procedures from WO96/13502, published 9 May 1996, Example 6 at page 40, line 31, thru page 43, line 34.

IV-I Using the procedures of WO96/13502, published 9 May 1996, Example 1 at page 29, line 25 thru page 33, line 2.

IV-J Wherein $R^2$ is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13 at page 56, line 19 thru page 59, line 4, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride. 3-Acetylaminoazetidine hydrochloride is prepared by the procedure of Nisato, et al., J. Heterocycl. Chem. 1985, *22*, 961-3.

IV-J Wherein $R^2$ is methyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting methoxyacetyl chloride in place of benzyloxyacetyl chloride.

IV-J Wherein $R^2$ is benzyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride.

IV-J Wherein $R^2$ is acetyl; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting acetoxyacetyl chloride in place of benzyloxyacetyl chloride.

IV-K Wherein $R^3$ is methyl, ethyl, propyl, or phenyl; using the procedure

described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetyl-amino)pyrrolidine hydrochloride and substituting methyl, ethyl, propyl, or phenyl chloroformate in place of benzyloxyacetyl chloride.

IV-L Wherein $R^4$ is hydrogen; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting methyl formate in place of benzyloxyacetyl chloride.

IV-L Wherein $R^4$ is all others listed; using the procedure described in WO96/13502, published 9 May 1996, Examples 12, 13 and 14 at page 56 line 19 thru page 59 line 27, but substituting 3-acetylaminoazetidine hydrochloride in place of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.

IV-M Using the general procedures of WO96/13502, published 9 May 1996, Example 1, Steps 2 thru 7, at page 30, line 14 thru page 33, line 2, but substituting methyl N-benzylazetidine-3-carboxylate in place of 1-(diphenyl-methyl)-3-methoxyazetidine. Methyl N-benzylazetidine-3-carboxylate can be prepared by the procedure of Mason, et al, EP 169602 A1.

IV-N Starting with IV-M and using the general procedures of WO 95/25106, published 21 September 1995, page 22, line 11 through line 20.

CHART V

V-A Using the procedure from WO 95/25106, published 21 September 1995, page 20, Example 1, but using pyrrolidine instead of piperidine.

V-B Using the procedures of WO96/13502, published 9 May 1996, Example 11 at page 53, line 32, thru page 56, line 3.

V-C From V-B, following the procedure of WO96/13502, published 9 May 1996, page 56, lines 4 through 17.

V-D From V-C, using the general procedure of WO 95/25106, published 21 September 1995, page 28, line 26, thru page 29, line 5.

V-E Using the procedures described in WO96/13502, published 9 May 1996, Example 10 at page 50, line 25, thru page 53, line 30. Or, from V-C by reduction using methods well known in the art such as sodium borohydride in methanol.

V-F From V-E using standard acetylation procedures; e.g., acetic anhydride in pyridine.

V-G As described in WO96/13502, published 9 May 1996, Example 7 at page 43, line 36, thru page 47, line 28 but substituting 1-benzyl-3-methyl-3-pyrrolidinol hydrochloride for 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride. 1-Benzyl-3-methyl-3-pyrrolidinol hydrochloride can be prepared from 1-benzyl-3-pyrrolidinone by methods known in the art, eg, reaction with methylmagnesium bromide and treatment of the product with one equivalent of hydrochloric acid. 1-Benzyl-3-pyrrolidinone is commercially available.

V-H Using the general procedures of WO96/13502, published 9 May 1996, Example 6 at page 40, line 31 through page 43, line 34, but substituting 1-benzyl-3-methyl-3-pyrrolidinol hydrochloride (prepared as described above) in place of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride.

V-I As described in WO96/13502, published 9 May 1996, Example 1 at page 29, line 25, thru page 33, line 2, but substituting commercially available 1-benzyl-3-pyrrolidinol for 1-(diphenylmethyl)-3-azetidinol.

V-J Wherein $R^2$ is H and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13 at page 56, line 19, thru page 59, line 4;

V-J Wherein $R^2$ is methyl and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methoxyacetyl chloride for benzyloxyacetyl chloride.

V-J Wherein $R^2$ is benzyl and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27.

V-J Wherein $R^2$ is acetyl and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting acetoxyacetyl chloride for benzyloxyacetyl chloride.

V-J Where $R^2$ is H and $R^5$ is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15 at page 62, lines 5-28.

V-J Wherein $R^2$ is benzyl and $R^5$ is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15, Step 1, at page 62, lines 5-19.

V-J Wherein $R^2$ is methyl or acetyl and $R^5$ is methyl; using the procedures described in WO96/13502, published 9 May 1996, Example 15, Step 1, at page 62, lines 5-19, but substituting methoxyacetyl chloride or acetoxyacetyl chloride for benzyloxyacetyl chloride.

V-J Wherein $R^5$ is other alkyl; using the general procedures described above but subsituting other 4-alkyl-3-aminopyrrolidines in place of 3-amino-4-methylpyrrolidine.

V-K Wherein $R^3$ is methyl, ethyl, propyl or phenyl and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methyl chloroformate, ethyl choroformate, propylchloroformate, or phenylchloroformate for benzyloxyacetyl chloride.

V-K Wherein $R^3$ is methyl, ethyl, propyl, or phenyl and $R^5$ is methyl; by reaction of (*S*)-(N)-[[[3-fluoro-4-(3-amino-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide with the appropriate chloroformate. The above amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

V-K Wherein $R^5$ is other alkyl; From the appropriate amine and chloroformate. The amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29, but starting with other 3-alkyl-4-aminopyrrolidines in place of 4-amino-3-methylpyrrolidine.

V-L Where $R^4$ is H and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting methyl formate in place of benzyloxyacetyl chloride.

V-L Where $R^4$ is all others listed and $R^5$ is H; using the procedure described in WO96/13502, published 9 May 1996, Example 12 at page 56, line 19 thru page 58, line 27 but substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.

V-L Where $R^4$ is H and $R^5$ is methyl; by reaction of formic acid and dicyclohexylcarbodiimide. The required amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

V-L Where $R^4$ is all others and $R^5$ is methyl; by reaction of (*S*)-(N)-[[[3-fluoro-4-(3-amino-4-methylpyrrolidinyl)phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide with the appropriate acid chloride. The required amine is prepared according to the procedures of WO96/13502, published 9 May 1996, Example 14, Steps 1-8, at page 59, line 6 through page 61, line 29.

V-L Where $R^5$ is other alkyl; Using the above procedures, but starting with other 3-alkyl-4-aminopyrrolidines in place of 4-amino-3-methylpyrrolidine.

V-M Using the general procedure from WO 95/25106, published 21 September 1995, page 22, lines 6 through 12, 5, but using pyrrolidine-3-carboxylic acid methyl ester instead of piperidine-4-carboxylic acid ethyl ester. Pyrrolidine-3-carboxylic acid methyl ester is prepared by the procedure of Morgans, et al, *Tetrahedron Lett.*, 1979, 1959.

V-N From V-M, using the general procedure of WO 95/25106, published 21 September 1995, page 22, lines12 through 20.

CHART VI

VI-A Using the general procedures from WO 95/25106, published 21 September 1995, page 20, line 27, thru page 22, line 5.

VI-B Using the procedure of WO 95/25106, published 21 September 1995, WO 95/25106, published 21 September 1995, page 22, line 21 thru line 26.

VI-C From VI-B, using the procedure from WO 95/25106, published 21 September 1995, page 22, lines 27 through 35.

VI-D From VI-C, using the procedure from WO 95/25106, published 21 September 1995, page 28, line 26 thru page 29, line 5.

VI-E Prepared from VI-C by reduction via standard procedures known in the art; eg, sodium borohydride in methanol.

VI-F Prepared from VI-E by procedures known in the art; eg, acetic anhydride and triethylamine.

VI-G Using the procedures from WO96/13502, published 9 May 1996, Example 7, page 43, line 36 thru page 47, line 28 but substituting commercially available 4-hydroxy-4-methylpiperidine for 3-hydroxy-3-methylazetidine.

VI-H Using the procedures from WO 95/25106, published 21 September 1995, page 20, line 27 thru page 22, line 5, but substituting 4-methoxy-4-methylpiperidine in place of piperidine. 4-Methoxy-4-methylpiperidine can be prepared according to the procedure of McManus, et al, *J. Med. Chem.*, 1965, *8*, 766-776.

VI-I Using the procedures from WO 95/25106, published 21 September 1995, page 20 line 27 thru page 22, line 5, but substituting 4-methoxypiperidine

for piperidine. 4-Methoxypiperidine can be made by the procedure of McManus, et al, *J. Med. Chem.*, 1965, *8*, 766-776.

VI-J Wherein $R^2$ = H; Prepared by reaction of (S)-N-[[3-[4-(4-aminopiperidinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared according to the procedures of WO 95/25106, published 21 September 1995, page 22, line36 thru page 23, line 24) with acetoxyacetyl chloride and triethylamine followed by hydrolysis of the acetoxy group with methanolic potassium carbonate.

VI-J Wherein $R^2$ = methyl; prepared by reaction of the starting material of VI-J ($R^2$ = H) with methoxyacetyl chloride and triethylamine.

VI-J Wherein $R^2$ is benzyl; prepared by reaction of the starting material of VI-J ($R^2$ = H) with benzyloxyacetyl chloride and triethylamine.

VI-J Wherein $R^2$ is acetyl; prepared by reaction of the starting material of VI-J ($R^2$ = H) with acetoxyacetyl chloride and triethylamine.

VI-K Wherein $R^3$ is methyl, ethyl, propyl, or phenyl; prepared by reaction of the starting material of VI-J ($R^2$ = H) with methyl-, ethyl-, propyl-, or phenylchloroformate.

VI-L Wherein $R^4$=H; By reaction of the starting material of VI-J ($R^2$ = H) with methylformate.

VI-L Wherein $R^4$ = all others listed; By reaction of the starting material of VI-J ($R^2$ = H) with the appropriate acid chloride.

VI-M Using the procedure from WO 95/25106, published 21 September 1995, page 22, line 6 thru line 12.

VI-N Using the procedure from WO 95/25106, published 21 September 1995, page 22, lines 12 through 20.

CHART VII

VII-A Using the general procedures of WO 95/25106, published 21 September 1995, page 20, line 27 through page 22, line 5, but substituting commercially available azepine in place of piperidine.

VII-B Using the procedure of WO 95/25106, published 21 September 1995, page 22, line 21 thru line 26 but substituting 1,4-dioxo-8-aza-spiro[4.6]undecane for 1,4-dioxo-8-aza-spiro[4.5]decane. 1,4-Dioxo-8-aza-spiro[4.6]undecane can be prepared by the procedure of R. A. Johnson, et al, *J. Org. Chem.*, 1968, *33*, 3187-3195.

VII-C From VII-B, following the procedure of WO96/13502, published 9 May 1996, page 56, lines 4 through 17.

VII-D From VII-C using the general procedure of WO 95/25106, published 21 September 1995, page 28, line 26, thru page 29, line 5.

VII-E Prepared from VII-C by reduction via standard procedures known in the art; eg, sodium borohydride in methanol.

VII-F Prepared from VII-E by procedures known in the art; eg, acetic anhydride and triethylamine.

VII-G Using the procedures from WO96/13502, published 9 May 1996, Example 7, page 43, line 36 thru page 47, line 28 but substituting 4-hydroxy-4-methyl-azepine for 3-hydroxy-3-methylazetidine. 4-Hydroxy-4-methylazepine can be prepared by the procedure pf Grob, et al, *Helv. Chim.Acta*, 1962, *45*, 1823-1830.

VII-H Using the general procedures of WO96/13502, published 9 May 1996, Example 6, page 40, line 31 through page 43, line 34, but substituting 1-benzyl-4-methyl-4-azepinol in place of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride. 1-Benzyl-4-methyl-4-azepinol can be prepared by the reaction of methyl magnesium bromide with 1-benzyl-4-azepinone. 1-Benzyl-4-azepinone can be prepared by the procedure of Casy, et al, *J. Chem. Soc.* 1964, 5130-5132.

VII-I As described in WO96/13502, published 9 May 1996, Example 1, at page 29, line 25, thru page 33, line 2, but substituting 1-benzyl-4-azepinol for 1-(diphenylmethyl)-3-azetidinol. 1-Benzyl-4-azepinol can be prepared by the procedure of S. Sakanoue, et al, *Chem. Pharm. Bull.*, 1990 *38*, 2981-2985.

VII-J Wherein $R^2$ is H; using the procedure described in WO96/13502, published 9 May 1996, Examples 12 and 13, page 56, line 19, thru page 59, line 4 but substituting 4-(trifluoroacetylamino)azepine in place of 3-(trifluoroacetylamino)pyrrolidine. 4-(Trifluoroacetylamino)azepine can be prepared by reaction of 1-benzyl-4-azepinamine with trifluoroacetic anhydride in a suitable solvent such as chloroform, followed by removal of the benzyl protecting group via hydrogenolysis using palladium on carbon as a catalyst in a solvent such as ethyl acetate. 1-Benzyl-4-azepinamine can be prepared by the procedure of Morosawa, et al, *Bull. Chem. Soc. Jpn.*, 1958, *31*, 418-422.

VII-J Wherein $R^2$ is methyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetylamino)azepine for 4-(trifluoroacetylamino)pyrrolidine and substituting methoxyacetyl chloride in

place of benzyloxyacetyl chloride.

VII-J Wherein $R^2$ is benzyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetylamino)azepine for 4-(trifluoroacetylamino)pyrrolidine.

VII-J Wherein $R^2$ is acetyl; using the procedure described in WO96/13502, published 9 May 1996, Example 12, page 56, line 19 through page 58, line 27, but substituting 4-(trifluoroacetylamino)azepine for 4-(trifluoroacetylamino)pyrrolidine and substituting acetoxyacetyl chloride in place of benzyloxyacetyl chloride.

VII-K Wherein $R^3$ is methyl, ethyl, propyl, or phenyl; prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (prepared as an intermediate in the synthesis of VII-J) with the appropriate chloroformate and triethylamine in chloroform.

VII-L Wherein $R^4$ is H; Prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared as an intermediate in the synthesis of VII-J) with formic acid according to the general procedure of WO 93/23384, published 25 November 1993, page 23, lines 4-17.

VII-L Wherein $R^4$ is all others; Prepared by reaction of (S)-N-[[3-[4-(4-aminoazepinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared as an intermediate in the synthesis of VII-J) with the appropriate acid chloride and triethylamine.

VII-M Using the procedure from WO 95/25106, published 21 September 1995, page 22, line 6 thru line 12, but substituting azepine-4-carboxylic acid ethyl ester in place of piperidine-4-carboxylic acid ethyl ester. Azepine-4-carboxylic acid ethyl ester can be prepared from azepine-4-carboxylic acid by normal procedures known in the art, eg, reaction with ethanol and hydrochloric acid. Azepine-4-carboxylic acid can be prepared by the procedure of Krogsgaard-Larsen, et al, *Eur. J. Med. Chem. Chim. Ther.*, 1979, *14*, 157-164.

VII-N From VII-M, using the general procedure of WO 95/25106, published 21 September 1995, page 22, lines12 through 20.

CHART VIII

VIII-A Wherein $R^2$ = H; According to the procedure of WO 95/14684, published 1 June 1995, page 9, lines 1-28.

VIII-A Wherein $R^2$ = methyl; According to the general procedures of WO 93/23384, published 25 November 1993, page 19, lines 26- 33.

VIII-A Wherein $R^2$ = benzyl; According to the procedure of WO 95/14684, published 1 June 1995, page 9, lines 1-14.

VIII-A Wherein $R^2$ = acetyl; According to the procedure of WO 95/14684, published 1 June 1995, page 28, lines 24-35.

VIII-B Wherein $R^3$ = Me, Et, Pr, or Ph; Using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28 and substituting methyl-, ethyl, propyl, or phenylchloroformate as appropriate.

VIII-C Wherein $R^4$ = H; Using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 4-17.

VIII-C Wherein $R^4$ = all others; Using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 19-28, and substituting the appropriate acid chloride for methylchloroformate.

VIII-D Prepared according to the general procedure found in WO 93/23384, published 25 November 1993, page 25, lines 13-25.

VIII-E Prepared according to the general procedure from WO 93/23384, published 25 November 1993, page 25, lines 13-25, but substituting commercially available 5-oxo-2-tetrahydrofurancarboxylic acid in place of (R)-2-tetrahydrofuranoic acid.

VIII-F Prepared according to the procedure of WO 93/23384, published 25 November 1993, page 18, lines 10-17.

VIII-G Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate sulfonyl chloride using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28. Methyl, chloromethyl, allyl, and substituted arylsulfonyl chlorides are commercially available. Cyanomethylsulfonyl chloride can be prepared according to the procedure of M. P. Sammes, et al, *J. Chem. Soc. (C).*, 1971, 2151-2155.

VIII-H Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and piperonyl chloride using the general procedure from WO 93/23384, published 25 November 1993, page 23, lines 19-28. Piperonyl chloride is commercially available.

VIII-I Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate carboxylic acid using the general procedure of WO 95/14684, published 1 June 1995, page 10,

lines 4-17. The acids are commercially available.

VIII-J Prepared from N-[[3-[4-[3-fluoro-4-(1-piperazinyl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide and the appropriate isocyanate. The required isocyanates are commercially available.

CHART IX

IX-A Wherein $R^2$ is H; Prepared according to the procedures of PCT/US96/05202, filed 18 April 1996, Examples 1, 2 and 3, page 12, line 11 through page 15, line 7.

IX-A Wherein $R^2$ is methyl; Prepared according to the general procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting methoxyacetyl chloride for benzyloxyacetyl chloride.

IX-A Wherein $R^2$ is benzyl; Prepared accroding to the procedures of PCT/US96/05202, filed 18 April 1996. Example 2, page 14, lines 16-32.

IX-A Wherein $R^2$ is acetyl; Prepared according to the general procedures of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting acetoxyacetyl chloride for benzyloxyacetyl chloride.

IX-B Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate chloroformate for benzyloxyacetyl chloride.

IX-C Wherein $R^4$ is H; Prepared from (*S*)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]-octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) using the general procedures from WO 93/23384, published 25 November 1993, page 23, lines 4-16.

IX-C Wherein $R^4$ is all others listed; Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate acid chloride in place of benzyloxyacetyl chloride.

IX-D Using the general procedure of PCT/US96/05202, filed 18 April 1996, Example 2, page 14, lines 16-32, but substituting the appropriate sulfonyl chloride in place of benzyloxyacetyl chloride. The sulfonyl chlorides can be obtained as described for VIII-G.

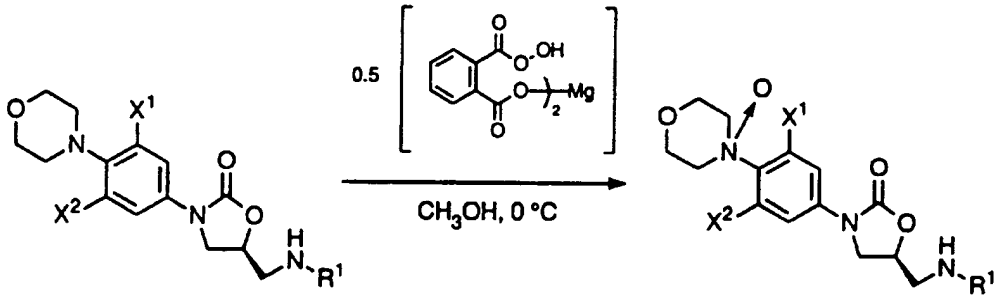
IX-E Prepared from (*S*)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) and the appropriate carboxylic acid using the general procedures of WO 93/23384, published 25 November 1993,

page 18, lines 10-17. The appropriate carboxylic acids are commercially available.

IX-F Prepared by combining (*S*)-N-[[3-[4-[cis-3,7-diazabicyclo[3.3.0]octan-7-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (PCT/US96/05202, filed 18 April 1996, page 14, lines 21-24) and the appropriate isocyanate. The required isocyanates are commercially available.

GENERAL PROCEDURE:

The compounds of this invention are prepared by oxidation of a suitable precursor amine with any of a variety of oxidizing agents. Suitable oxidants include pertrifluoroacetic acid, meta-chloroperbenzoic acid (MCPBA), and magnesium monoperoxyphthalate (MMPP). For example, the synthesis is shown below for the case wherein $Q^1$ is morpholine and the oxidant is MMPP.




Oxidation of any of the oxazolidinones of Charts I-IX in which $Q^2$ is any of the other groups previously described is carried out similarly.

Charts X-XVIII show the final N-oxide compounds of the present invention which are prepared from the parent amines of Charts I-IX, respectively, by using the above General Procedures.

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative synthetic processes are known to one of ordinary skill in organic chemistry.

The compounds of the present invention have an advantage over the parent amines in being exceedingly water soluble (see Table 1 below). For example, the compound of Example No. 2 has a solubility of 409 mg/ml. The parent amine has a water solubility of only 3.7 mg/ml. The N-oxide compounds of the present invention also retain all the *in vitro* and *in vivo* activities of the parent amines. The enhanced water solubility makes the N-oxide compounds of the present invention ideal for intravenous or injectable formulations.

Table 1. Solubility Data for the N-oxides and parent amines.

| Example Number | Parent Amine Solubility (mg/mL) | N-Oxide Solubility (mg/mL) |
|---|---|---|
| 1 | 4.2 | 348 |
| 2 | 3.7 | 534 |
| 3 | 0.28 | 12.9 |
| 6 | 0.031 | 1.1 |

Procedure for Measuring Solubility:

In all solubility studies, an excess of compound is added to 0.5 to 1 ml of pH 7, 50 mM phosphate buffer or other vehicle of interest. The samples are capped and stirred via magnetic stir bars for 24 to 48 hours at room temperature. Samples are filter centrifuged (800 x g) for 5-10 minutes through Millipore Ultrafree-MC 0.22 micron filter units. The supernate is analyzed by either UV or HPLC to quantitate the drug concentration. Results of the solubility testing of the compounds of the present invention are given above in Table 1.

The oxazolidinone compounds of the present invention have useful activity against a variety of microorganisms. The *in vitro* activity of compounds of the present invention are assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Methods for Dilution Antimicrobial Susceptiblity Tests for Bacteria That Grow Aerobically" (MFT) published January 1993 by the National Committee for Clinical Laboratory Standards (NCCLS), 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The activity of selected compounds of the present invention against *Staphylococcus aureus* and *Streptococcus pneumoniae* are shown in Table 2.

Table 2. Activity of the N-oxides against *S. Aureus* and *S. Pneumoniae*.

| Example Number | MIC (μg/mL) *S. Aureus UC® 9213* | MIC (μg/mL) *S. Pneumoniae UC® 9912* |
|---|---|---|
| 1 | 2 | 0.5 |
| 2 | 4 | 1 |
| 3 | 4 | 1 |
| 4 | 2 | 0.5 |
| 5 | 4 | 0.5 |
| 6 | 2 | 0.25 |

As such, the compounds of the present invention are useful for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I. The compound is administered in a pharmaceutical composition orally, parenterally (such as subcutaneously or intravenously), or topically. Preferably the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

The following compounds of the present invention (with cross-references to the formulas in the charts below) are preferred:

X-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiazolidin-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

X-B $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(3-oxazolidinyl)]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide N-oxide.

XI-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XI-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide.

XII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide N-oxide.

XII-A $R^1 = COCH_2OH$, $X^1 = F$, $X^2 = H$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]hydroxyacetamide N-oxide.

XII-A $R^1 = CHO$, $X^1 = F$, $X^2 = H$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]formamide N-oxide.

XII-A $R^1 = CO_2CH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]methylcarbamate N-oxide.

XII-A $R^1 = COCH_2Cl_2$, $X^1 = F$, $X^2 = H$: (S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]dichloroacetamide N-oxide.

XII-B $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-H $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-K $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^3 = CH_3$: (*S*)-N-[[3-[3-fluoro-4-[3-[(methoxy-carbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIII-J $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[3-[(hydroxy-acetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIV-E $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[[3-[3-Fluoro-4-(3-hydroxypyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XIV-J $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^2 = H$, $R^5 = CH_3$: (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(hydroxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide.

XIV-K $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^3 = CH_3$, $R^5 = CH_3$: (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XV-B $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XV-D $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XV-M $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-1-[4-[5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-piperidine-4-carboxylic acid ethyl ester N-oxide.

XV-N $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[3-[3-fluoro-4-(4-hydroxymethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XVI-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (S)-N-[3-[3-fluoro-4-(4-oxoazepin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide.

XVII-B $R^1 = COCH_3$, $X^1 = H$, $X^2 = H$, $R^3 = CH_3$: (S)-4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester N-oxide.

XVII-B $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^3 = CH_2CH_3$: (S)-4-(4-(5-((acetylamino)-methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester N-oxide.

XVIII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxy-acetyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide N-oxide.

XVIII-C $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^4$ = cyclopropyl: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVIII-D $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$, $R^9 = CH_3$: (*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7- yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxy-acetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[4-(hydroxy-acetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = X^2 = F$: (*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = F$, $X^2 = H$: (*S*)-4-[4-[5-[(acetylamino)-methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

The following compounds of the present invention (with cross references to the formulas in the charts below) are most preferred:

XII-A $R^1 = COCH_3$, $X^1 = X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

XII-A $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide N-oxide;

XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = X^2 = F$: (*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxy-acetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

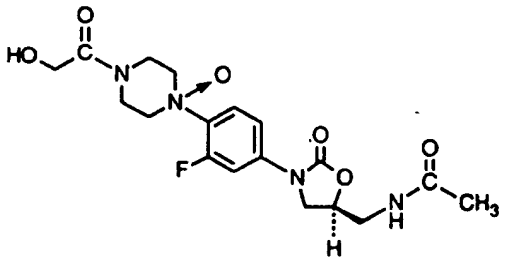
XVII-A $R^1 = COCH_3$, $R^2 = H$, $X^1 = F$, $X^2 = H$: (*S*)-N-[[3-[3-fluoro-4-[4-(hydroxy-acetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = X^2 = F$: (*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]- 1-piperazinecarboxylic acid, methyl ester N-oxide;

XVII-B $R^1 = COCH_3$, $R^3 = CH_3$, $X^1 = F$, $X^2 = H$: (*S*)-4-[4-[5-[(acetylamino)-methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

## DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1. (*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]- 2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide



(S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (VIII-A, $R^1 = COCH_3$, $R^2 = H$, $X^1 = F$, $X^2 = H$) (11.8 g) is dissolved in 200 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 18.5 g) is added and the resulting suspension is stirred at 25°C for two hours. The reaction is filtered and the filtrate is concentrated to afford a white solid. This solid is chromatographed on silica gel using 20% methanol in chloroform as eluent to afford the N-oxide. Lyophilization of this material affords the purified product as a hydrate (9.5 g).

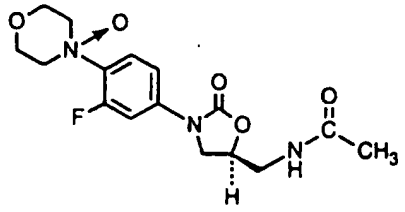
Physical characteristics are as follows:

Mp 158-160 °C;

IR (mull) 3276, 3071, 1754, 1658, 1622, 1502, 1444, 1410, 1286, 1255, 1224, 1204, 1135, 1095, 752 $cm^{-1}$;

MS (FAB) *m/z* 411, 565, 412, 411, 396, 395, 394, 393, 392, 335, 56.

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



(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (III-A, $R^1 = COCH_3$, $X^1 = F$, $X^2 = H$) (12.5 g) is suspended in 200 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 11.5 g) is added and the resulting suspension is stirred at 25°C for two hours. The reaction mixture is filtered and the filtrate is concentrated to afford a light-yellow solid. This material is chromatographed on silica gel using 10% methanol (saturated with ammonia) in chloroform as eluent to afford 8.75 g of the N-oxide.

Physical characteristics are as follows:

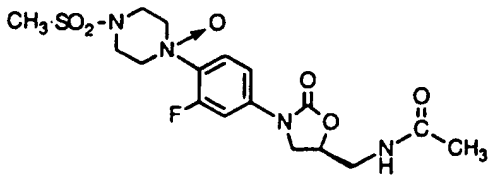
Mp 202-204 °C;

IR (mull) 1747, 1669, 1620, 1556, 1508, 1495, 1445, 1413, 1341, 1295, 1269, 1232, 1204, 1124, 755 $cm^{-1}$;

MS (FAB) *m/z* 354, 708, 707, 355, 354, 339, 338, 337, 336, 86, 56.

Anal. Found: C, 53.99; H, 5.70; N, 11.76.

EXAMPLE 3. (*S*)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide



Pertrifluoroacetic acid is prepared in situ by the addition of 30% $H_2O_2$ solution (0.15 mL) to trifluoroacetic anhydride (0.45 mL) in 5 mL of methylene chloride at 0°C. This solution is stirred at 0°C for ten minutes, at 25°C for 30 minutes and then cooled back to 0 °C. (*S*)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide (VIII-G, $R^1 = COCH_3$, $R^9 = CH_3$, $X^1 = F$, $X^2 = H$) (0.207 g) is added and the reaction is stirred at 25°C for 30 minutes and then concentrated. The residue is chromatographed on silica gel using

10% methanol (saturated with ammonia) in chloroform as the eluent to afford 0.14 g of the N-oxide as a hydrate.

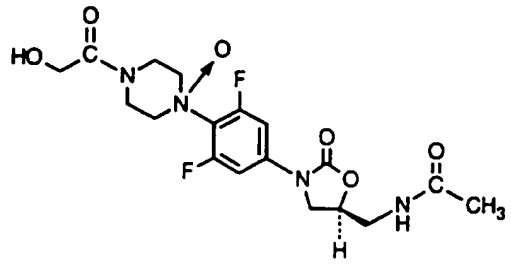
Physical characteristics are as follows:

Mp 168-170 °C;

IR (mull) 1751, 1668, 1658, 1503, 1443, 1408, 1340, 1328, 1277, 1260, 1226, 1157, 1130, 1081, 855 $cm^{-1}$;

MS (FAB) *m/z* 431, 862, 861, 432, 431, 416, 415, 414, 413, 335, 56.

EXAMPLE 4. (*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide.



(S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]- acetamide (VIII-A, $R^1 = COCH_3$, $R^2 = H$, $X^1 = X^2 = F$) (0.13 g) is dissolved in 5 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.2 g) is added and the resulting suspension is stirred at 25°C for 72 hours. An additional 0.2 g of monoperoxyphthalic acid is added and the reaction is stirred an additional 48 hours. The reaction mixture is filtered and the filtrate is concentrated to afford a light-yellow oil. This material is chromatographed on silica gel using 20% methanol (saturated with ammonia) in chloroform as eluent to afford 55 mg of the N-oxide.

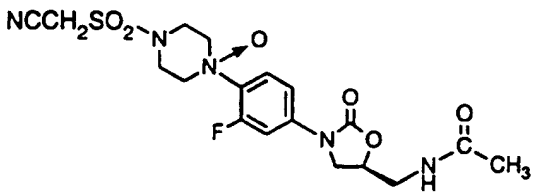
Physical characteristics are as follows:

Mp 100-105 °C;

IR (mull) 3292, 1757, 1658, 1636, 1584, 1557, 1497, 1413, 1287, 1245, 1213, 1098, 1054, 1043, 1020 $cm^{-1}$;

MS (FAB) *m/z* 429 (M+H), 857, 429, 413, 412, 411, 353, 161, 145, 73, 56.

EXAMPLE 5. (S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.



(S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, $R^1$ = $COCH_3$, $R^9$ = $NCCH_2$, $X^1$ = F, $X^2$ = H) (0.550 g) is dissolved in 15 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.616 g) is added and the reaction is stirred at room temperature for 4 hours. The reaction is then filtered and the filtrate is concentrated to afford an oil. This oil is chromatographed on silica gel using 10% methanol (saturated with ammonia) in chloroform as eluent to afford 0.42 g of the N-oxide.

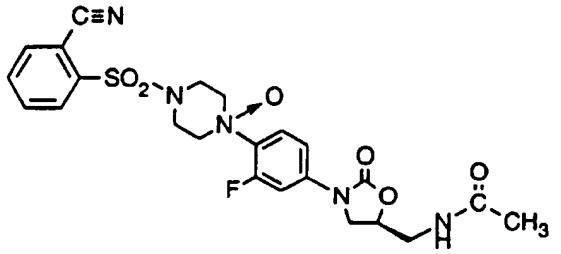
Physical characteristics are as follows:

Mp 153-156 °C.

IR (mull) 1748, 1656, 1625, 1503, 1443, 1406, 1357, 1342, 1257, 1224, 1161, 1148, 1137, 931, 756 $cm^{-1}$;

MS (FAB) *m/z* 456 (M+H), 457, 456, 441, 440, 439, 438, 336, 335, 91, 56.

EXAMPLE 6. (S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.



(S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (VIII-G, $R^1$ = $COCH_3$, $R^9$ = 2-cyanophenyl, $X^1$ = F, $X^2$ = H) (0.5 g) is suspended in 10 mL of methanol. Monoperoxyphthalic acid, magnesium salt hexahydrate (80% pure, 0.616 g) is added and the reaction mixture is stirred at room temperature for 2 hours. The reaction is concentrated and the resulting oil is chromatographed on silica gel using 7% methanol (saturated with ammonia) in chloroform as eluent to afford 0.33 g of the N-oxide.

Physical characteristics are as follows:

Mp 190-192 °C.

IR (mull) 1756, 1678, 1661, 1620, 1500, 1486, 1408, 1280, 1256, 1222, 1181, 1168, 1129, 1082, 924 $cm^{-1}$;

MS (FAB) $m/z$ 518 (M+H), 520, 519, 518, 503, 502, 501, 500, 336, 335, 56.

EXAMPLE 7: Reduction of the N-oxide of Example 2 *in vivo* Following Intravenous and Oral Administration to Rats.

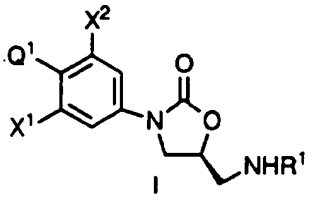
The rate and extent of reduction of the N-oxide of Example 2 was investigated *in vivo* using the following procedures: Six male Sprague-Dawley rats are used for this study. Three rats are given a single intravenous 10 mg/kg dose of the N-oxide and three rats are given a single oral 25 mg/kg dose of the N-oxide. Blood is collected pre-dose and up to 24 h post dose. The plasma is analyzed for the N-oxide and the parent amine by LC-MS.

Results:

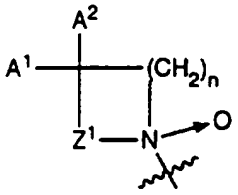
Only traces of the N-oxide were found in plasma in the first time point immediately post intravenous injection. The parent amine was detected in plasma up to 10 h post dosing. The lower limit of quantitation for the assay was ≈0.01 µg/mL. Because the N-oxide was reduced to the parent amine so rapidly, pharmacokinetic parameters were measured for the parent amine rather than for the N-oxide.

After both intravenous and oral dosing of the N-oxide, the Cmax, Tmax and AUC values for the parent amine were very similar to those found when the parent amine compound was administered directly to rats using the same doses and protocol. The relative bioavailability of the parent amine from the orally administered N-oxide was approximately 100% when compared to orally administered parent amine. The rapid and essentially quantitative conversion of the N-oxide to the parent amine *in vivo* demonstrates that the N-oxide is a suitable prodrug for the parent amine.

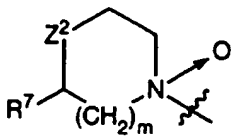
## FORMULA CHART



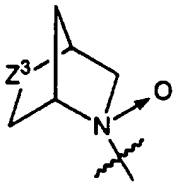

I



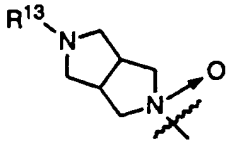

II



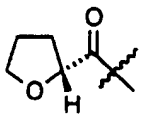

III



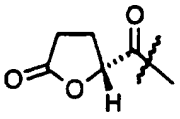

IV



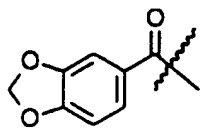

V



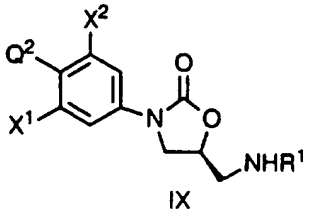

VI




VII

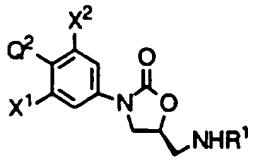



VIII



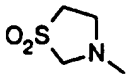

IX

CHART I - THIAZOLIDINES

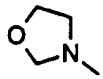


IX

wherein $Q^2$ is



I-A



I-B

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

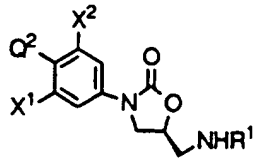
$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

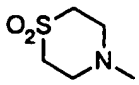
$-COCH_2OH$.

CHART II - THIOMORPHOLINES - BRIDGED THIOMORPHOLINES

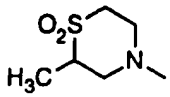


IX

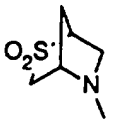
wherein $Q^2$ is



II-A



II-B



II-C

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

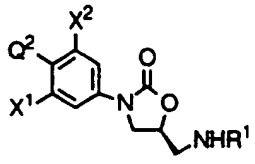
-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

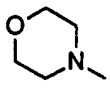
-$COCH_2OH$.

CHART III - MORPHOLINES - BRIDGED MORPHOLINES

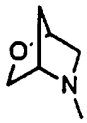


IX

wherein $Q^2$ is



III-A



III-B

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

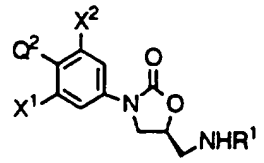
-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

-$COCH_2OH$.

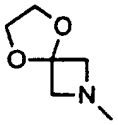
## CHART IV - AZETIDINES



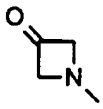
IX

wherein $Q^2$ is

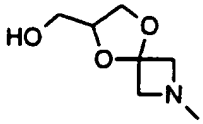
IV-A



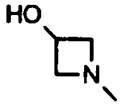
IV-B



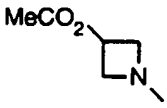
IV-C



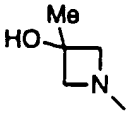
IV-D



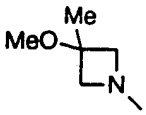
IV-E



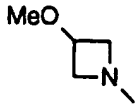
IV-F



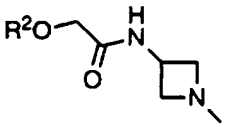
IV-G



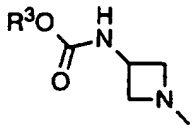
IV-H



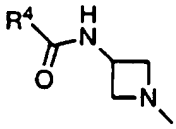
IV-I



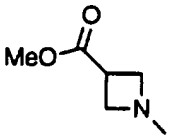
IV-J



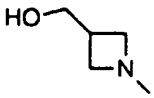
IV-K



IV-L



IV-M



IV-N

CHART IV - AZETIDINES (Continued)

wherein $X^1$ and $X^2$ are independently
- -H,
- -F, or
- -Cl;

wherein $R^1$ is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein $R^2$ is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein $R^3$ is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

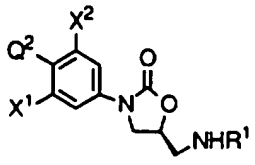
wherein $R^4$ is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- $CH_2F$,
- $-CHF_2$,
- -substituted aryl,

CHART IV- AZETIDINES (Continued)

-$CH_2$-(aryl), or

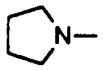
-cycloalkyl (rings of 3-6 carbons).

## CHART V - PYRROLIDINES

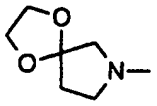


IX

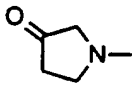
wherein $Q^2$ is



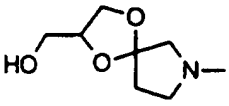
V-A



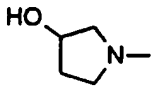
V-B



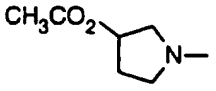
V-C



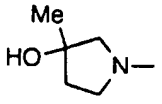
V-D



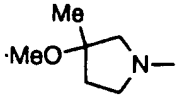
V-E



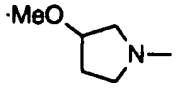
V-F



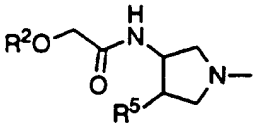
V-G



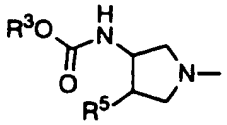
V-H



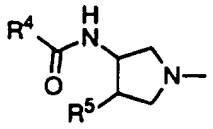
V-I



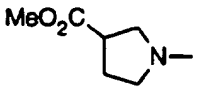
V-J



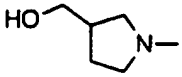
V-K



V-L



V-M



V-N

CHART V - PYRROLIDINES (Continued)

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$-COCH_2OH$;

wherein $R^2$ is

-H,

$-CH_3$,

$-CH_2Ph$, or

$-COCH_3$;

wherein $R^3$ is

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$,

$-CH_2CH_2CH_2CH_3$,

-phenyl,

$-CH_2Cl$,

$-CHCl_2$,

$CH_2F$,

$-CHF_2$,

-substituted aryl,

CHART V - PYRROLIDINES (Continued)

-$CH_2$-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein $R^5$ is

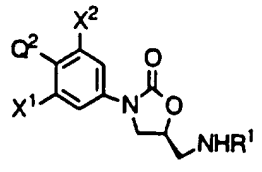
-H,

-$CH_3$,

-$CH_2CH_3$, or

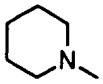
-$CH_2CH_2CH_3$.

## CHART VI - PIPERIDINES

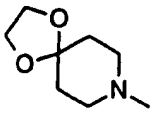


IX

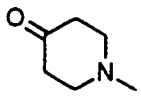
wherein $Q^2$ is



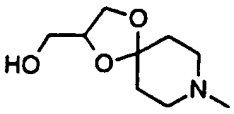
VI-A



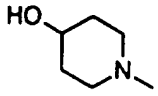
VI-B



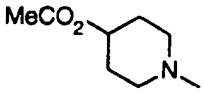
VI-C



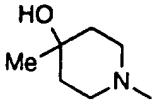
VI-D



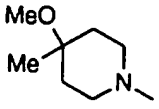
VI-E



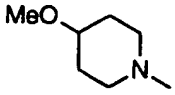
VI-F



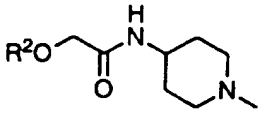
VI-G



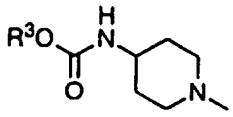
VI-H



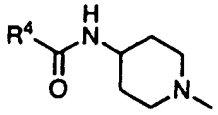
VI-I



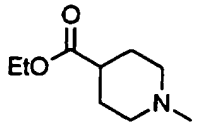
VI-J



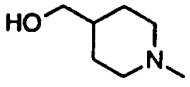
VI-K



VI-L



VI-M



VI-N

CHART VI - PIPERIDINES (Continued)

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$COCH_2OH$;

wherein $R^2$ is

-H,

$-CH_3$,

$-CH_2Ph$, or

$-COCH_3$;

wherein $R^3$ is

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$,

$-CH_2CH_2CH_2CH_3$,

-phenyl,

$-CH_2Cl$,

$-CHCl_2$,

$CH_2F$,

$-CHF_2$,

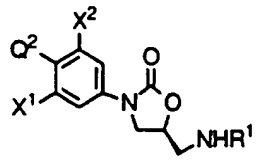
-substituted aryl,

CHART VI - PIPERIDINES (continued)

-$CH_2$-(aryl), or

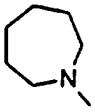
-cycloalkyl (rings of 3-6 carbons).

## CHART VII - AZEPINES

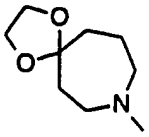


IX

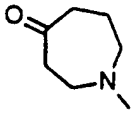
wherein $Q^2$ is



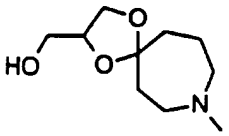
VII-A



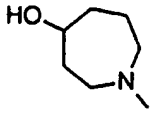
VII-B



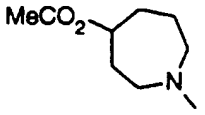
VII-C



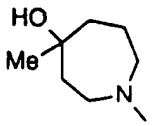
VII-D



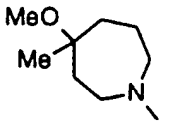
VII-E



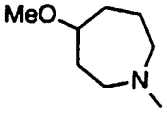
VII-F



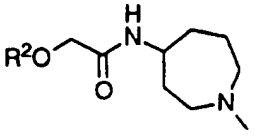
VII-G



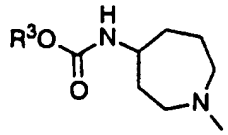
VII-H



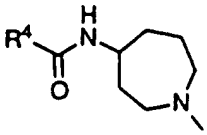
VII-I



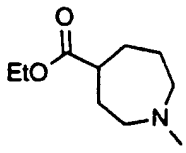
VII-J



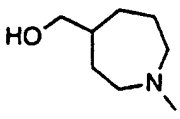
VII-K



VII-L



VII-M



VII-N

CHART VII - AZEPINES (Continued)

wherein $X^1$ and $X^2$ are independently
- -H,
- -F, or
- -Cl;

wherein $R^1$ is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein $R^2$ is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein $R^3$ is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

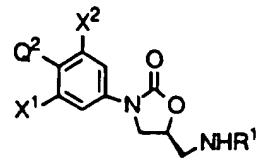
wherein $R^4$ is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- $CH_2F$,
- $-CHF_2$,
- -substituted aryl,

CHART VII - AZEPINES (Continued)

-$CH_2$-(aryl), or

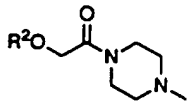
-cycloalkyl (rings of 3-6 carbons).

## CHART VIII - PIPERAZINES

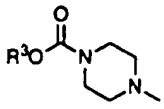


IX

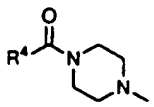
wherein $Q^2$ is



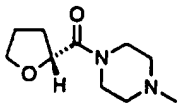
VIII-A



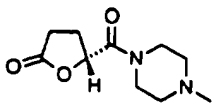
VIII-B



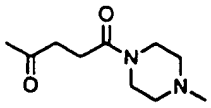
VIII-C



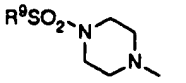
VIII-D



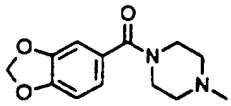
VIII-E



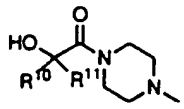
VIII-F



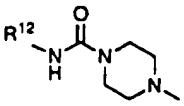
VIII-G



VIII-H



VIII-I



VIII-J

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

-$COCH_2OH$;

CHART VIII - PIPERAZINES (Continued)

wherein $R^2$ is

-H,

-$CH_3$,

-$CH_2Ph$, or

-$COCH_3$;

wherein $R^3$ is

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$,

-$CH_2CH_2CH_2CH_3$,

-phenyl,

-$CH_2Cl$,

-$CHCl_2$,

$CH_2F$,

-$CHF_2$,

-substituted aryl,

-$CH_2$-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein $R^9$ is

-$CH_3$,

-$CH_2Cl$,

-$CH_2CH{=}CH_2$,

substituted aryl, or

-$CH_2CN$;

wherein $R^{10}$ and $R^{11}$ are independently

-H,

-$CH_3$, or

-together form a cyclopropyl ring;

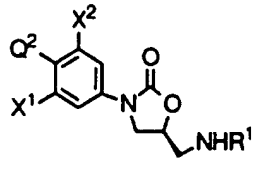
CHART VIII - PIPERAZINES (Continued)

wherein $R^{12}$ is

-$CH_2Ph$, or

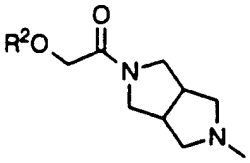
-substituted aryl.

## CHART IX - PYRROLOPYRROLIDINES

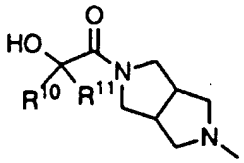


IX

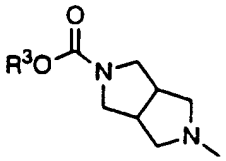
wherein $Q^2$ is



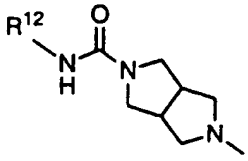
IX-A



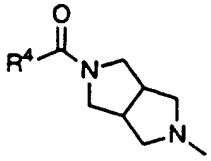
IX-E



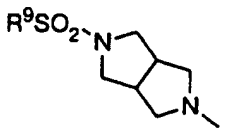
IX-B



IX-F



IX-C



IX-D

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

CHART IX - PYRROLOPYRROLIDINES (Continued)

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

-$COCH_2OH$;

wherein $R^2$ is

-H,

-$CH_3$,

-$CH_2Ph$, or

-$COCH_3$;

wherein $R^3$ is

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$,

-$CH_2CH_2CH_2CH_3$,

-phenyl,

-$CH_2Cl$,

-$CHCl_2$,

-$CH_2F$,

-$CHF_2$,

-substituted aryl,

-$CH_2$-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein $R^9$ is

-$CH_3$,

CHART IX - PYRROLOPYRROLIDINES (Continued)

-$CH_2Cl$,

-$CH_2CH{=}CH_2$,

substituted aryl, or

-$CH_2CN$;

wherein $R^{10}$ and $R^{11}$ are independently

-H,

-$CH_3$, or

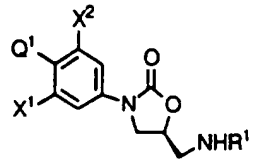
-together form a cyclopropyl ring;

wherein $R^{12}$ is

-$CH_2Ph$, or

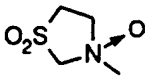
-substituted aryl.

CHART X - THIAZOLIDINES

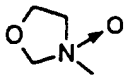


I

wherein $Q^1$ is



X-A



XI-B

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

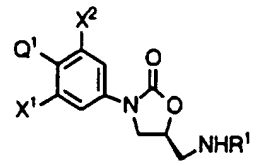
$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

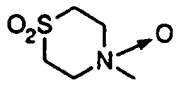
$-COCH_2OH$.

CHART XI - THIOMORPHOLINES - BRIDGED THIOMORPHOLINES

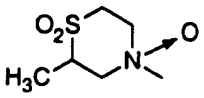


I

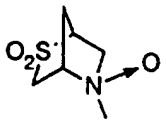
wherein $Q^1$ is



XI-A



XI-B



XI-C

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

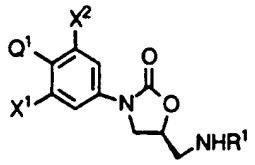
$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

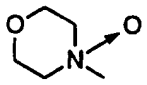
$-COCH_2OH$.

CHART XII - MORPHOLINES - BRIDGED MORPHOLINES

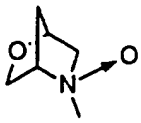



I

wherein $Q^1$ is




XII-A




XII-B

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

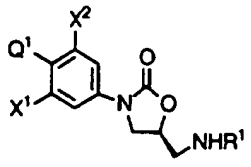
-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

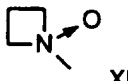
-$COCH_2OH$.

## CHART XIII - AZETIDINES

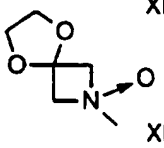


I

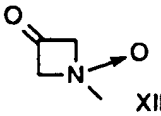
wherein $Q^1$ is



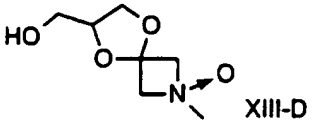
XIII-A



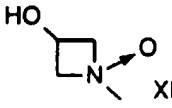
XIII-B



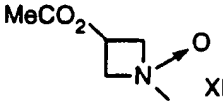
XIII-C



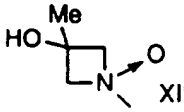
XIII-D



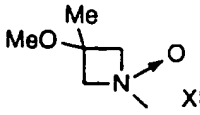
XIII-E



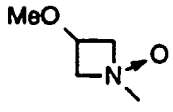
XIII-F



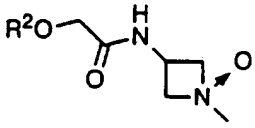
XIII-G



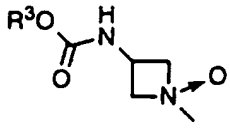
XIII-H



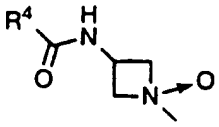
XIII-I



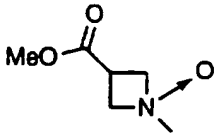
XIII-J



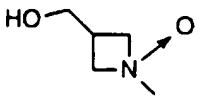
XIII-K



XIII-L



XIII-M



XIII-N

CHART XIII - AZETIDINES (Continued)

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$-COCH_2OH$;

wherein $R^2$ is

-H,

$-CH_3$,

$-CH_2Ph$, or

$-COCH_3$;

wherein $R^3$ is

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$,

$-CH_2CH_2CH_2CH_3$,

-phenyl,

$-CH_2Cl$,

$-CHCl_2$,

$CH_2F$,

$-CHF_2$,

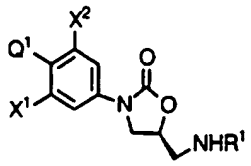
-substituted aryl,

CHART XIII- AZETIDINES (Continued)

-$CH_2$-(aryl), or

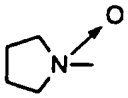
-cycloalkyl (rings of 3-6 carbons).

## CHART XIV - PYRROLIDINES

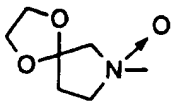


I

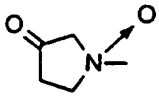
wherein $Q^1$ is



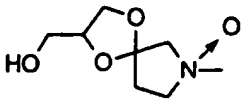
XIV-A



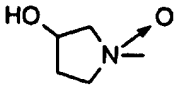
XIV-B



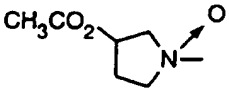
XIV-C



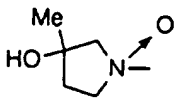
XIV-D



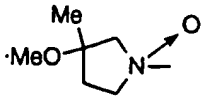
XIV-E



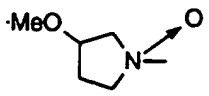
XIV-F



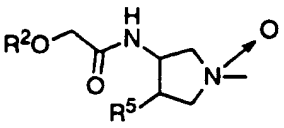
XIV-G



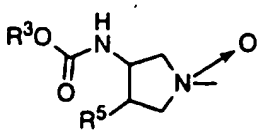
XIV-H



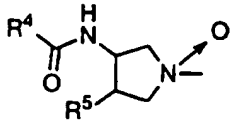
XIV-I



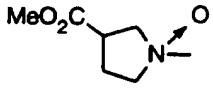
XIV-J



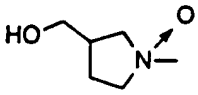
XIV-K



XIV-L



XIV-M



XIV-N

CHART XIV - PYRROLIDINES (Continued)

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

-$COCH_2OH$;

wherein $R^2$ is

-H,

-$CH_3$,

-$CH_2Ph$, or

-$COCH_3$;

wherein $R^3$ is

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$,

-$CH_2CH_2CH_2CH_3$,

-phenyl,

-$CH_2Cl$,

-$CHCl_2$,

$CH_2F$,

-$CHF_2$,

-substituted aryl,

CHART XIV - PYRROLIDINES (Continued)

-$CH_2$-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein $R^5$ is

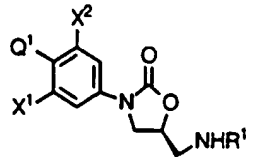
-H,

-$CH_3$,

-$CH_2CH_3$, or

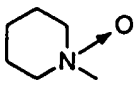
-$CH_2CH_2CH_3$.

## CHART XV - PIPERIDINES

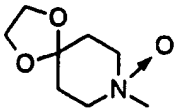


I

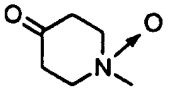
wherein $Q^1$ is



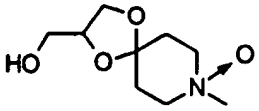
XV-A



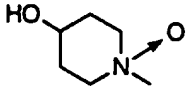
XV-B



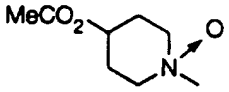
XV-C



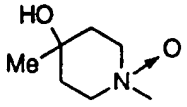
XV-D



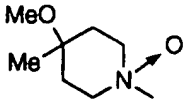
XV-E



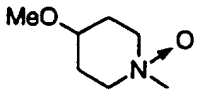
XV-F



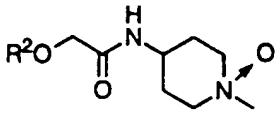
XV-G



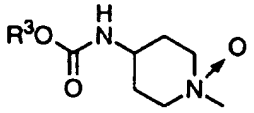
XV-H



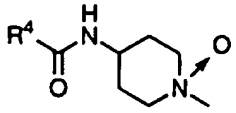
XV-I



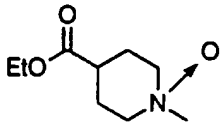
XV-J



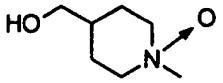
XV-K



XV-L



XV-M



XV-N

CHART XV - PIPERIDINES (Continued)

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$COCH_2OH$;

wherein $R^2$ is

-H,

$-CH_3$,

$-CH_2Ph$, or

$-COCH_3$;

wherein $R^3$ is

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$,

$-CH_2CH_2CH_2CH_3$,

-phenyl,

$-CH_2Cl$,

$-CHCl_2$,

$CH_2F$,

$-CHF_2$,

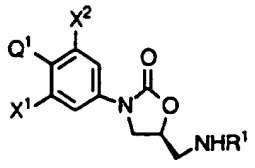
-substituted aryl,

CHART XV - PIPERIDINES (continued)

-$CH_2$-(aryl), or

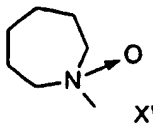
-cycloalkyl (rings of 3-6 carbons).

## CHART XVI - AZEPINES

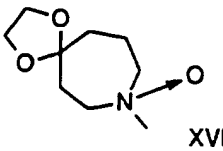


I

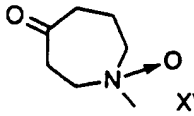
wherein $Q^1$ is



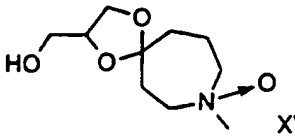
XVI-A



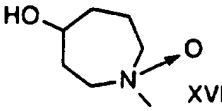
XVI-B



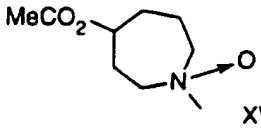
XVI-C



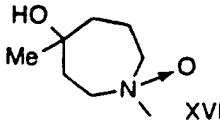
XVI-D



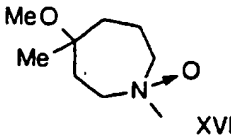
XVI-E



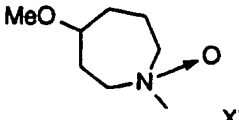
XVI-F



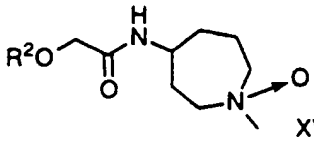
XVI-G



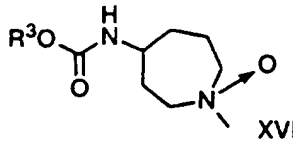
XVI-H



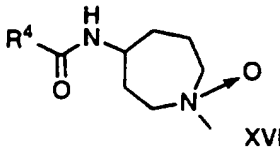
XVI-I



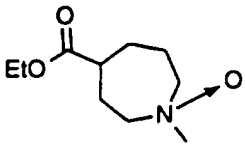
XVI-J



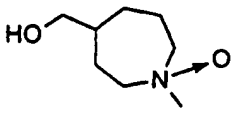
XVI-K



XVI-L



XVI-M



XVI-N

CHART XVI - AZEPINES (Continued)

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

wherein $R^1$ is

-CHO,

$-COCH_3$,

$-COCHCl_2$,

$-COCHF_2$,

$-CO_2CH_3$,

$-SO_2CH_3$, or

$-COCH_2OH$;

wherein $R^2$ is

-H,

$-CH_3$,

$-CH_2Ph$, or

$-COCH_3$;

wherein $R^3$ is

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

$-CH_3$,

$-CH_2CH_3$,

$-CH_2CH_2CH_3$,

$-CH_2CH_2CH_2CH_3$,

-phenyl,

$-CH_2Cl$,

$-CHCl_2$,

$CH_2F$,

$-CHF_2$,

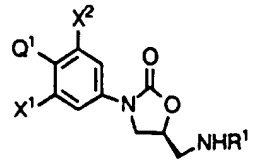
-substituted aryl,

CHART XVI - AZEPINES (Continued)

-$CH_2$-(aryl), or

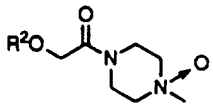
-cycloalkyl (rings of 3-6 carbons).

## CHART XVII - PIPERAZINES

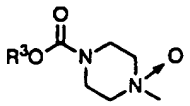


I

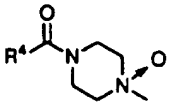
wherein $Q^1$ is



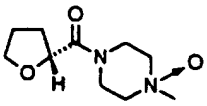
XVII-A



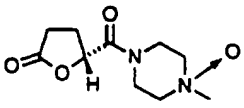
XVII-B



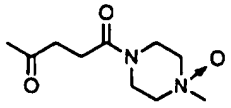
XVII-C



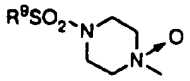
XVII-D



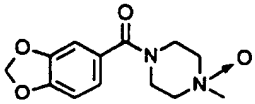
XVII-E



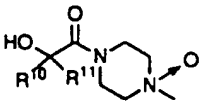
XVII-F



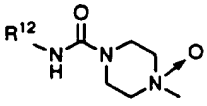
XVII-G



XVII-H



XVII-I



XVII-J

CHART XVII - PIPERAZINES (Continued)

wherein $X^1$ and $X^2$ are independently
- -H,
- -F, or
- -Cl;

wherein $R^1$ is
- -CHO,
- $-COCH_3$,
- $-COCHCl_2$,
- $-COCHF_2$,
- $-CO_2CH_3$,
- $-SO_2CH_3$, or
- $-COCH_2OH$;

wherein $R^2$ is
- -H,
- $-CH_3$,
- $-CH_2Ph$, or
- $-COCH_3$;

wherein $R^3$ is
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$, or
- -phenyl;

wherein $R^4$ is
- -H,
- $-CH_3$,
- $-CH_2CH_3$,
- $-CH_2CH_2CH_3$,
- $-CH_2CH_2CH_2CH_3$,
- -phenyl,
- $-CH_2Cl$,
- $-CHCl_2$,
- $CH_2F$,
- $-CHF_2$,
- -substituted aryl,

CHART XVII - PIPERAZINES (Continued)

-$CH_2$-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein $R^9$ is

-$CH_3$,

-$CH_2Cl$,

-$CH_2CH{=}CH_2$,

substituted aryl, or

-$CH_2CN$;

wherein $R^{10}$ and $R^{11}$ are independently

-H,

-$CH_3$, or

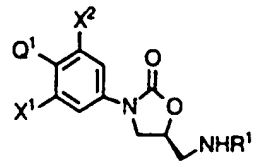
-together form a cyclopropyl ring;

wherein $R^{12}$ is

-$CH_2Ph$, or

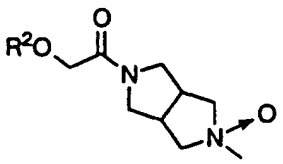
-substituted aryl.

## CHART XVIII - PYRROLOPYRROLIDINES

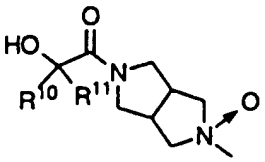


I

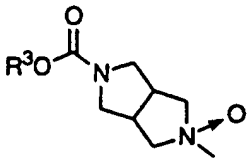
wherein $Q^1$ is



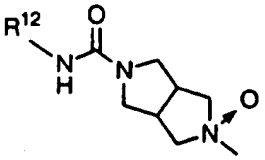
XVIII-A



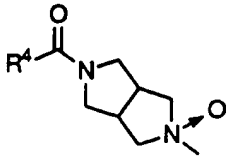
XVIII-E



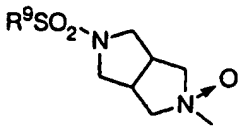
XVIII-B



XVIII-F



XVIII-C



XVIII-D

wherein $X^1$ and $X^2$ are independently

-H,

-F, or

-Cl;

CHART XVIII - PYRROLOPYRROLIDINES (Continued)

wherein $R^1$ is

-CHO,

-$COCH_3$,

-$COCHCl_2$,

-$COCHF_2$,

-$CO_2CH_3$,

-$SO_2CH_3$, or

-$COCH_2OH$;

wherein $R^2$ is

-H,

-$CH_3$,

-$CH_2Ph$, or

-$COCH_3$;

wherein $R^3$ is

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$, or

-phenyl;

wherein $R^4$ is

-H,

-$CH_3$,

-$CH_2CH_3$,

-$CH_2CH_2CH_3$,

-$CH_2CH_2CH_2CH_3$,

-phenyl,

-$CH_2Cl$,

-$CHCl_2$,

-$CH_2F$,

-$CHF_2$,

-substituted aryl,

-$CH_2$-(aryl), or

-cycloalkyl (rings of 3-6 carbons);

wherein $R^9$ is

-$CH_3$,

CHART XVIII - PYRROLOPYRROLIDINES (Continued)

-$CH_2Cl$,

-$CH_2CH{=}CH_2$,

substituted aryl, or

-$CH_2CN$;

wherein $R^{10}$ and $R^{11}$ are independently

-H,

-$CH_3$, or

-together form a cyclopropyl ring;

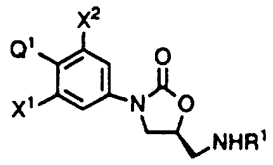
wherein $R^{12}$ is

-$CH_2Ph$, or

-substituted aryl.

CLAIMS

1. A compound of the formula I



I

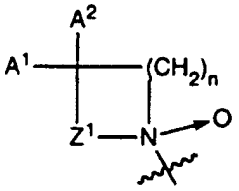
wherein $X^1$ and $X^2$ are independently

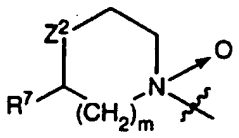
-H,

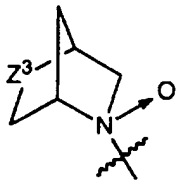
-F, or

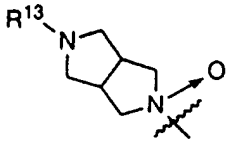
-Cl;

wherein $Q^1$ is:

a)  II

b)  III

c)  IV, or

d)  V;

wherein $Z^1$ is

a) $-CH_2-$, or

b) $-CH(R^5)-CH_2-$;

wherein $Z^2$ is

a) $-O_2S-$,
b) -O-, or
c) $-N(R^8)-$;

wherein $Z^3$ is

a) $-O_2S-$, or
b) -O-;

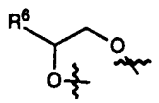
wherein $A^1$ is

a) H-, or
b) $CH_3-$;

wherein $A^2$ is

a) H-,
b) HO-,
c) $CH_3CO_2-$,
d) $CH_3-$,
e) $CH_3O-$,
f) $R^2O-CH_2-C(O)-NH-$
g) $R^3O-C(O)-NH-$,
h) $R^4-C(O)-NH-$,
i) $(C_1-C_2)$alkyl-O-C(O)-, or
j) $HO-CH_2-$; or

$A^1$ and $A^2$ taken together are:

a)  or

b) o= ;

wherein $R^1$ is

a) -CHO,
b) $-COCH_3$,
c) $-COCHCl_2$,
d) $-COCHF_2$,
e) $-CO_2CH_3$,
f) $-SO_2CH_3$, or
g) $-COCH_2OH$;

wherein $R^2$ is

a) H-,
b) $CH_3$-,
c) phenyl-$CH_2$-, or
d) $CH_3C(O)$-;

wherein $R^3$ is
a) $(C_1$-$C_3)$alkyl-, or
b) phenyl-;

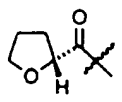
wherein $R^4$ is
a) H-,
b) $(C_1$-$C_4)$alkyl,
c) aryl -$(CH_2)_p$,
d) $ClH_2C$-,
e) $Cl_2HC$-,
f) $FH_2C$-,
g) $F_2HC$-, or
h) $(C_3$-$C_6)$cycloalkyl;

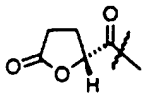
wherein $R^5$ is
a) H-, or
b) $(C_1$-$C_3)$alkyl;

wherein $R^6$ is
a) H-, or
b) $HOH_2C$-;

wherein $R^7$ is
a) H-, or
b) $H_3C$-;

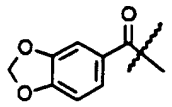
wherein $R^8$ is
a) $R^2O$-$C(R_{10})(R_{11})$-C(O)-,
b) $R^3O$-C(O)-,
c) $R^4$-C(O)-,

d)  VI ,

e)  VII ,

f) $H_3C$-C(O)-$(CH_2)_2$-C(O)-,

g) $R^9$-$SO_2$-,

h)  VIII , or

i) $R^{12}$-NH-C(O)-;

wherein $R^9$ is

a) $-CH_3$,

b) $-CH_2Cl$

c) $-CH_2CH=CH_2$,

d) aryl, or

e) $-CH_2CN$;

wherein $R^{10}$ and $R^{11}$ are independently

a) H-,

b) $CH_3$-; or

$R^{10}$ and $R^{11}$ taken together are $-CH_2-CH_2-$;

wherein $R^{12}$ is $-(CH_2)_p$-aryl;

wherein $R^{13}$ is

a) $R^2O$-C($R_{10}$)($R_{11}$)-C(O)-,

b) $R^3O$-C(O)-,

c) $R^4$-C(O)-,

d) $R^9$-$SO_2$-, or

e) $R^{12}$-NH-C(O)-;

wherein m is zero (0) or one (1);

wherein n is one (1) to three (3), inclusive;

wherein p is zero (0) or one (1);

wherein aryl is phenyl substituted with zero (0) or one (1) of the following:

a) -F,

b) -Cl,

c) $-OCH_3$,

d) -OH,

e) $-NH_2$,

f) $-(C_1-C_4)$alkyl,

g) $-O-C(O)-OCH_3$,

h) $-NO_2$, or

i) -CN;

with the following provisos:

1) in the moiety of formula II, $Z^1$ is -CH($R^5$)-$CH_2$- wherein $R^5$ is ($C_1$-$C_3$)alkyl, only when n is one (1), $A^1$ is H and $A^2$ is $R^2O$-$CH_2$-C(O)-NH-, $R^3O$-C(O)-NH-, or $R^4$-C(O)-NH-; and

2) in the moiety of formula II, when $Z^1$ is -$CH_2$-, n is one (1).

2. The compound of claim 1 wherein $Q^1$ is the moiety of formula II.

3. The compound of claim 1 wherein $Q^1$ is the moiety of formula III.

4. The compound of claim 1 wherein $Q^1$ is the moiety of formula IV.

5. The compound of claim 1 wherein $Q^1$ is the moiety of formula V.

6. The compound of claim 1 wherein one of $X^1$ and $X^2$ is -H and the other is -F or wherein $X^1$ is -F and $X^2$ is -F.

7. The compound of claim 1 wherein $R^1$ is acetyl.

8. The compound of claim 1 selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiazolidin-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxazolidinyl)]phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(1,1-dioxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-hydroxyacetamide N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-

formamide N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-methylcarbamate N-oxide;

(S)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-dichloroacetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[3-[(methoxycarbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[3-[(hydroxyacetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

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

(S)-N-[[3-[3-Fluoro-4-(*cis*-3-(hydoxyacetylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(S)-N-[3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-N-[3-[3-fluoro-4-(2-hydroxymethyl-1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-1-[4-[5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-piperidine-4-carboxylic acid ethyl ester N-oxide;

(S)-N-[3-[3-fluoro-4-(4-hydroxymethylpiperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-N-[3-[3-fluoro-4-(4-oxoazepin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide N-oxide;

(S)-4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)phenyl)-1-piperazinecarboxylic acid, methyl ester N-oxide;

(S)-4-(4-(5-((acetylamino)methyl)-2-oxo-3-oxazolidinyl)-2-fluorophenyl)-1-piperazinecarboxylic acid, ethyl ester N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(hydroxyacetyl)-3,7-diazabicyclo[3.3.0]octan-7-

yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-[(cyclopropyl)carbonyl]-3,7-diazabicyclo[3.3.0]-octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[*cis*-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.0]octan-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide; and

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

9. The compound of claim 8 selected from the group consisting of:

(*S*)-N-[[3-[3,5-difluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide;

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2,6-difluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide; and

(*S*)-4-[4-[5-[(acetylamino)methyl]-2-oxo-3-oxazolidinyl]-2-fluorophenyl]-1-piperazinecarboxylic acid, methyl ester N-oxide.

10. The compound of claim 1 selected from the group consisting of:

(*S*)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]- 2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

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

(*S*)-N-[[3-[3-fluoro-4-[4-(methylsulfonyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide N-oxide;

(*S*)-N-[[3-[3,5-difluoro-4-[4-(hydroxyacetyl)-1- piperazinyl]phenyl]-2-oxo-5-

oxazolidinyl]-methyl]acetamide N-oxide;

(S)-N-[[3-[4-[4-[(cyanomethyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide; and

(S)-N-[[3-[4-[4-[(2-cyanophenyl)sulfonyl]-1-piperazinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide N-oxide.

# INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/US 96/14135

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/20 A61K31/42 C07D417/10 C07D495/08 C07D491/08
C07D413/10 C07D471/04 C07D491/10

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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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 |
|---|---|
| 9 December 1996 | 17. 12. 96 |

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

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

# INTERNATIONAL SEARCH REPORT

Interr ·al Application No
PC1/US 96/14135

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| P,Y | WO 96 15130 A (THE UPJOHN COMPANY) 23 May 1996<br>cited in the application<br>see claims | 1-10 |
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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PCT/US 96/14135

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Information on patent family members

Inter vnal Application No
PCI/US 96/14135

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BK

(19) Europäisches Patentamt
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(11) EP 0 785 200 A2

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(71) Anmelder: **BAYER AG**
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- **Kroll, Hein-Peter, Dr.**
  **42115 Wuppertal (DE)**

## (54) Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone

(57) Die vorliegende Erfindung betrifft neue Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

EP 0 785 200 A2

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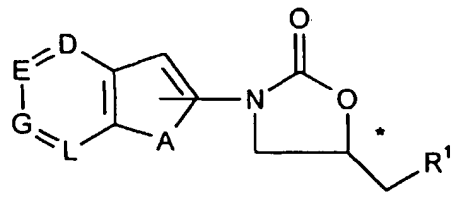
## Beschreibung

Die vorliegende Erfindung betrifft neue Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

N-Aryloxazolidinone mit antibakterieller Wirkung sind beispielsweise aus den Publikationen EP 311 090 und US 4 705 799 bekannt. Außerdem sind 3-(Stickstoff-substituierte)phenyl-5-beta-amidomethyloxazolidin-2-one aus der EP 609 905 A1 bekannt.

Ferner sind unter anderem in der WO 93 08 179 A Oxazolidinonderivate mit einer Monoaminoxidase inhibitorischen Wirkung und in der EP 645 376 mit Wirkung als Adhäsionsrezeptor-Antagonisten publiziert.

Die vorliegende Erfindung betrifft Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone der allgemeinen Formel (I)



(I)

in welcher

| | |
|---|---|
| A | für ein Sauerstoff- oder Schwefelatom oder für die $SO_2$-Gruppe steht, und |
| D, E, G und L | gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin |
| $R^2$ | Wasserstoff, Cyano, Nitro, Carboxyl, geradkettiges oder verzweigtes Alkyl, Acyl oder Alkoxy mit jeweils bis zu 7 Kohlenstoffatomen, Halogen oder eine Gruppe der Formel $-NR^3R^4$, $-CO-NR^5R^6$, $-NR^7-CO-R^8$ oder $-S(O)_aR^9$ bedeutet, worin |
| $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ und $R^8$ | gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, |
| a | eine Zahl 0, 1 oder 2 bedeutet, |
| $R^9$ | Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet, |
| $R^1$ | für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin |
| $R^{10}$ | geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet, |
| $R^{11}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet, das gegebenenfalls durch geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen substituiert ist, |
| $R^{12}$ und $R^{13}$ | gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 8 Kohlenstoffatomen oder eine Aminoschutzgruppe bedeuten, oder |

| | |
|---|---|
| $R^{12}$ oder $R^{13}$ | eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet, worin |
| $R^{14}$ und $R^{14'}$ | gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten, oder |
| $R^{14}$ und $R^{14'}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert ist,<br>oder<br>geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeuten,<br>oder<br>eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,<br>worin |
| $R^{18}$ und $R^{19}$ | gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,<br>oder<br>einen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeuten, |
| $R^{15}$ und $R^{16}$ | gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, |
| $R^{17}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet |

und deren Salze.

Physiologisch unbedenkliche Salze der neuen Pyrido-annellierten Thienyl- und Furanyl-Oxazolidinone können Salze der erfindungsgemäßen Stoffe mit Mineralsäuren, Carbonsäuren oder Sulfonsäuren sein. Besonders bevorzugt sind z.B. Salze mit Chlorwasserstoffsäure, Bromwasserstoffsäure, Schwefelsäure, Phosphorsäure, Methansulfonsäure, Ethansulfonsäure, Toluolsulfonsäure, Benzolsulfonsäure, Naphthalindisulfonsäure, Essigsäure, Propionsäure, Milchsäure, Weinsäure, Zitronensäure, Fumarsäure, Maleinsäure oder Benzoesäure.

Als Salze können weiterhin Salze mit üblichen Basen genannt werden, wie beispielsweise Alkalimetallsalze (z.B. Natrium- oder Kaliumsalze), Erdalkalisalze (z.B. Calcium- oder Magnesiumsalze) oder Ammoniumsalze, abgeleitet von Ammoniak oder organischen Aminen wie beispielsweise Diethylamin, Triethylamin, Ethyldiisopropylamin, Prokain, Dibenzylamin, N-Methylmorpholin, Dihydroabietylamin, 1-Ephenamin oder Methyl-piperidin.

Als Salze können außerdem Reaktionsprodukte mit $C_1$-$C_4$-Alkylhalogeniden, insbesondere $C_1$-$C_4$-Alkyljodiden fungieren.

Hydroxyschutzgruppe im Rahmen der oben angegebenen Definition steht im allgemeinen für eine Schutzgruppe aus der Reihe: Trimethylsilyl, Triisopropylsilyl, tert.Butyl-dimethylsilyl, Benzyl, Benzyloxycarbonyl, 2-Nitrobenzyl, 4-Nitrobenzyl, tert. Butyloxycarbonyl, Allyloxycarbonyl, 4-Methoxybenzyl, 4-Methoxybenzyloxycarbonyl, Tetrahydropyranyl, Formyl, Acetyl, Trichloracetyl, 2,2,2-Trichlorethoxycarbonyl, Methoxyethoxymethyl, [2-(Trimethylsilyl)ethoxy]methyl, Benzoyl, 4-Methylbenzoyl, 4-Nitrobenzoyl, 4-Fluorbenzoyl, 4-Chlorbenzoyl oder 4-Methoxybenzoyl. Bevorzugt sind Acetyl, tert. Butyldimethylsilyl und Tetrahydropyranyl.

Aminoschutzgruppen im Rahmen der Erfindung sind die üblichen in der Peptid-Chemie verwendeten Aminoschutzgruppen.

Hierzu gehören bevorzugt: Benzyloxycarbonyl, 2,4-Dimethoxybenzyloxycarbonyl, 4-Methoxybenzyloxycarbonyl, Methoxycarbonyl, Ethoxycarbonyl, tert.Butoxycarbonyl, Allyloxycarbonyl, Phthaloyl, 2,2,2-Trichlorethoxycarbonyl, Fluorenyl-9-methoxycarbonyl, Formyl, Acetyl, 2-Chloracetyl, 2,2,2-Trifluoracetyl, 2,2,2-Trichloracetyl, Benzoyl, 4-Chlorbenzoyl, 4-Brombenzoyl, 4-Nitrobenzoyl, Phthalimido, Isovaleroyl oder Benzyloxymethylen, 4-Nitrobenzyl, 2,4-Dinitrobenzyl, 4-Nitrophenyl, 4-Methoxyphenyl oder Triphenylmethyl.

Die erfindungsgemäßen Verbindungen können in stereoisomeren Formen, die sich entweder wie Bild und Spiegelbild (Enantiomere), oder die sich nicht wie Bild und Spiegelbild (Diastereomere) verhalten, existieren. Die Erfindung betrifft sowohl die Enantiomeren oder Diastereomeren oder deren jeweiligen Mischungen. Die Racemformen lassen sich ebenso wie die Diastereomeren in bekannter Weise in die stereoisomer einheitlichen Bestandteile trennen.

Bevorzugt sind Verbindungen der allgemeinen Formel (I),
in welcher

| | |
|---|---|
| A | für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2$-Gruppe steht, und |
| D, E, G und L | gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin |
| $R^2$ | Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen, Fluor, Chlor oder Brom bedeutet, |
| $R^1$ | für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin |
| $R^{10}$ | geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet, |
| $R^{11}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen, Phenyl oder Tolyl bedeutet, |
| $R^{12}$ und $R^{1}$ | $^3$ gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten, oder |
| $R^{12}$ oder $R^{13}$ | eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet, worin |
| $R^{14}$ und $R^{14'}$ | gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten, oder |
| $R^{14}$ und $R^{14'}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeuten, oder eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten, worin |
| $R^{18}$ und $R^{19}$ | gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, oder Isoxazolyl, Furyl, Thienyl, Pyrryl, Oxazolyl oder Imidazolyl bedeuten, |
| $R^{15}$ und $R^{16}$ | gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten, |
| $R^{17}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet |

und deren Salze.

Besonders bevorzugt sind Verbindungen der allgemeinen Formel (I), in welcher

| | |
|---|---|
| A | für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2$-Gruppe steht, und |
| D, E, G und L | gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin |
| $R^2$ | Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Fluor bedeutet, |

$R^1$ für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin

$R^{10}$ geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet,

$R^{11}$ Methyl, Ethyl, Phenyl oder Toluolyl bedeutet,

$R^{12}$ und $R^{13}$ gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 5 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten,
oder

$R^{12}$ oder $R^{13}$ eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2R^{17}$ bedeutet, worin

$R^{14}$ und $R^{14'}$ gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluorethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten,
oder

$R^{14}$ und $R^{14'}$ geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 4 Kohlenstoffatomen bedeuten, oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

$R^{18}$ und $R^{19}$ gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten, oder
Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeuten,

$R^{15}$ und $R^{16}$ gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

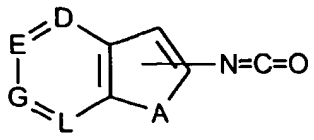
$R^{17}$ Methyl oder Phenyl bedeutet

und deren Salze.

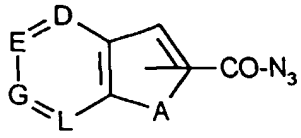
Ganz besonders bevorzugt sind die erfindungsgemäßen Verbindungen der allgemeinen Formel (I), in welcher
der Oxazolidinonrest in der Position 2 am 5-Ring-Heterocyclus angebunden ist.

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

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




(II) oder

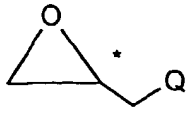



(III)

in welchen

A, D, E, G und L die oben angegebene Bedeutungen haben,

mit Lithiumbromid/$(C_4H_9)_3P(O)$ und Epoxiden der allgemeinen Formel (IV)



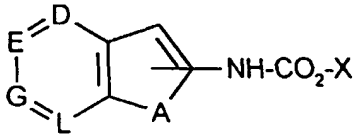

(IV)

in welcher

Q für $C_1$-$C_6$-Acyloxy steht,

in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base
umsetzt,
und im Fall $R^1$ = OH durch eine typische Esterverseifung oder durch eine typische Umesterung die Hydroxyfunktion freisetzt,
oder

[B] Verbindungen der allgemeinen Formel (V)




(V)

in welcher

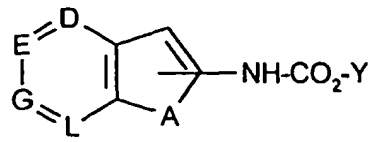
A, D, E, G und L die oben angegebene Bedeutung haben
und

X für eine typische Schutzgruppe, vorzugsweise Benzyl steht,

in inerten Lösemitteln und in Anwesenheit einer Base, beispielsweise Lithiumalkylen oder Lithium-N-alkyl- oder Lithium-N-silylalkylamiden, vorzugsweise N-Butyllithium, mit Epoxiden der allgemeinen Formel (IV) umsetzt,

oder

[C] im Fall $R^1$ = OH, zunächst Verbindungen der allgemeinen Formel (III) durch Abspaltung von Stickstoff in Alkoholen in die Verbindungen der allgemeinen Formel (Va)




(Va)

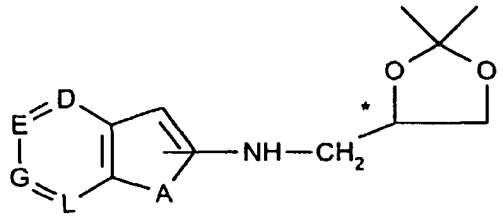
in welcher

A, D, E, G und L die oben angegebene Bedeutung haben
und

Y für geradkettiges oder verzweigtes $C_2$-$C_6$-Alkyl, vorzugsweise n-Butyl steht,

überführt,
und in einem zweiten Schritt wie unter [A] beschrieben in inerten Lösemitteln und in Anwesenheit einer Base, vorzugsweise Lithium-N-alkyl- oder N-Silylalkylamiden oder n-Butyllithium mit Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

[D] Verbindungen der allgemeinen Formel (VI)

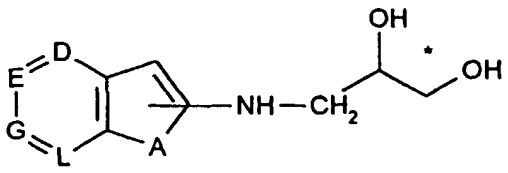



(VI)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

entweder direkt mit Säuren und Kohlensäurediethylester
umsetzt,
oder zunächst durch Umsetzung der Verbindungen der allgemeinen Formel (VI) mit Säuren die Verbindungen der allgemeinen Formel (VII)



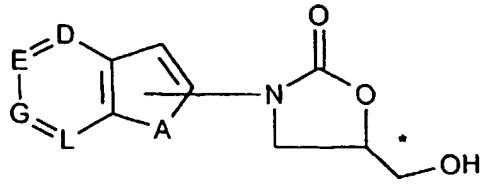

(VII)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert,
oder

[E] zunächst Verbindungen der allgemeinen Formel (Ia)

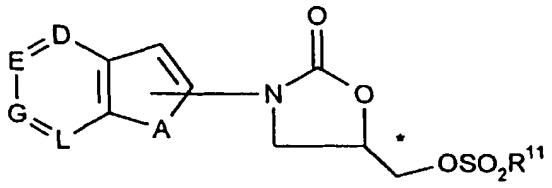


(Ia)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

durch Umsetzung mit ($C_1$-$C_4$)-Alkyl- oder Phenylsulfonsäurechloriden, die gegebenenfalls entsprechend substituiert sind, in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)

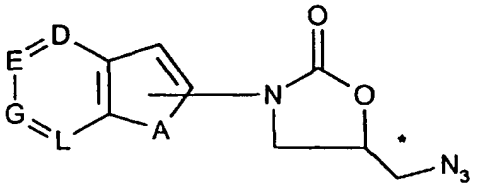


(Ib)

in welcher

A, D, E, G, L und $R^{11}$ die oben angegebene Bedeutung haben,

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



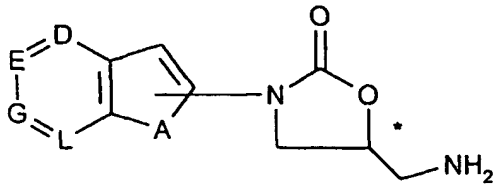
(Ic)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
in einem weiteren Schritt durch Umsetzung mit ($C_1$-$C_4$-O)$_3$-P oder $PPh_3$, vorzugsweise $(CH_3O)_3P$ in inerten Löse-

mitteln und mit Säuren in die Amine der allgemeinen Formel (Id)



(Id)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

überführt,
und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (VIII)

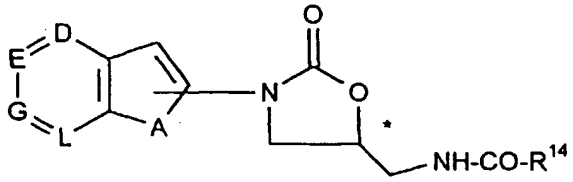
$$R^{20}\text{-}CO\text{-}R^{14} \qquad \text{(VIII)}$$

in welcher

$R^{14}$ die oben angegebene Bedeutung hat
und

$R^{20}$ für Halogen, vorzugsweise für Chlor oder für den Rest $-OCOR^{14}$ steht,

in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



(Ie)

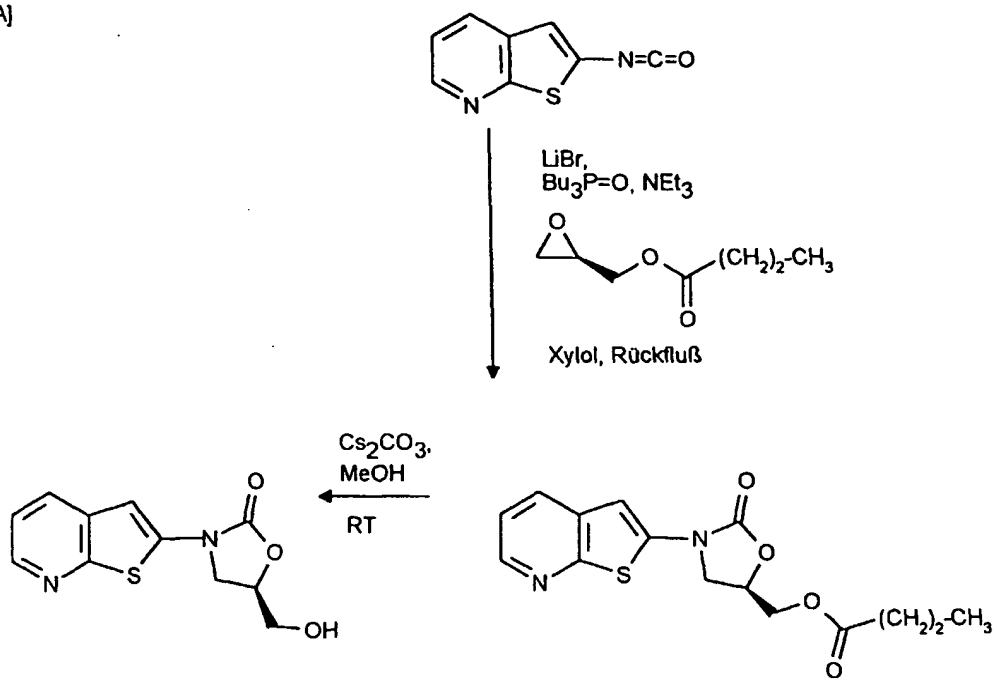
in welcher

A, D, E, G, L und $R^{14}$ die oben angegebene Bedeutung haben,

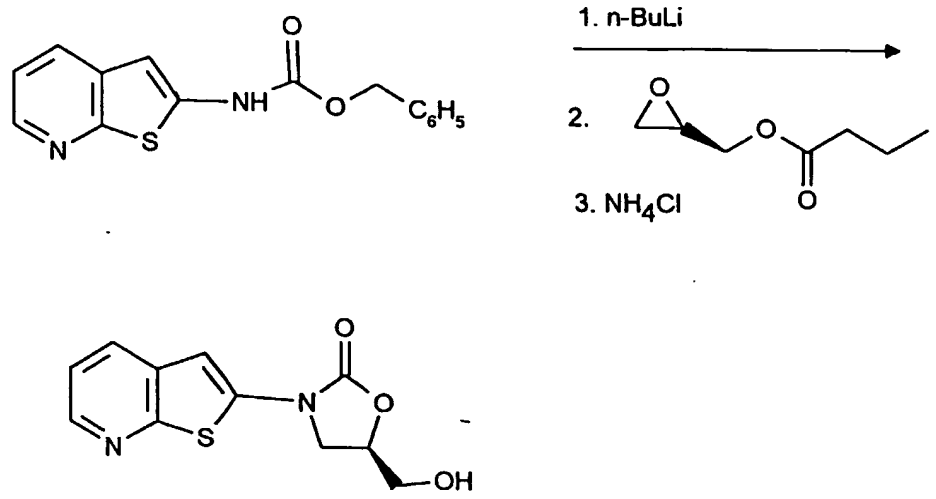
herstellt,
und im Fall $R^1 = NR^{12}\text{-}CS\text{-}R^{14'}$ Verbindungen der allgemeinen Formel (Id) mit Ethyldithiocarboxylaten und Triethylamin und im Fall $R^1 = NR^{12}\text{-}CS\text{-}NR^{18}R^{19}$ mit Thioisocyanaten umsetzt,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
und gegebenenfalls weitere Substituenten oder bereits vorhandene funktionelle Gruppen nach üblichen Methoden, wie beispielsweise Alkylierung, Redoxreaktionen, Substitutionsreaktionen und/oder Verseifungen oder Ein- und Abbau von Schutzgruppen, einführt bzw. derivatisiert.

Die erfindungsgemäßen Verfahren können durch folgende Formelschemata beispielhaft erläutert werden:

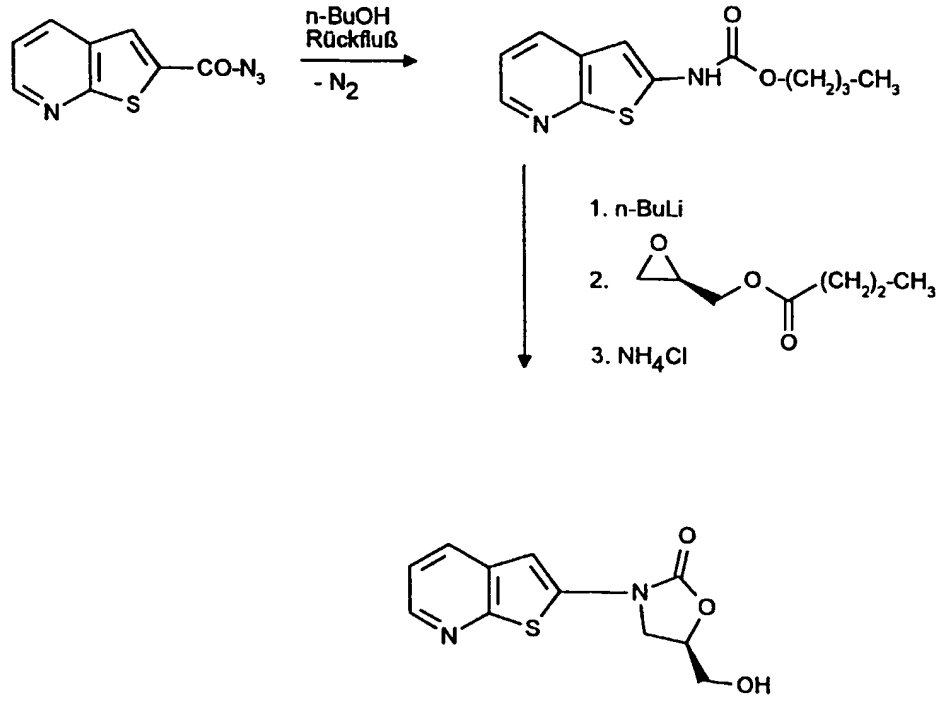
[A]


N=C=O
LiBr,
Bu3P=O, NEt3
(CH2)2-CH3
Xylol, Rückfluß
Cs2CO3,
MeOH
RT
OH

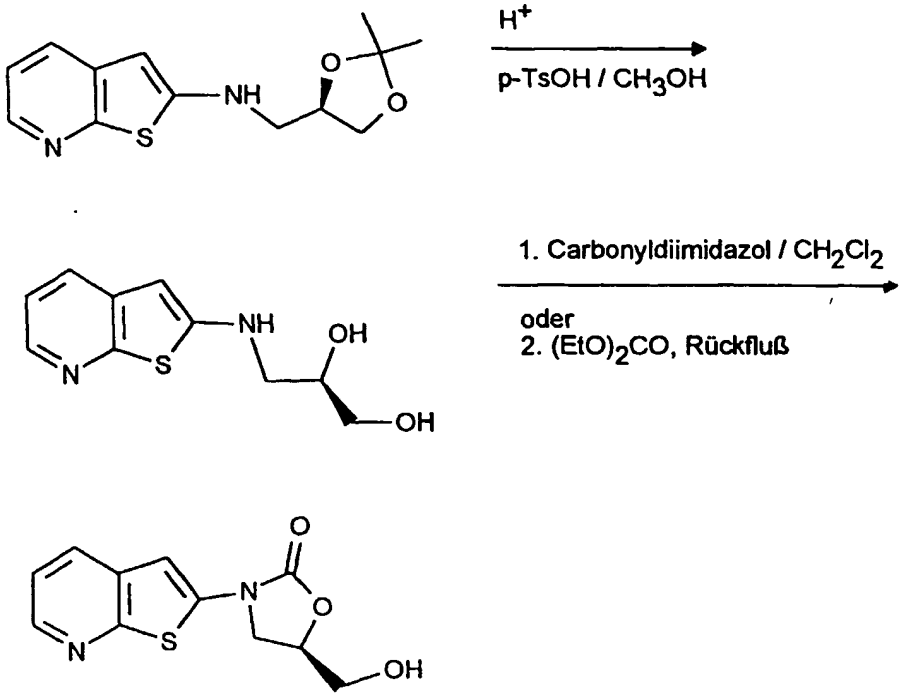
[B]



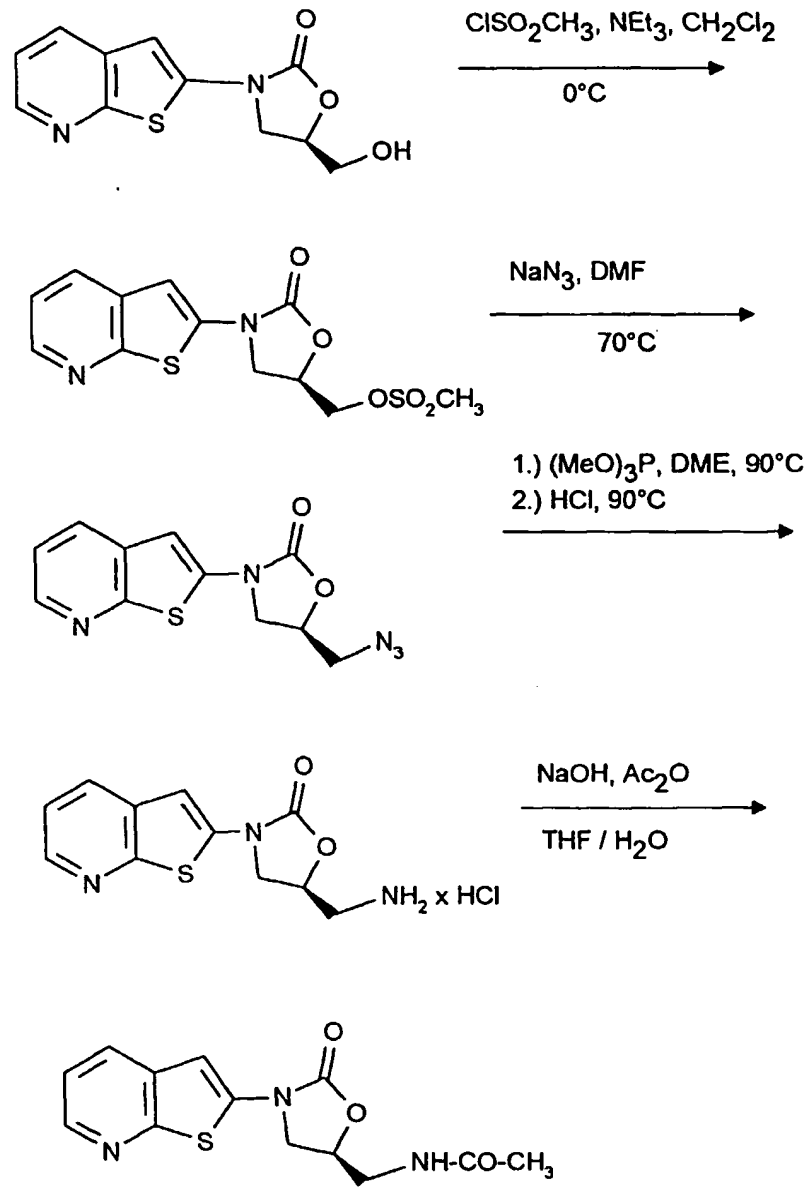

[C]



[D]


H+
p-TsOH / CH3OH
1. Carbonyldiimidazol / CH2Cl2
oder
2. (EtO)2CO, Rückfluß
NH
O
O
N
S
OH
OH
O
N
O
OH

[E]




Als Lösemittel eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether oder tert.Butylmethylether, oder Ketone wie Aceton oder Butanon, oder Amide wie Dimethylformamid oder Hexamethyl-phosphorsäuretriamid, oder Kohlenwasserstoffe wie Hexan, Benzol, Dichlorbenzol, Xylol oder Toluol, oder Dimethylsulfoxid, Acetonitril, Essigester, oder Halogenkohlenwasserstoffe wie Methylenchlorid, Chloroform oder Tetrachlorkohlenstoff, oder Pyridin, Picolin oder N-Methylpiperidin. Ebenso können Gemische der genannten Lösemittel verwendet werden.

Als Basen eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen anorganischen oder

organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natrium- oder Kaliummethanolat, oder Natrium- oder Kaliumethanolat, oder organische Amine wie Ethyldiisopropylamin, Triethylamin, Picolin, Pyridine oder N-Methylpiperidin, oder Amide wie Natriumamid oder Lithiumdiisopropylamid, oder Lithium-N-silylalkylamide, wie beispielsweise Lithium-N-(bis)triphenylsilylamid oder Lithiumalkyle wie n-Butyllithium.

Die Base wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 3 mol bezogen auf 1mol der Verbindungen der allgemeinen Formeln (II), (III), (IV) und (Va) eingesetzt.

Alle Umsetzungen werden im allgemeinen bei normalem, erhöhtem oder bei erniedrigtem Druck durchgeführt (z.B. 0,5 bis 5 bar). Im allgemeinen arbeitet man bei Normaldruck.

Das Verfahren [A] erfolgt bevorzugt in Xylol oder Dichlorbenzol, gegebenenfalls in Gegenwart von Triethylamin, unter Rückfluß.

Die basenkatalysierte Umesterung wird mit einem der oben aufgeführten Alkohole, vorzugsweise Methanol, in einem Temperaturbereich von -10°C bis +40°C, vorzugsweise bei Raumtemperatur durchgeführt.

Als Basen eignen sich im allgemeinen Natriumhydrogencarbonat, Natriummethanolat, Hydrazinhydrat, Kaliumcarbonat oder Caesiumcarbonat. Bevorzugt ist Caesiumcarbonat.

Das Verfahren [B] erfolgt in einem der oben aufgeführten Ether mit Lithiumalkylverbindungen oder Lithium-N-silylamiden, wie beispielsweise n-Butyllithium, Lithiumdiisopropylamid oder Lithium-bistrimethylsilylamid, vorzugsweise in Tetrahydrofuran und Lithium-bis-trimethylsilylamid oder n-Butyllithium, in einem Temperaturbereich von -100°C bis +20°C, vorzugsweise von -75°C bis -40°C.

Für das Verfahren [C] eignen sich für den 1. Schritt vorzugsweise die oben aufgeführten Alkohole, im Falle der anschließenden Cyclisierung Tetrahydrofuran.

Als Basen für die Cyclisierung eignen sich vorzugsweise die oben aufgeführten Lithium-N-silylalkylverbindungen oder n-Butyllithium. Besonders bevorzugt ist n-Butyllithium.

Der erste Reaktionsschritt wird bei der Siedetemperatur des entsprechenden Alkohols, die Cyclisierung in einem Temperaturbereich von -70°C bis Raumtemperatur durchgeführt.

Die Cyclisierung [D] wird in Anwesenheit eines Hilfsmittels und/oder Anwesenheit einer Säure durchgeführt.

Als Säuren eignen sich im allgemeinen anorganische Säuren wie beispielsweise Salzsäure oder Schwefelsäure, oder organische Carbonsäuren mit 1-6 C-Atomen, gegebenenfalls substituiert durch Fluor, Chlor und/oder Brom, wie beispielsweise Essigsäure, Trifluoressigsäure, Trichloressigsäure oder Propionsäure, oder Sulfonsäuren mit $C_1$-$C_4$-Alkylresten oder Arylresten wie beispielsweise Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure oder Toluolsulfonsäure. Besonders bevorzugt ist Salzsäure.

Die Säure wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 2 mol, bezogen auf 1 mol der Verbindungen der allgemeinen Formel (VI) eingesetzt.

Als Hilfsmittel eignen sich die üblichen Reagenzien wie Phosgen, Carbonyldiimidazol oder Kohlensäurediethylester oder Chlorameisensäuretrichlormethylester. Bevorzugt sind Carbonyldiimidazol, Kohlensäurediethylester und Chlorameisensäuretrichlormethylester.

Als Lösemittel eignen sich die oben aufgeführten Halogenkohlenwasserstoffe. Bevorzugt ist Methylenchlorid.

Die Cyclisierungen erfolgen im allgemeinen in einem Temperaturbereich von -20°C bis 100°C, vorzugsweise bei -20°C bis Raumtemperatur.

Die Acylierung [E] erfolgt im allgemeinen in einem der oben aufgeführten Ether oder Halogenkohlenwasserstoffen, vorzugsweise Tetrahydrofuran oder Methylenchlorid, in einem Temperaturbereich von -30°C bis 50°C, bevorzugt von -10°C bis Raumtemperatur.

Die Reduktionen erfolgen im allgemeinen mit Hydriden in inerten Lösemitteln oder mit Boranen, Diboranen oder ihren Komplexverbindungen.

Die Reduktionen können im allgemeinen durch Wasserstoff in Wasser oder in inerten organischen Lösemitteln wie Alkoholen, Ethern oder Halogenkohlenwasserstoffen, oder deren Gemischen, mit Katalysatoren wie Raney-Nickel, Palladium, Palladium auf Tierkohle oder Platin, oder mit Hydriden oder Boranen in inerten Lösemitteln, gegebenenfalls in Anwesenheit eines Katalysators durchgeführt werden.

Bevorzugt werden die Reduktionen mit Hydriden, wie komplexen Borhydriden oder Aluminiumhydriden sowie Boranen durchgeführt. Besonders bevorzugt werden hierbei Natriumborhydrid, Lithiumborhydrid, Natriumcyanoborhydrid, Lithiumaluminiumhydrid, Natrium-bis-(2-methoxyethoxy)aluminiumhydrid oder Boran-Tetrahydrofuran eingesetzt.

Die Reduktion der Azide [E] erfolgt mit $(CH_3O)_3P$ und Salzsäure.

Die Reduktion erfolgt im allgemeinen in einem Temperaturbereich von -50°C bis zum jeweiligen Siedepunkt des Lösemittels, bevorzugt von -20°C bis +90°C.

Als Lösemittel eignen sich hierbei alle inerten organischen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, Tetrahydrofuran, Glykoldimethylether, oder Diethylenglykoldimethylether oder Amide wie Hexamethylphosphorsäuretriamid oder Dimethylformamid, oder Essigsäure. Ebenso ist es möglich, Gemische der genannten Lösemittel zu verwenden.

Die Abspaltung der Hydroxyschutzgruppen erfolgt im allgemeinen nach üblicher Methode, beispielsweise durch hydrogenolytische Spaltung der Benzylether in den oben aufgeführten inerten Lösemitteln in Anwesenheit eines Katalysators mit Wasserstoff-Gas.

Die Abspaltung der Aminoschutzgruppe erfolgt im allgemeinen ebenfalls nach üblichen Methoden, und zwar wird vorzugsweise Boc mit Salzsäure in Dioxan, Fmoc mit Piperidin und Z mit HBr/HOAc oder durch Hydrogenolyse abgespalten.

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

Als Lösemittel für die Alkylierung eignen sich übliche organische Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Ether wie Diethylether, Dioxan, Tetrahydrofuran, Glykoldimethylether, oder Kohlenwasserstoffe wie Benzol, Toluol, Xylol, Hexan, Cyclohexan oder Erdölfraktionen, oder Halogenkohlenwasserstoffe wie Dichlormethan, Trichlormethan, Tetrachlormethan, Dichlorethylen, Trichlorethylen oder Chlorbenzol, oder Essigester, oder Triethylamin, Pyridin, Dimethylsulfoxid, Dimethylformamid, Acetonitril, Aceton oder Nitromethan. Ebenso ist es möglich, Gemische der genannten Lösemittel zu verwenden. Bevorzugt sind Dichlormethan, Dimethylsulfoxid und Dimethylformamid.

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

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

Als Lösemittel eignen sich hierbei inerte organische Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören Halogenkohlenwasserstoffe wie Dichlormethan, Trichlormethan, Tetrachlormethan, 1,2-Dichlorethan, Trichlorethan, Tetrachlorethan, 1,2-Dichlorethylen oder Trichlorethylen, Kohlenwassserstoffe wie Benzol, Xylol, Toluol, Hexan, Cyclohexan, oder Erdölfraktionen, Nitromethan, Dimethylformamid, Acetonitril oder Tetrahydrofuran. Ebenso ist es möglich, Gemische der Lösemittel einzusetzen. Besonders bevorzugt sind Dichlormethan und Tetrahydrofuran.

Als Basen für die Amidierung und die Sulfoamidierung eignen sich die üblichen basischen Verbindungen. Hierzu gehören vorzugsweise Alkali- und Erdalkalihydroxide wie Lithiumhydroxid, Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, Alkalihydride wie Natriumhydrid, Alkali- oder Erdalkalicarbonate wie Natriumcarbonat, Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natriummethanolat oder -ethanolat, Kaliummethanolat oder -ethanolat oder Kalium-tert.-buylat, oder organische Amine wie Benzyltrimethylammoniumhydroxid, Tetrabutylammoniumhydroxid, Pyridin, Triethylamin oder N-Methylpiperidin.

Die Amidierung und die Sulfoamidierung werden im allgemeinen in einem Temperaturbereich von 0°C bis 150°C, bevorzugt bei 25°C bis 40°C, durchgeführt.

Die Amidierung und die Sulfoamidierung werden im allgemeinen bei Normaldruck durchgeführt. Es ist aber auch möglich, das Verfahren bei Unterdruck oder bei Überdruck durchzuführen (z.B. in einem Bereich von 0,5 bis 5 bar).

Bei der Durchführung der Amidierung und der Sulfoamidierung wird die Base im allgemeinen in einer Menge von 1 bis 3 Mol, bevorzugt von 1 bis 1,5 Mol, bezogen auf 1 Mol der jeweiligen Carbonsäure, eingesetzt.

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

Als Basen eignen sich für die Verseifung die üblichen anorganischen Basen. Hierzu gehören bevorzugt Alkalihydroxide oder Erdalkalihydroxide wie beispielsweise Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat oder Natriumhydrogencarbonat. Besonders bevorzugt werden Natriumhydroxid oder Kaliumhydroxid eingesetzt.

Als Lösemittel eignen sich für die Verseifung Wasser oder die für eine Verseifung üblichen organischen Lösemittel. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol, Isopropanol oder Butanol, oder Ether wie Tetrahydrofuran oder Dioxan, oder Dimethylformamid oder Dimethylsulfoxid. Besonders bevorzugt werden Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol verwendet. Ebenso ist es möglich, Gemische der genannten Lösemittel einzusetzen.

Die Verseifung wird im allgemeinen in einem Temperaturbereich von 0°C bis +100°C, bevorzugt von +20°C bis +80°C durchgeführt.

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

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

tanden.

Die Veresterung erfolgt im allgemeinen mit den entsprechenden Alkoholen in Anwesenheit von Säuren, vorzugsweise Schwefelsäure, in einem Temperaturbereich von 0°C bis 150°C, vorzugsweise von 50°C bis 100°C und Normaldruck.

Die Verbindungen der allgemeinen Formeln (IV) und (VIII) sind bekannt oder können nach üblichen Methoden hergestellt werden.

Die Verbindungen der allgemeinen Formel (VII) sind größtenteils neu und können beispielsweise wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (II) sind teilweise bekannt oder neu und können dann beispielsweise hergestellt werden, indem man die entsprechenden Amine mit Chlorameisensäuretrichlormethylester in einem der oben aufgeführten Lösemittel, vorzugsweise Xylol bei Rückflußtemperatur umsetzt.

Die Verbindungen der allgemeinen Formel (III) sind teilweise bekannt oder neu und können dann beispielsweise hergestellt werden, indem man ausgehend von den entsprechenen Carbonsäuren entweder mit Chlorameisensäureisobutylester / Aceton, Natriumazid/Wasser oder mit Diphenylphosphorylazid / Tetrahydrofuran oder mit Xylol oder Methylenchlorid in Gegenwart einer der oben angegebenen Basen, vorzugsweise Triethylamin, bei -10°C bis Raumtemperatur umsetzt.

Die Verbindungen der allgemeinen Formel (V) und (Va) sind teilweise bekannt oder neu und können entweder durch Abspaltung von Stickstoff aus den entsprechenden Carbonsäureaziden und Umsetzung mit den entsprechenden Alkoholen oder durch Umsetzung der entsprechenden Amine mit Chlorameisensäureestern, vorzugsweise Chlorameisensäurebenzylester in einem der oben aufgeführten Lösemittel, vorzugsweise Tetrahydrofuran oder Dioxan, in einem Temperaturbereich von -10°C bis 200°C, vorzugsweise von 0°C bis 150°C, hergestellt werden.

Die Verbindungen der allgemeinen Formel (Ia) sind neu und können beispielsweise wie unter [A], [B], [D] oder [E] beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formeln (Ib), (Ic), (Id) und (Ie) sind neu und können wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (VI) sind größtenteils bekannt oder neu und können beispielsweise hergestellt werden, indem man ausgehend von den freien Aminen (Ia) entweder mit dem Acetonid von Glycerinaldehyd in Methanol und in Anwesenheit von Natriumacetat / Natriumcyanborhydrid oder von Natriumboranat und Methanol in einem Temperaturbereich von -20°C bis +40°C, bevorzugt von -10°C bis 20°C und Normaldruck umsetzt.

Die minimalen Hemmkonzentrationen (MHK) wurden per Reihenverdünnungsverfahren auf Iso-Sensitest Agar (Oxoid) bestimmt. Für jede Prüfungssubstanz wurde eine Reihe von Agarplatten hergestellt, die abfallende Konzentrationen des Wirkstoffes enthielten. Die Agarplatten wurden mit einem Multipoint-Inokulator (Denley) beimpft. Zum Beimpfen wurden Übernachtkulturen der Erreger verwandt, die zuvor so verdünnt wurden, daß jeder Impfpunkt ca. $10^4$ koloniebildende Partikel enthielt. Die beimpften Agarplatten wurden bei 37°C bebrütet, und das Keimwachstum wurde nach ca. 20 Stunden abgelesen. Der MHK-Wert (µg/ml) gibt die niedrigste Wirkstoffkonzentration an, bei der mit bloßem Auge kein Wachstum zu erkennen war.

| MHK-Werte (µg/ml): | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bsp.- Nr. | Staph. 133 | Staph. 48N | Staph. 25701 | Staph. 9TV | E. coli Neumann | Klebs. 57 USA | Psdm. Bonn |
| 12 | 2 | 2 | 2 | 2 | >64 | >64 | >64 |
| 13 | 8 | 8 | 8 | 8 | >64 | >64 | >64 |
| 16 | 4 | 4 | 4 | 4 | >64 | >64 | >64 |
| 18 | 4 | 4 | 2 | 2 | >64 | >64 | >64 |
| 19 | 1 | 1 | 1 | 0,25 | >64 | >64 | >64 |

Für schnellwachsende Mykobakterien wurde die MHK-Bestimmung in Anlehnung an die von Swenson beschriebene Methode der Bouillon-Mikrodilution durchgeführt [vgl. J.M. Swenson, C. Thornberry, U.A. Silcox, Rapidly growing mycobacteria. Testing of susceptibility to 34 antimicrobial agents by broth microdilution. Antimicrobial Agents and Chemotherapy Vol, 22, 186-192 (1982)]. Abweichend davon war das mit 0,1 Vol.% Tween 80 versetzte Hirn-Herzextrakt Medium.

Die verwendeten Mykobakterienstämme wurden von der DSM (Dt. Sammlung von Mikroorganismen, Braunschweig) bezogen. Sie wurden in einer feuchten Kammer bei 37°C bebrütet.

Die MHK-Werte wurden nach 2-4 Tagen abgelesen, wenn die präparatfreien Kontrollen durch Wachstum trüb waren. Der MHK-Wert definiert sich als die niedrigste Präparatkonzentration, die makroskopisch sichtbares Wachstum völlig inhibiert.

| MHK Werte (µg/ml): Mycobacterium smegmatis | | |
|---|---|---|
| Stamm: | DSM 43061 | DSM 43465 |
| Bsp.-Nr. | | |
| 13 | 16 | 8 |
| 19 | 32 | 16 |
| Isoniazid | 4 | 1 |
| Streptomycin | 4 | 4 |

Die erfindungsgemäßen Verbindungen der allgemeinen Formeln (I), (Ia), (Ib), (Ic), (Id) und (Ie) weisen bei geringer Toxizität ein breites antibakterielles Spektrum, speziell gegen gram-positive Bakterien, Haemophilus influenzae, anaerobe Keime und für schnellwachsende Mykobakterien auf. Diese Eigenschaften ermöglichen ihre Verwendung als chemotherapeutische Wirkstoffe in der Human- und Tiermedizin.

Besonders wirksam sind die erfindungsgemäßen Verbindungen gegen Bakterien und bakterienännliche Mikroorganismen wie Mycoplasmen. Sie sind daher besonders gut zur Prophylaxe und Chemotherapie von lokalen und systemischen Infektionen in der Human- und Tiermedizin geeignet, die durch solche Erreger hervorgerufen werden.

Zur vorliegenden Erfindung gehören pharmazeutische Zubereitungen, die neben nicht-toxischen, inerten pharmazeutisch geeigneten Trägerstoffen eine oder mehrere erfindungsgemäße Verbindungen enthalten oder die aus einem oder mehreren erfindungsgemäßen Wirkstoffen bestehen, sowie Verfahren zur Herstellung dieser Zubereitungen.

Der oder die Wirkstoffe können gegebenenfalls in einem oder mehreren der oben angegebenen Trägerstoffe auch in mikroverkapselter Form vorliegen.

Die therapeutisch wirksamen Verbindungen sollen in den oben aufgeführten pharmazeutischen Zubereitungen in einer Konzentration von etwa 0,1 bis 99,5, vorzugsweise von etwa 0,5 bis 95 Gew.-%, der Gesamtmischung vorhanden sein.

Die oben aufgeführten pharmazeutischen Zubereitungen können außer den erfindungsgemäßen Verbindungen auch weitere pharmazeutische Wirkstoffe enthalten.

Im allgemeinen hat es sich sowohl in der Human- als auch in der Veterinärmedizin als vorteilhaft erwiesen, den oder die erfindungsgemäßen Wirkstoffe in Gesamtmengen von etwa 0,5 bis etwa 500, vorzugsweise 5 bis 100 mg/kg Körpergewicht je 24 Stunden, gegebenenfalls in Form mehrerer Einzelgaben, zur Erzielung der gewünschten Ergebnisse zu verabreichen. Eine Einzelgabe enthält den oder die erfindungsgemäßen Wirkstoffe vorzugsweise in Mengen von etwa 1 bis etwa 80, insbesondere 3 bis 30mg/kg Körpergewicht.

Die erfindungsgemäßen Verbindungen können zum Zweck der Erweiterung des Wirkungsspektrums und um eine Wirkungssteigerung zu erreichen auch mit anderen Antibiotika kombiniert werden.

Anhang zum experimentellen Teil

Liste der verwendeten Laufmittelgemische zur Chromatographie:

I Dichlormethan : Methanol
II Toluol : Ethylacetat
III Acetonitril : Wasser
IV Ethylacetat
V Petrolether : Ethylacetat

Abkürzungen:

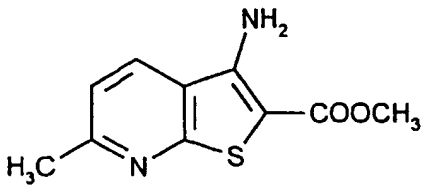
| | |
|---|---|
| Z | Benzyloxycarbonyl |
| Boc | tert.Butyloxycarbonyl |
| DMF | Dimethylformamid |

| | |
|---|---|
| Ph | Phenyl |
| Me | Methyl |
| THF | Tetrahydrofuran |
| CDI | Carbonyldiimidazol |
| DCE | Dichlorethan |

**Ausgangsverbindungen**

**Beispiel I**

3-Amino-6-methyl-thieno[2,3-b]pyridin-2-carbonsäuremethylester

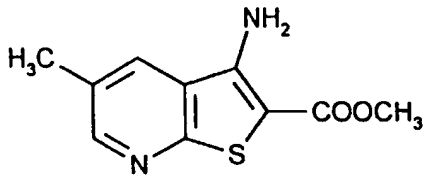


45 g (295 mmol)) 2-Chlor-6-methylpyridin-3-carbonitril werden in 180 ml DMSO gelöst, mit 90 ml (649 mmol) Triethylamin und 28 ml (310 mmol) Mercaptoessigsäuremethylester versetzt und 18 h bei 80°C verrührt. Man läßt auf Raumtemperatur kommen, kippt auf Eiswasser, saugt ab, wäscht den Rückstand mit Petrolether nach und trocknet 5 h im Umlufttrockenofen bei 60°C.

Ausbeute: 63 g (96%)
MS: 222 [$M^+$, 100%]
$^1$H-NMR ($D_6$-DMSO, TMS): 8,4 (d, J = 9 Hz, 1H); 7,83 (d, J = 9 Hz, 1H); 7,26 (s, 2H); 3,8 (s, 3H); 2,58 (s, 3H).

**Beispiel II**

3-Amino-5-methyl-thieno[2,3-b]pyridin-2-carbonsäuremethylester

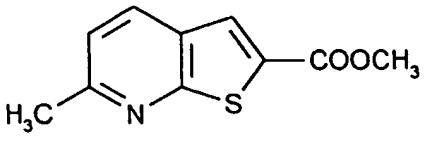


37,5 g (250 mmol) 2-Mercapto-3-cyano-5-methylpyridin werden in 175 ml DMSO gelöst und mit 76 ml (550 mmol) Triethylamin versetzt. Zu der so erhaltenen Lösung tropft man innerhalb von 5 min 22 ml (250 mmol) Chloressigsäuremethylester zu. Man verrührt 5 h bei 80°C, gibt auf Eiswasser, saugt vom ausgefallenen Feststoff ab, wäscht diesen mit Diethylether gut nach und trocknet im Umlufttrockenofen bei 50°C.

Ausbeute: 53,5 g (96%)
MS: 222 [$M^+$, 100%]
$^1$H-NMR ($D_6$-DMSO): 8,55 (s, 1H); 8,35 (s, 1H); 7,25 (s, 2H); 3,7 (s, 3H); 2,4 (s, 3H).

**Beispiel III**

6-Methyl-thieno[2,3-b]pyridin-2-carbonsäuremethylester

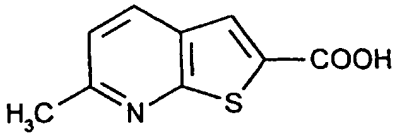


209 ml Wasser werden vorsichtig mit 628 ml $H_2SO_4$ konz. versetzt, auf 0°C gekühlt und mit 62 g (279 mmol) der Verbindung aus Beispiel I versetzt. Nun wird eine Lösung von 61,5 g (894 mmol) Natriumnitrit in 280 ml Wasser so zugetropft, daß die Innentemperatur der Reaktionslösung +5°C nicht übersteigt. Nach beendeter Zugabe wird 1 h bei 0°C nachgerührt. Die so erhaltene Reaktionslösung wird so in 1,675 l 50%ige Hypophosphorsäure eingetragen, daß die Innentemperatur nicht über +7°C ansteigt. Nach beendeter Zugabe läßt man 30 min bei 0°C nachrühren und hält über Nacht bei +4°C. Nun wird mit festem $NaHCO_3$ neutral gestellt (schäumt heftig) und vom ausgefallenen Feststoff abgesaugt. Der Rückstand wird in 2 l Aceton 10 min verrührt, abgesaugt und im Umlufttrockenofen bei 50°C getrocknet.

Ausbeute: 24,3 g (42%)
MS: 207 [$M^+$, 90%]
$^1$H-NMR ($D_6$-DMSO, TMS): 8,3 (d, J = 9 Hz, 1H); 8,15 (s, 1H); 7,4 (d, J = 9 Hz, 1H); 3,9 (d, 3H); 2,63 (s, 3H).

**Beispiel IV**

6-Methyl-thieno[2,3-b]pyridin-2-carbonsäure

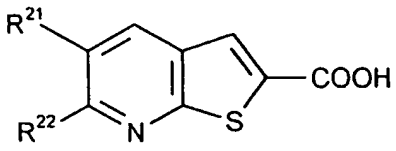


23 g (111 mmol) der Verbindung aus Beispiel III werden in 660 ml Ethanol gelöst, mit 93,5 g (1,66 mol) Kaliumhydroxid versetzt und 30 min am Rückfluß gekocht. Nach Abkühlen auf Raumtemperatur wird vom Niederschlag abgesaugt und dieser gut mit Ethanol nachgewaschen. Der Niederschlag wird in Wasser gelöst und mit Essigsäure auf pH 4 angesäuert. Von der ausgefallenen Säure wird abgesaugt, mit 2 l Petrolether nachgewaschen und im Umlufttrockenschrank bei 50°C getrocknet.

Ausbeute: 18,6 g (87%)
$^1$H-NMR ($D_6$-DMSO, TMS): 12,1 (s, 1H); 8,28 (d, J = 9 Hz, 1H); 8,05 (s, 1H); 7,39 (d, J = 9 Hz, 1H); 2,62 (s, 3H).

Analog den Vorschriften der Verbindungen I - IV werden die in der Tabelle I aufgeführten Verbindungen dargestellt:

Tabelle I

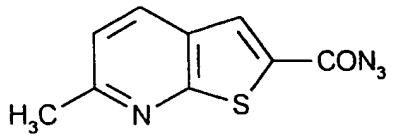


| Bsp.-Nr. | $R^{21}$ | $R^{22}$ | Ausbeute (%d.Th.) | MS | Smp. (°C) |
|---|---|---|---|---|---|
| V | $CH_3$ | H | 91 | - | 263 u.Z. |
| VI * | H | H | 86 | 180 $[M+H]^+$ | 312 u.Z. |

* S.W. Schneller, F.W. Clough, I.E. Hardee, J. Heterocycl. Chem. (1976) 273-5

**Beispiel VII**

6-Methyl-thieno[2,3-b]pyridin-2-carbonsäureazid

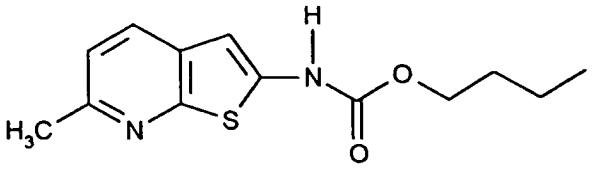


18 g (93,2 mmol) der Verbindung aus Beispiel IV werden in 180 ml Aceton gelöst und mit 15,4 ml (110 mmol) Triethylamin versetzt. Diese Reaktionsmischung wird auf -15°C gekühlt und langsam mit einer Lösung von 15,4 ml (121 mmol) Chlorameisensäureisobutylester in 77 ml Aceton versetzt, so daß die Innentemperatur -5°C nicht übersteigt. Man rührt 2 h bei -10°C nach und tropft eine Lösung von 9 g (140 mmol) Natriumazid in Wasser zu, rührt 2 h bei 0°C nach, kippt auf 2,5 l Eiswasser, saugt vom ausgefallenen Niederschlag ab, wäscht diesen mit Wasser gut nach und trocknet an der Luft.

Ausbeute: 18 g (89% d.Th.)

**Beispiel VIII**

2-Butyloxycarbonylamino-6-methyl-thieno[2,3-b]pyridin

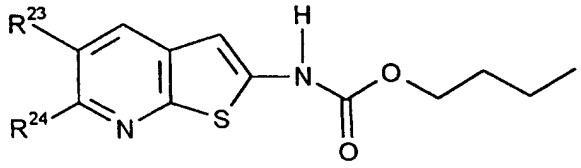


18 g (82 mmol) der Verbindung aus Beispiel VII werden portionsweise in 390 ml siedendes Butanol eingetragen. Nach beendeter Zugabe wird 10 min unter Rückfluß nachgerührt, auf Raumtemperatur abgekühlt, eingeengt, in Diethylether verrührt, abgesaugt und im Umlufttrockenofen bei 50°C getrocknet.

Ausbeute: 20,3 g (93%)
Smp.: 162°C
$^1$H-NMR ($D_6$-DMSO, TMS): 7,88 (d, J = 9 Hz, 1H); 7,24 (d, J = 9 Hz, 1H); 6,75 (s, 1H); 4,18 (t, J = 7 Hz, 2H); 2,53 (s, 3H); 1,65 (q, J = 7 Hz, 2H); 1,39 (h, J = 7 Hz, 2H); 0,93 (t, J = 7 Hz, 3H).

Analog den Vorschriften der Verbindungen VII und VIII werden die in der Tabelle II aufgeführten Verbindungen dargestellt:

**Tabelle II**

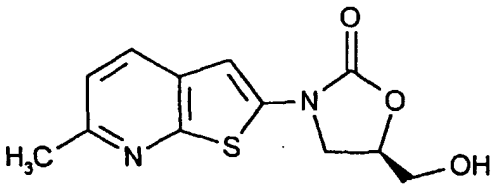


| Bsp.-Nr. | $R^{23}$ | $R^{24}$ | Ausbeute (% d.Th.) | Smp. (°C) |
|---|---|---|---|---|
| IX | $CH_3$ | H | 84 | 180 |
| X | H | H | 68 | 204 |

**Herstellungsbeispiele**

**Beispiel 1**

(5R)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-hydroxymethyl-oxazolidin-2-on

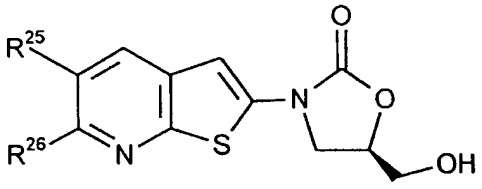


20,3 g (76,8 mmol) der Verbindung aus Beispiel VIII werden in 150 ml THF gelöst, mit 10 mg Benzylidenbenzylimin versetzt und auf -70°C gekühlt. Nun werden langsam ca. 31 ml 2,5 n-Butyllithium.-Lösung in Hexan bis zum Farbumschlag nach rot zugetropft. Anschließend werden 10,9 ml (76,8 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf Raumtemperatur kommen, versetzt mit gesättigter Ammoniumchlorid-Lösung, rührt 30 min bei Raumtemperatur nach und saugt vom ausgefallenen Niederschlag ab. Der Rückstand wird mit wenig Wasser und mit viel Diethylether gewaschen und im Umluftttrockenofen bei 50°C getrocknet.

Ausbeute: 19,7 g (97% d.Th.)
Smp.: 245°C u.Z.
$R_f$: 0,24 (I, 100:5)
MS: 265 [$(M+H)^+$, 100%]
$^1$H-NMR ($D_6$-DMSO, TMS): 7,95 (d, J = 9 Hz, 1H); 7,25 (d, J= 9 Hz, 1H); 6,69 (s, 1H); 5,3 (s, 1H); 4,8 - 4,96 (m, 1H); 4,18 (t, J = 9,5 Hz, 1H); 3,93 (dd, J = 9,5 Hz, 6,5 Hz, 1H); 3,55 - 3,8 (m, 2H); 2,55 (s, 3H).

Analog Verbindung 1 wurden die in der Tabelle 1 aufgeführten Verbindungen dargestellt:

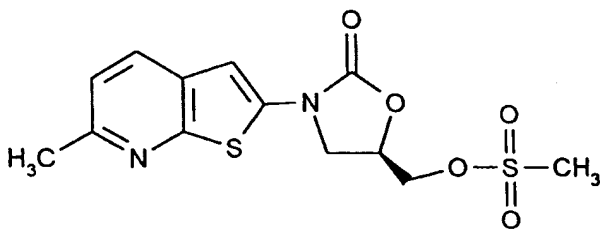
**Tabelle 1**



| Bsp.-Nr. | $R^{25}$ | $R^{26}$ | Ausbeute (% d.Th.) | MS | Smp. (°C) |
|---|---|---|---|---|---|
| 2 | $CH_3$ | H | 88 | - | 245 u.Z. |
| 3 | H | H | 98 | 251 $[M+H]^+$; 100% | 235 u.Z. |

**Beispiel 4**

(5R)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-methansulfonyloxymethyl-oxazolidin-2-on

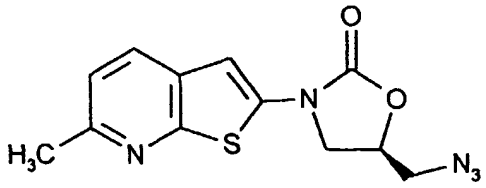


Eine Lösung von 18,8 g (71 mmol) der Verbindung aus Beispiel 1 in 290 ml Pyridin wird auf 0°C gekühlt und langsam mit 11 ml (142 mmol) Methansulfonsäurechlorid versetzt. Es wird 16 h bei 4°C gehalten und eingeengt. Der Rückstand wird in 5%iger Natriumhydrogencarbonatlösung verrührt, abgesaugt und mit Wasser und Diethylether nachgewaschen und im Umlufttrockenofen bei 50°C getrocknet.

Ausbeute: 23 g (95% d.Th.)
$R_f$ = 0,47 (I, 100:5)

**Beispiel 5**

(5R)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-azido-methyl-oxazolidin-2-on

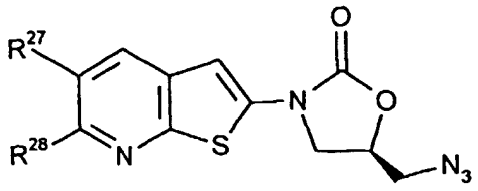


23 g (67,1 mmol) der Verbindung aus Beispiel 4 werden in 160 ml DMF gelöst und mit 4,8 g (74 mmol) Natriumazid versetzt. Die so erhaltene Reaktionsmischung wird 16 h bei 70°C verrührt. Man läßt auf Raumtemperatur abkühlen und kippt auf 2 l Eiswasser. Man saugt vom ausgefallenen Feststoff ab, wäscht mit Wasser und Petrolether nach und trocknet an der Luft.

Ausbeute: 17,9 g (92% d.Th.)
$R_f$: 0,31 (I, 100:2)
Smp.: 181°C u.Z.
MS: 290 [$(M+H)^+$; 100%]
$^1$H-NMR ($D_6$-DMSO, TMS): 7,96 (d, J ) 9 Hz, 1H); 7,75 (d, J = 9 Hz, 1H); 6,72 (s, 1H); 4,98 - 5,12 (m, 1H); 4,24 (t, J = 9,5 Hz, 1H); 3,78 - 3,9 (m, 3H); 2,55 (s, 3H).

Analog den Vorschriften der Beispiele 4 und 5 werden die in der Tabelle 2 aufgeführten Verbindungen dargestellt:

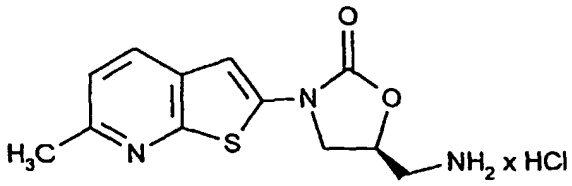
**Tabelle 2**



| Bsp.-Nr. | $R^{27}$ | $R^{28}$ | Ausbeute (% d.Th.) | MS | Smp. (°C) |
|---|---|---|---|---|---|
| 6 | $CH_3$ | H | 95 | 289 [$M^+$] | 204 u.Z. |
| 7 | H | H | 54 | - | 197 u.Z. |

**Beispiel 8**

(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-aminomethyl-oxazolidin-2-on Hydrochlorid

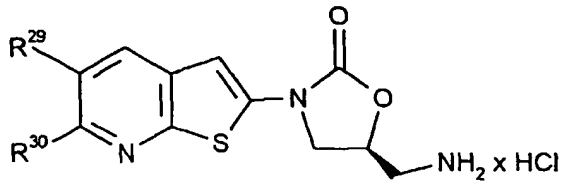


5 g (17,3 mmol) der Verbindung aus Beispiel 5 werden in 400 ml Ethanol gelöst, mit 500 mg 5%igem Palladium auf Aktivkohle versetzt und 16 h unter 3 bar Wasserstoffdruck hydriert. Man filtriert vom Katalysator ab, engt ein, nimmt in Methylenchlorid auf und versetzt langsam mit 5 ml 4,5 N HCl in Ether. Man rührt 1 h bei Raumtemperatur nach, saugt ab und wäscht mit Ether nach. Der Rückstand wird bei 40°C im Umlufttrockenofen getrocknet.

Ausbeute: 5,74 g (98% d.Th.)
$^1$H-NMR ($D_2O$): 8,3 (d, J = 9 Hz, 1H); 7,5 (d, J = 9 Hz, 1H); 6,78 (s, 1H); 5,11 - 5,27 (m, 1H); 4,37 (t, J = 9,5 Hz, 1H); 3,95 (dd, J = 9,5 Hz, J = 6,5 Hz, 1H); 3,30 - 3,5 (m, 2H); 2,65 (s, 3H).

Analog der Verbindung 8 werden die in der Tabelle 3 aufgeführten Verbindungen dargestellt:

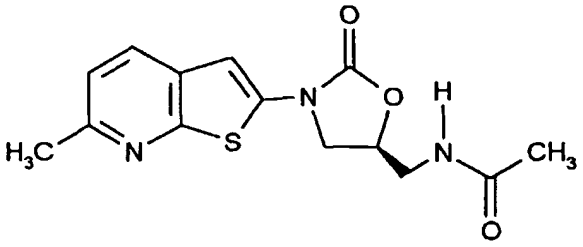
**Tabelle 3**




| Bsp.-Nr. | $R^{29}$ | $R^{30}$ | Ausbeute (% d.Th.) | MS | Smp. (°C) |
|---|---|---|---|---|---|
| 9 | $CH_3$ | H | 68 | 363 ($[M+H]^+$; 40%) | - |
| 10 | H | H | 81 | 249 ($[M^+]$; 60%) | 257 u.Z. |

**Beispiel 11**

(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-acetylaminomethyl-oxazolidin-2-on

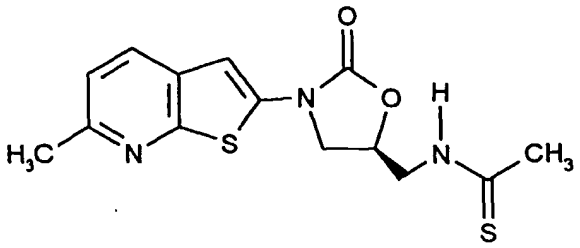



1,5 g (4,1 mmol) der Verbindung aus Beispiel 8 werden mit 1,14 ml (8,2 mmol) Triethylamin versetzt und in 8 ml Pyridin gelöst. Man kühlt die Reaktionslösung auf 0°C ab und tropft 0,73 ml (10,2 mmol) Acetylchlorid zu. Nach 4 Stunden bei 0°C wird mit 1 ml Methanol versetzt, eingeengt und an Kieselgel (Methlyenchlorid : Methanol = 100:3) chromatographiert.

Ausbeute: 0,84 g (67%)
Smp.: 215°C u.Z.
$R_f$: 0,44 (I; 10:1)
MS: 306 [$(M+H)^+$; 100%]
$^1$H-NMR ($D_6$-DMSO, TMS) 8,3 (t, J = 6,5 Hz, 1H); 7,95 (d, J= 9 H, 1H); 7,25 (d, J = 9 Hz, 1H); 6,68 (s, 1H); 4,83 - 4,98 (m, 1H); 4,2 (t, J = 9,5 Hz, 1H); 3,83 (dd, J = 9,5 Hz, J = 6,5 Hz, 1H); 3,47 (t, J = 6 Hz, 2H); 2,55 (s, 3H); 1,85 (s, 3H).

**Beispiel 12**

(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-thioacetylaminomethyl-oxazolidin-2-on

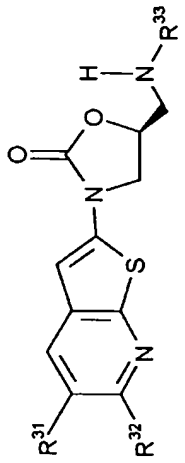


673 mg (2 mmol) der Verbindung aus Beispiel 8 werden in 4 ml THF gelöst, mit 0,61 ml (4,4 mmol) Triethylamin und 0,26 ml (2,2 mmol) Ethyldithioacetat versetzt und 18 h bei Raumtemperatur gerührt. Man engt ein und chromatographiert an Kieselgel (Methylenchlorid : Methanol = 100:1).

Ausbeute: 475 mg (74%)
Smp.: 202 u.Z.
$R_f$: 0,3 (I; 100:5)
MS: 321 ($M^+$, 20%)
$^1$H-NMR ($D_6$-DMSO, TMS): 10,45 (s, 1H); 7,95 (d, J = 9 Hz, 1H); 7,25 (d, J = 9 Hz, 1H); 6,68 (s, 1H); 5,05 - 5,2 (m, 1H); 4,25 (t, J = 9,5 Hz, 1H); 3,98 (t, J = 6,5 Hz, 2H); 3,9 (dd, J = 9,5 Hz, J = 6,5 Hz, 1H); 2,55 (s 3H); 2,43 (s, 3H).

Analog den Vorschriften der Beispiele 11 und 12 wurden die in Tabelle 4 aufgeführten Verbindungen dargestellt:

Tabelle 4

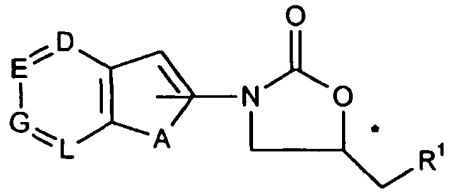


| Bsp.-Nr. | $R^{31}$ | $R^{32}$ | Acetylierungsmittel | $R^{33}$ | Equivalente $Et_3N$ | Ausbeute (% d.Th.) | MS | Smp. (°C) | $R_f$ (Laufmittelgemisch; Verhältnis) |
|---|---|---|---|---|---|---|---|---|---|
| 13 | $CH_3$ | H | $CH_3COCl$ |  | 2,3 | 46 | 306 $[M+H]^+$; 100% | 221 u.Z. | 0,23 [I; 100:5] |
| 14 | H | H | $CH_3COCl$ |  | 2,3 | 45 | 291 $[M]^+$; 100% | 220 u.Z. | 0,25 [I; 100:5] |
| 15 | H | H | $CH_3NCS$ |  | 3 | 54 | 323 $[M+H]^+$; 10% | 148 u.Z. | 0,25 [I; 100:5] |
| 16 | H | H | $CH_3CSSCH_2CH_3$ |  | 2 | 66 | 308 $M+H]^+$; 50% | 190 u.Z. | 0,30 [I; 100:5] |
| 17 | H | $CH_3$ | $CH_3NCS$ |  | 3 | 70 | 337 $[M+H]^+$; 10% | 178 u.Z. | 0,14 [I: 100:5] |

| Bsp.-Nr. | $R^{31}$ | $R^{32}$ | Acetylierungsmittel | $R^{33}$ | Equivalente $Et_3N$ | Ausbeute (% d.Th.) | MS | Smp. (°C) | $R_f$ (Laufmittelgemisch; Verhältnis) |
|---|---|---|---|---|---|---|---|---|---|
| 18 | $CH_3$ | H | $CH_3NCS$ | $CH_3NH-\overset{S}{\overset{\|}{C}}-$ | 3 | 40 | 337 $[M+H]^+$; 30% | 167 u.Z. | 0,27 [I; 100:5] |
| 19 | $CH_3$ | H | $CH_3CSSCH_2CH_3$ | $CH_3-\overset{S}{\overset{\|}{C}}-$ | 2 | 39 | 321 $[M]^+$, 10% | 186 u.Z. | 0,37 [I; 100:5] |
| 20 | H | $CH_3$ | $CH_2CH_2COCl$ | $CH_3CH_2-\overset{O}{\overset{\|}{C}}-$ | 3 | 25 | 320 $[M+H]^+$ 100% | 222 u.Z. | 0,26 (I; 100:5) |
| 21 | H | $CH_3$ |  |  | 3 | 46 | 322 $[M+H]^+$ 100% | 228 u.Z. | 0,26 (I; 100:5) |
| 22 | H | $CH_3$ |  |  | 3 | 47 | 322 $[M+H]^+$ 100% | 227 u.Z. | 0,34 (I; 100:5) |

**Patentansprüche**

1. Verbindungen der allgemeinen Formel (I)



(I)

in welcher

| | |
|---|---|
| A | für ein Sauerstoff- oder Schwefelatom oder für die $SO_2$-Gruppe steht, und |
| D, E, G und L | gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen, worin |
| $R^2$ | Wasserstoff, Cyano, Nitro, Carboxyl, geradkettiges oder verzweigtes Alkyl, Acyl oder Alkoxy mit jeweils bis zu 7 Kohlenstoffatomen, Halogen oder eine Gruppe der Formel $-NR^3R^4$, $-CO-NR^5R^6$, $-NR^7-CO-R^8$ oder $-S(O)_aR^9$ bedeutet, worin |
| $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ und $R^8$ | gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, |
| a | eine Zahl 0, 1 oder 2 bedeutet, |
| $R^9$ | Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet, |
| $R^1$ | für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht, worin |
| $R^{10}$ | geradkettiges oder verzweigtes Acyl mit bis zu 8 Kohlenstoffatomen oder eine Hydroxyschutzgruppe bedeutet, |
| $R^{11}$ | geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet, das gegebenenfalls durch geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen substituiert ist, |
| $R^{12}$ und $R^{13}$ | gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 8 Kohlenstoffatomen oder eine Aminoschutzgruppe bedeuten, oder |
| $R^{12}$ oder $R^{13}$ | eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet, worin |
| $R^{14}$ und $R^{14'}$ | gleich oder verschieden sind und Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Trifluormethyl, geradkettiges oder verzweigtes Alkoxy mit bis zu 8 Kohlenstoffatomen, Phenyl, |

Benzyloxy oder Wasserstoff bedeuten, oder

$R^{14}$ und $R^{14'}$ geradkettiges oder verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Halogen oder Trifluormethyl substituiert ist,
oder
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen bedeuten,
oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

$R^{18}$ und $R^{19}$ gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
oder
einen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O bedeuten,

$R^{15}$ und $R^{16}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,

$R^{17}$ geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeutet

als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

2. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher

A für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2$-Gruppe steht,
und

D, E, G und L gleich oder verschieden sind und mindestens einer dieser Substituenten für ein Stickstoffatom steht und die übrigen für einen Rest der Formel $-CR^2$ stehen,
worin

$R^2$ Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen, Fluor, Chlor oder Brom bedeutet,

$R^1$ für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht,
worin

$R^{10}$ geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,

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

$R^{12}$ und $R^{13}$ gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten,
oder

$R^{12}$ oder $R^{13}$ eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2-R^{17}$ bedeutet,
worin

$R^{14}$ und $R^{14'}$ gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluormethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten, oder

$R^{14}$ und $R^{14'}$ geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder

geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 5 Kohlenstoffatomen bedeuten, oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

$R^{18}$ und $R^{19}$ gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten, oder
oder
Isoxazolyl, Furyl, Thienyl, Pyrryl, Oxazolyl oder Imidazolyl bedeuten,

$R^{15}$ und $R^{16}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,

$R^{17}$ geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Phenyl bedeutet

als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

3. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher

A für ein Sauerstoff- oder Schwefelatom oder für die $-SO_2$-Gruppe steht,
und

D, E, G und L gleich oder verschieden sind und für mindestens ein Stickstoffatom oder für den Rest der Formel $-CR^2$ stehen,
worin

$R^2$ Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Fluor bedeutet,

$R^1$ für Azido, Hydroxy oder für eine Gruppe der Formel $-OR^{10}$, $O-SO_2R^{11}$ oder $-NR^{12}R^{13}$ steht,
worin

$R^{10}$ geradkettiges oder verzweigtes Acyl mit bis zu 5 Kohlenstoffatomen oder Benzyl bedeutet,

$R^{11}$ Methyl, Ethyl, Phenyl oder Tolyl bedeutet,

$R^{12}$ und $R^{13}$ gleich oder verschieden sind und Cyclopropyl, Cyclopentyl, Cyclohexyl, Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl oder Alkoxy mit jeweils bis zu 5 Kohlenstoffatomen, tert.Butoxycarbonyl oder Benzyloxycarbonyl bedeuten,
oder

$R^{12}$ oder $R^{13}$ eine Gruppe der Formel $-CO-R^{14}$, $-CS-R^{14'}$, $P(O)(OR^{15})(OR^{16})$ oder $-SO_2R^{17}$ bedeutet,
worin

$R^{14}$ und $R^{14'}$ gleich oder verschieden sind und Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Trifluorethyl oder geradkettiges oder verzweigtes Alkoxy mit bis zu 5 Kohlenstoffatomen, Phenyl, Benzyloxy oder Wasserstoff bedeuten,
oder

$R^{14}$ und $R^{14'}$ geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Fluor, Chlor, Brom oder Trifluormethyl substituiert ist, oder
geradkettiges oder verzweigtes Thioalkyl oder Acyl mit jeweils bis zu 4 Kohlenstoffatomen bedeuten, oder
eine Gruppe der Formel $-NR^{18}R^{19}$ bedeuten,
worin

$R^{18}$ und $R^{19}$ gleich oder verschieden sind und Wasserstoff, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten, oder Isoxazolyl, Furyl, Oxazolyl oder Imidazolyl bedeu-

ten,

$R^{15}$ und $R^{16}$ gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,

$R^{17}$ Methyl oder Phenyl bedeutet

als reine Stereoisomeren oder als Stereoisomerengemisch,
und deren Salze.

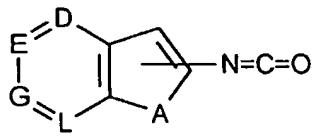
4. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, in welcher der Oxazolidinonrest in der Position 2 am 5-Ring-Heterocyclus angebunden ist, als reine Stereoisomere oder als Stereoisomerengemisch, und deren Salze.

5. Verbindungen gemäß Anspruch 1, ausgewählt aus der Gruppe

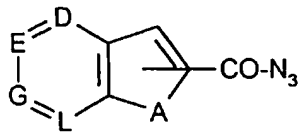
(5S)-3-[6-Methyl-pyrido[2,3-b]thienyl]-5-thioacetylaminomethyl-oxazolidin-2-on,
(5S)-3-[5-Methyl-pyrido[2,3-b]thienyl]-5-acetylaminomethyl-oxazolidin-2-on,
(5S)-3-[Pyrido[2,3-b]thien-2-yl]-5-thioacetyl-aminomethyl-oxazolidin-2-on, 1-Methyl-3-(2-oxo-3-[5-(5S)-methyl-thieno-[2,3-b]pyridin-2-yl]-oxazolidin-5-ylmethyl)-thioharnstoff und
(5S)-3-[5-Methyl-pyrido[2,3-b]-thienyl]-5-thioacetylaminomethyl-oxazolidin-2-on.

6. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, dadurch gekennzeichnet, daß man

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




(II) oder

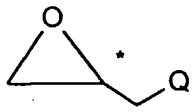



(III)

in welchen

A, D, E, G und L die in Anspruch 1 angegebenen Bedeutungen haben,

mit Lithiumbromid/$(C_4H_9)_3$ P(O) und Epoxiden der allgemeinen Formel (IV)




(IV)

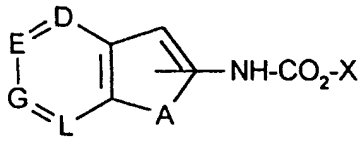
in welcher

Q für $C_1$-$C_6$-Acyloxy steht,

in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base

umsetzt,
und im Fall $R^1$ = OH durch eine typische Esterverseifung oder durch eine typische Umesterung die Hydroxyfunktion freisetzt,
oder

[B] Verbindungen der allgemeinen Formel (V)




(V)

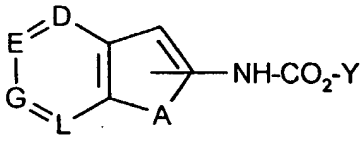
in welcher

A, D, E, G und L die oben angegebene Bedeutung haben
und

X für eine typische Schutzgruppe steht,

in inerten Lösemitteln und in Anwesenheit einer Base mit Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

[C] im Fall $R^1$ = OH, zunächst Verbindungen der allgemeinen Formel (III) durch Abspaltung von Stickstoff in Alkoholen in die Verbindungen der allgemeinen Formel (Va)




(Va)

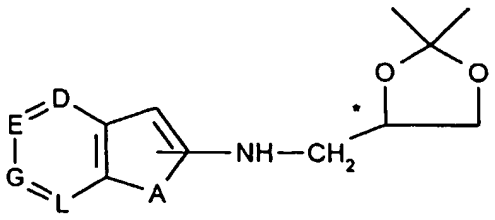
in welcher

A, D, E, G und L die oben angegebene Bedeutung haben
und

Y für geradkettiges oder verzweigtes $C_2$-$C_6$-Alkyl steht,

überführt,
und in einem zweiten Schritt wie unter [A] beschrieben in inerten Lösemitteln und in Anwesenheit einer Base mit Epoxiden der allgemeinen Formel (IV) umsetzt,
oder

[D] Verbindungen der allgemeinen Formel (VI)

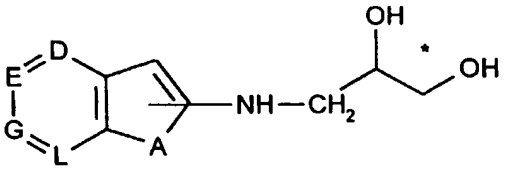


(VI)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

entweder direkt mit Säuren und Kohlensäurediethylester umsetzt,
oder zunächst durch Umsetzung der Verbindungen der allgemeinen Formel (VI) mit Säuren die Verbindungen der allgemeinen Formel (VII)



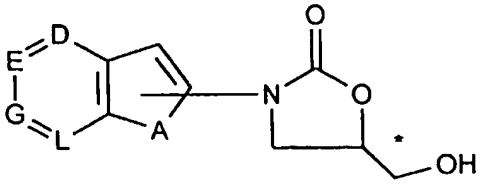
(VII)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
und anschließend in Anwesenheit eines Hilfsmittels in inerten Lösemitteln cyclisiert,
oder

[E] zunächst Verbindungen der allgemeinen Formel (Ia)

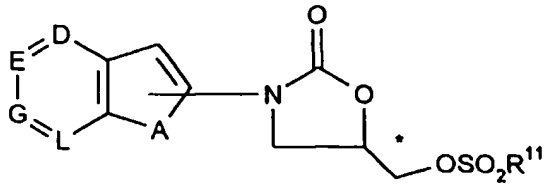


(Ia)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

durch Umsetzung mit ($C_1$-$C_4$)-Alkyl- oder Phenylsulfonsäurechloriden, die gegebenenfalls entsprechend substituiert sind, in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (Ib)



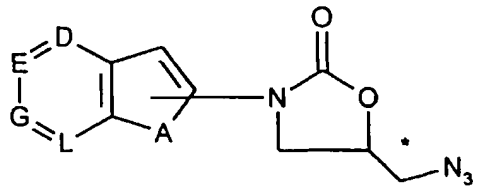
(Ib)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben und

$R^{11}$ die in Anspruch 1 angegebene Bedeutung hat,

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

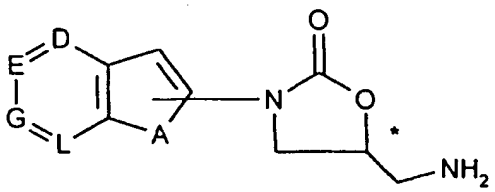


(Ic)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

herstellt,
in einem weiteren Schritt durch Umsetzung mit $(C_1\text{-}C_4\text{-}O)_3\text{-}P$ oder $PPh_3$ in inerten Lösemitteln und mit Säuren in die Amine der allgemeinen Formel (Id)



(Id)

in welcher

A, D, E, G und L die oben angegebene Bedeutung haben,

überführt,
und durch Umsetzung mit Acetanhydrid oder anderen Acylierungsmitteln der allgemeinen Formel (VIII)

$$R^{20}\text{-}CO\text{-}R^{14} \qquad \text{(VIII)}$$

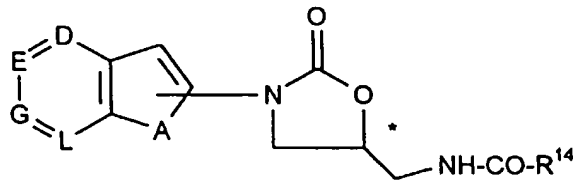
in welcher

$R^{14}$ die in Anspruch 1 angegebene Bedeutung hat

und

$R^{20}$ für Halogen oder für den Rest -OCOR$^{14}$ steht,

in inerten Lösemitteln die Verbindungen der allgemeinen Formel (Ie)



(Ie)

in welcher

A, D, E, G, L und $R^{14}$ die oben angegebene Bedeutung haben,

herstellt,
und im Fall $R^1$ = $NR^{12}$-CS-$R^{14'}$ Verbindungen der allgemeinen Formel (Id) mit Ethyldithiocarboxylaten und Triethylamin und im Fall $R^1$ = $NR^{12}$-CS-$NR^{18}R^{19}$ mit Thioisocyanaten umsetzt,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
und gegebenenfalls weitere Substituenten oder bereits vorhandene funktionelle Gruppen nach üblichen Methoden, wie beispielsweise Alkylierung, Redoxreaktionen, Substitutionsreaktionen und/oder Verseifungen oder Ein- und Abbau von Schutzgruppen, einführt bzw. derivatisiert,
und gegebenenfalls nach üblichen Methoden die Stereoisomeren trennt.

7. Verbindungen nach einem der Ansprüche 1 bis 5 zur Verwendung bei der Bekämpfung von Krankheiten.

8. Verwendung von Verbindungen nach einem der Ansprüche 1 bis 5 zur Herstellung von Arzneimitteln.

9. Arzneimittel enthaltend Verbindungen nach einem der Ansprüche 1 bis 5.

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

(11) EP 0 785 200 A3

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  **42115 Wuppertal (DE)**

## (54) Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone

(57) Die vorliegende Erfindung betrifft neue Pyrido-annellierte Thienyl- und Furanyl-Oxazolidinone, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

EP 0 785 200 A3

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Europäisches Patentamt

# EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung
EP 97 10 0025

## EINSCHLÄGIGE DOKUMENTE

| Kategorie | Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile | Betrifft Anspruch | KLASSIFIKATION DER ANMELDUNG (Int.Cl.6) |
|---|---|---|---|
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Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

| Recherchenort | Abschlußdatum der Recherche | Prüfer |
|---|---|---|
| BERLIN | 9. Dezember 1998 | Kyriakakou, G |

KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
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E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
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EPO FORM 1503 03.82 (P04C03)

## ANHANG ZUM EUROPÄISCHEN RECHERCHENBERICHT ÜBER DIE EUROPÄISCHE PATENTANMELDUNG NR. EP 97 10 0025

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten europäischen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

09-12-1998

| Im Recherchenbericht angeführtes Patentdokument | Datum der Veröffentlichung | Mitglied(er) der Patentfamilie | Datum der Veröffentlichung |
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EPO FORM P0461

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

## ANHANG ZUM EUROPÄISCHEN RECHERCHENBERICHT ÜBER DIE EUROPÄISCHE PATENTANMELDUNG NR. EP 97 10 0025

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten europäischen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

09-12-1998

| Im Recherchenbericht angeführtes Patentdokument | Datum der Veröffentlichung | Mitglied(er) der Patentfamilie | Datum der Veröffentlichung |
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EPO FORM P0461

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Offenlegungsschrift**

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(43) Offenlegungstag: 7. 8. 97

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C 07 D 413/14
C 07 D 417/14
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C 07 F 9/6584
A 61 K 31/42
A 61 K 31/425
A 61 K 31/44
A 61 K 31/50

DE 196 04 223 A1

// C07M 9:00 (C07D 413/14,263:20,213:24,333:36) (C07D 417/04,263:20,277:74)C07D 215/12,237/08,261/08,231/12, 235/24,307/79,521/00,471/04 (A61K 31/42,31:425,31:44,31:50)

(71) Anmelder:
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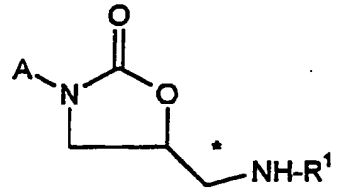
(72) Erfinder:
Riedl, Bernd, Dr., 42115 Wuppertal, DE; Häbich, Dieter, Dr., 42115 Wuppertal, DE; Stolle, Andreas, Dr., 42115 Wuppertal, DE; Ruppelt, Martin, Dr., 42115 Wuppertal, DE; Bartel, Stefan, Dr., 51465 Bergisch Gladbach, DE; Guarnieri, Walter, Dr., 53909 Zülpich, DE; Endermann, Rainer, Dr., 42113 Wuppertal, DE; Kroll, Hein-Peter, Dr., 42115 Wuppertal, DE

(54) **Neue substituierte Oxazolidinone**

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



(I)

in welcher die Substituenten die in der Beschreibung angegebene Bedeutung haben, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als antibakterielle Arzneimittel.

DE 196 04 223 A1

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

BUNDESDRUCKEREI 08. 97 702 032/432 32/30

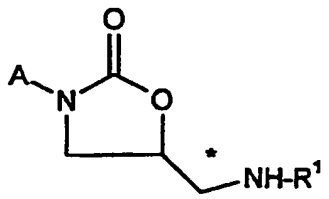
## Beschreibung

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

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

Ferner sind in der EP 609 491 und EP 657 440 Oxazolidinonderivate mit einer Monoaminoxidase inhibitorischen Wirkung und in der EP 645 376 mit Wirkung als Adhäsionsrezeptor-Antagonisten publiziert.

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



(I)

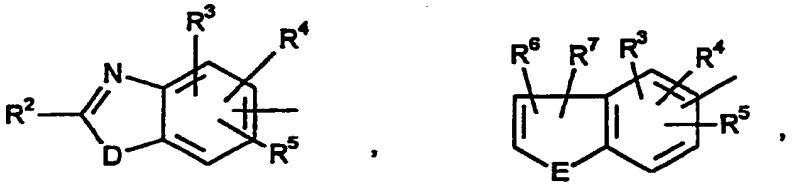
in welcher

A für einen über ein Kohlenstoffatom direkt gebundenen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der zusätzlich einen annellierten Benzol- oder Naphthylring besitzen kann, oder

für einen über ein Kohlenstoffatom direkt gebundenen 6-gliedrigen, aromatischen Heterocyclus mit mindestens einem Stickstoffatom steht, oder für einen über ein Kohlenstoffatom direkt gebundenen, jeweils 6-gliedrigen, bi- oder tricyclischen aromatischen Rest mit mindestens einem stickstoffhaltigen Ring steht, oder

für β-Carbolin-3-yl oder für über den 6-Ring direkt gebundenes Indolizinyl steht, wobei die Cyclen gegebenenfalls jeweils bis zu 3-fach gleich oder verschieden durch Carboxy, Halogen, Cyano, Mercapto, Formyl, Pyridyl, Phenyl, Trifluormethyl, Nitro, geradkettiges oder verzweigtes Alkoxy, Alkoxycarbonyl, Alkylthio oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen substituiert sind, die ihrerseits durch Phenyl substituiert sein können, oder

für einen Rest der Formel



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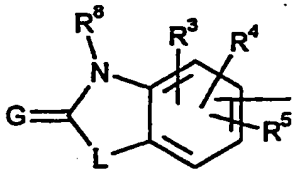

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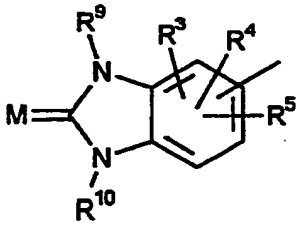

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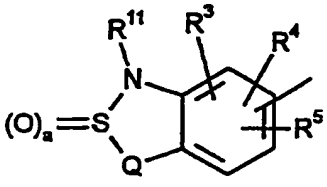

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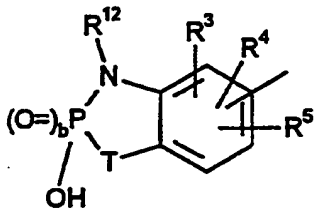
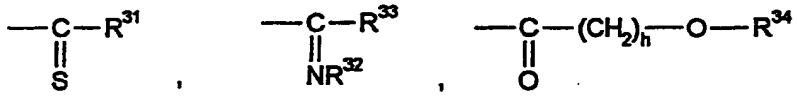


steht, worin

$R^3$, $R^4$, $R^5$, $R^6$ und $R^7$ gleich oder verschieden sind und Wasserstoff oder Carboxy, Halogen, Cyano, Formyl, Trifluormethyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder für eine Gruppe der Formel $-CO-NR^{13}R^{14}$ stehen,

worin
$R^{13}$ und $R^{14}$ gleich oder verschieden sind und Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeuten,
$R^2$, $R^8$, $R^9$, $R^{10}$, $R^{11}$ und $R^{12}$ gleich oder verschieden sind und Wasserstoff, Cycloalkylcarbonyl oder Cycloalkyl mit jeweils 3 bis 6 Kohlenstoffatomen, oder geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder geradkettiges oder verzweigtes Alkyl mit bis zu 10 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Trifluormethyl, Halogen, Phenyl, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen, Aryl mit 6 bis 10 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen und/oder durch eine Gruppe der Formel $-(CO)_c-NR^{15}R^{16}$, $R^{17}-N-SO_2-R^{18}$, $R^{19}R^{20}-N-SO_2-$ oder $R^{21}-S(O)_d$ substituiert ist,
worin
c eine Zahl 0 oder 1 bedeutet,
$R^{15}$, $R^{16}$ und $R^{17}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind, oder gemeinsam mit dem Stickstoffatom einen 5- bis 6-gliedrigen, gesättigten Heterocyclus mit gegebenenfalls einem weiteren Heteroatom aus der Serie N, S und/oder O bilden, der seinerseits gegebenenfalls, auch an einem weiteren Stickstoffatom, durch geradkettiges oder verzweigtes Alkyl oder Acyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,
$R^{19}$ und $R^{20}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
d eine Zahl 0, 1 oder 2 bedeutet,
$R^1$ und $R^{21}$ gleich oder verschieden sind und geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder
geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls Trifluormethyl, Trichlormethyl oder durch eine Gruppe der Formel $-OR^{22}$ substituiert ist,
worin
$R^{22}$ Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Aryl mit bis zu 10 Kohlenstoffatomen substituiert ist,
oder
eine Gruppe der Formel $(CO)_e-NR^{23}R^{24}$, $-NR^{25}-SO_2R^{26}$, $R^{27}R^{28}-NSO_2-$ oder $R^{29}-S(O)_f$ bedeuten,
worin
e die oben angegebene Bedeutung von c hat und mit dieser gleich oder verschieden ist,
$R^{23}$ und $R^{24}$ und $R^{25}$ jeweils die oben angegebene Bedeutung von $R^{15}$, $R^{16}$ und $R^{17}$ haben und mit dieser gleich oder verschieden sind,
$R^{27}$ und $R^{28}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
f die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist,
$R^{26}$ und $R^{29}$ die jeweils oben angegebene Bedeutungen von $R^{18}$ und $R^{21}$ haben und mit dieser gleich oder verschieden sind,
D ein Sauerstoffatom oder einen Rest der Formel $-S(O)_g$ bedeutet,
worin
g eine Zahl 0, 1 oder 2 bedeutet,
E und L gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom bedeuten,
G, M, T und Q gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom, oder eine Gruppe der Formel $-NR^{30}$ bedeuten,
worin
$R^{30}$ Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
a und b gleich oder verschieden sind und eine Zahl 1 oder 2 bedeuten,
$R^1$ für einen Rest der Formel



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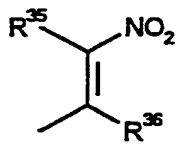


steht, worin
$R^{31}$ geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
$R^{38}$ und $R^{39}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
$R^{32}$ Wasserstoff, Cyano, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder geradkettiges oder verzweigtes

Alkyl mit bis zu 7 Kohlenstoffatomen bedeutet,
$R^{33}$ Wasserstoff geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Phenyl, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
$R^{40}$ und $R^{41}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
$R^{34}$ geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,
$R^{35}$ und $R^{36}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
oder
$R^1$ für Cyano oder für einen 5- bis 7-gliedrigen, gesättigten, partiell ungesättigten oder ungesättigten Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der gegebenenfalls auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Halogen oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen substituiert ist,
und deren Salze.

Physiologisch unbedenkliche Salze der substituierten Oxazolidinone können Salze der erfindungsgemäßen Stoffe mit Mineralsäuren, Carbonsäuren oder Sulfonsäuren sein. Besonders bevorzugt sind z. B. Salze mit Chlorwasserstoffsäure, Bromwasserstoffsäure, Schwefelsäure, Phosphorsäure, Methansulfonsäure, Ethansulfonsäure, Toluolsulfonsäure, Benzolsulfonsäure, Naphthalindisulfonsäure, Essigsäure, Propionsäure, Milchsäure, Weinsäure, Zitronensäure, Fumarsäure, Maleinsäure oder Benzoesäure.

Als Salze können Salze mit üblichen Basen genannt werden, wie beispielsweise Alkalimetallsalze (z. B. Natrium- oder Kaliumsalze), Erdalkalisalze (z. B. Calcium- oder Magnesiumsalze) oder Ammoniumsalze, abgeleitet von Ammoniak oder organischen Aminen wie beispielsweise Diethylamin, Triethylamin, Ethyldiisopropylamin, Prokain, Dibenzylamin, N-Methylmorpholin, Dihydroabiethylamin, 1-Ephenamin oder Methyl-piperidin.

Als Salze können außerdem Reaktionsprodukte mit $C_1-C_4$-Alkylhalogeniden, insbesondere mit $C_1-C_4$-Alkyljodide fungieren.

Heteroyclus steht im allgemeinen für einen 5- bis 6-gliedrigen, gesättigten oder ungesättigten Ring, der als Heteroatome bis zu 3 Sauerstoff-, Schwefel- und/oder Stickstoffatome enthalten kann. Bevorzugt werden genannt: Thienyl, Furyl, Pyrrolyl, Pyrazolyl, Pyridyl, Pyrimidyl, Pyrazinyl, Pyridazinyl, Thiazolyl, Oxazolyl, Imidazolyl, Pyrrolidinyl, Piperidinyl oder Piperazinyl.

Dazu gehören auch über N-gebundene, 5- bis 6-gliedrige gesättigte Heterocyclen, die außerdem als Heteroatome bis zu 2 Sauerstoff-, Schwefel- und/oder Stickstoffatome enthalten können, wie beispielsweise Piperidyl, Morpholinyl oder Piperazin oder Pyrrolidinyl. Besonders bevorzugt sind Piperidyl, Morphlinyl und Pyrrolidinyl.

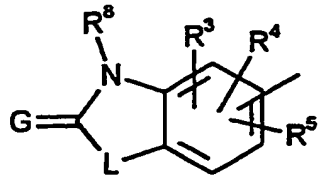
Hydroxyschutzgruppe im Rahmen der oben angegebenen Definition steht im allgemeinen für eine Schutzgruppe aus der Reihe: Trimethylsilyl, Triisopropylsilyl, tert.Butyl-dimethylsilyl, Benzyl, Benzyloxycarbonyl, 2-Nitrobenzyl, 4-Nitrobenzyl, tert. Butyloxycarbonyl, Allyloxycarbonyl, 4-Methoxybenzyl, 4-Methoxybenzyloxycarbonyl, Tetrahydropyranyl, Formyl, Acetyl, Trichloracetyl, 2,2,2-Trichlorethoxycarbonyl, Methoxyethoxymethyl, [2-(Trimethylsilyl)ethoxy]methyl, Benzoyl, 4-Methylbenzoyl, 4-Nitrobenzoyl, 4-Fluorbenzoyl, 4-Chlorbenzoyl oder 4-Methoxybenzoyl. Bevorzugt sind Acetyl, tert. Butyldimethylsilyl oder Tetrahydropyranyl.

Aminoschutzgruppe im Rahmen der Erfindung sind die üblichen in der Peptid-Chemie verwendeten Aminoschutzgruppen.

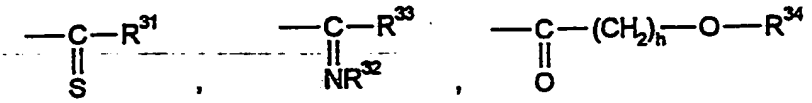
Hierzu gehören bevorzugt: Benzyloxycarbonyl, 2,4-Dimethoxybenzyloxycarbonyl, 4-Methoxybenzyloxycarbonyl, Methoxycarbonyl, Ethoxycarbonyl, tert.Butoxycarbonyl, Allyloxycarbonyl, Phthaloyl, 2,2,2-Trichlorethoxycarbonyl, Fluorenyl-9-methoxycarbonyl, Formyl, Acetyl, 2-Chloracetyl, 2,2,2-Trifluoracetyl, 2,2,2-Trichloracetyl, Benzoyl, 4-Chlorbenzoyl, 4-Brombenzoyl, 4-Nitrobenzoyl, Phthalimido, Isovaleroyl oder Benzyloxymethylen, 4-Nitrobenzyl, 2,4-Dinitrobenzyl, 4-Nitrophenyl, 4-Methoxyphenyl oder Triphenylmethyl.

Die erfindungsgemäßen Verbindungen können in stereoisomeren Formen, die sich entweder wie Bild und Spiegelbild (Enantiomere), oder die sich nicht wie Bild und Spiegelbild (Diastereomere) verhalten, existieren. Die Erfindung betrifft sowohl die Enantiomeren oder Diastereomeren oder deren jeweiligen Mischungen. Die Racemformen lassen sich ebenso wie die Diastereomeren in bekannter Weise in die stereoisomer einheitlichen Bestandteile trennen.

Bevorzugt sind Verbindungen der allgemeinen Formel (I),
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 3-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 4 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 4 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder
für einen Rest der Formel



steht, worin
G ein Sauerstoff- oder Schwefelatom bedeutet,
L ein Sauerstoff- oder Schwefelatom bedeutet,
$R^8$ geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet,
$R^3$, $R^4$ und $R^5$ gleich oder verschieden sind und Wasserstoff, Fluor, Chlor oder Brom bedeuten,
$R^1$ für einen Rest der Formel



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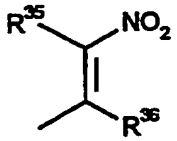
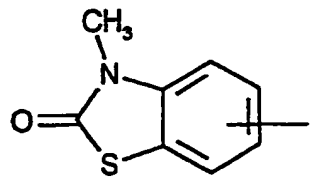
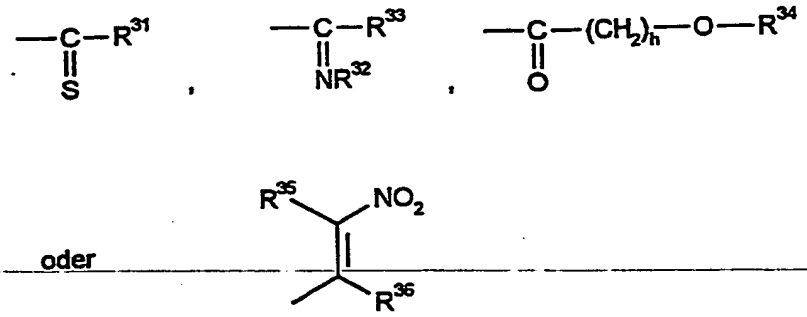


steht, worin
$R^{31}$ geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{35}R^{39}$ bedeutet,
worin
$R^{38}$ und $R^{39}$ gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,
$R^{32}$ Wasserstoff Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
$R^{33}$ Wasserstoff geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
$R^{40}$ und $R^{41}$ die oben angegebene Bedeutung von $R^{38}$ und $R^{39}$ haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
$R^{34}$ geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Benzyl bedeutet,
$R^{35}$ und $R^{36}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,
oder
$R^1$ für Cyano oder für Thienyl, Oxazolyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls, auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sind,
und deren Salze.

Besonders bevorzugt sind erfindungsgemäße Verbindungen der allgemeinen Formel (I),
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 2-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 3 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 3 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder
für einen Rest der Formel

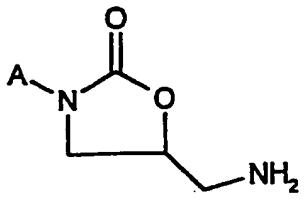


steht,
$R^1$ für einen Rest der Formel



steht, worin
$R^{31}$ geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
$R^{38}$ und $R^{39}$ gleich oder verschieden sind und Wasserstoff oder Methyl bedeuten,
$R^{32}$ Wasserstoff, Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet,
$R^{33}$ Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
$R^{40}$ und $R^{41}$ die oben angegebene Bedeutung von $R^{38}$ und $R^{39}$ haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
$R^{34}$ geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Benzyl bedeutet,
$R^{35}$ und $R^{36}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,
oder
$R^1$ für Cyano oder für Thienyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls auch über eine N-Funktion bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,
und deren Salze.

Außerdem wurde ein Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) gefunden, dadurch gekennzeichnet, daß man
[A] Verbindungen der allgemeinen Formel (II)

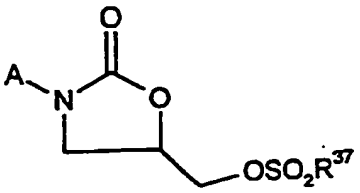


(II)

in welcher
A die oben angegebene Bedeutung hat,
mit Verbindungen der allgemeinen Formel (III)

$R^1-Y$ (III)

in welcher
$R^1$ die oben angegebene Bedeutung hat, und
Y in Abhängigkeit von $R^1$ für Wasserstoff, Halogen oder für $C_1-C_4$ geradkettiges oder verzweigtes Alkoxy oder Oxyalkoxycarbonyl steht, oder
[B] Verbindungen der allgemeinen Formel (IV)



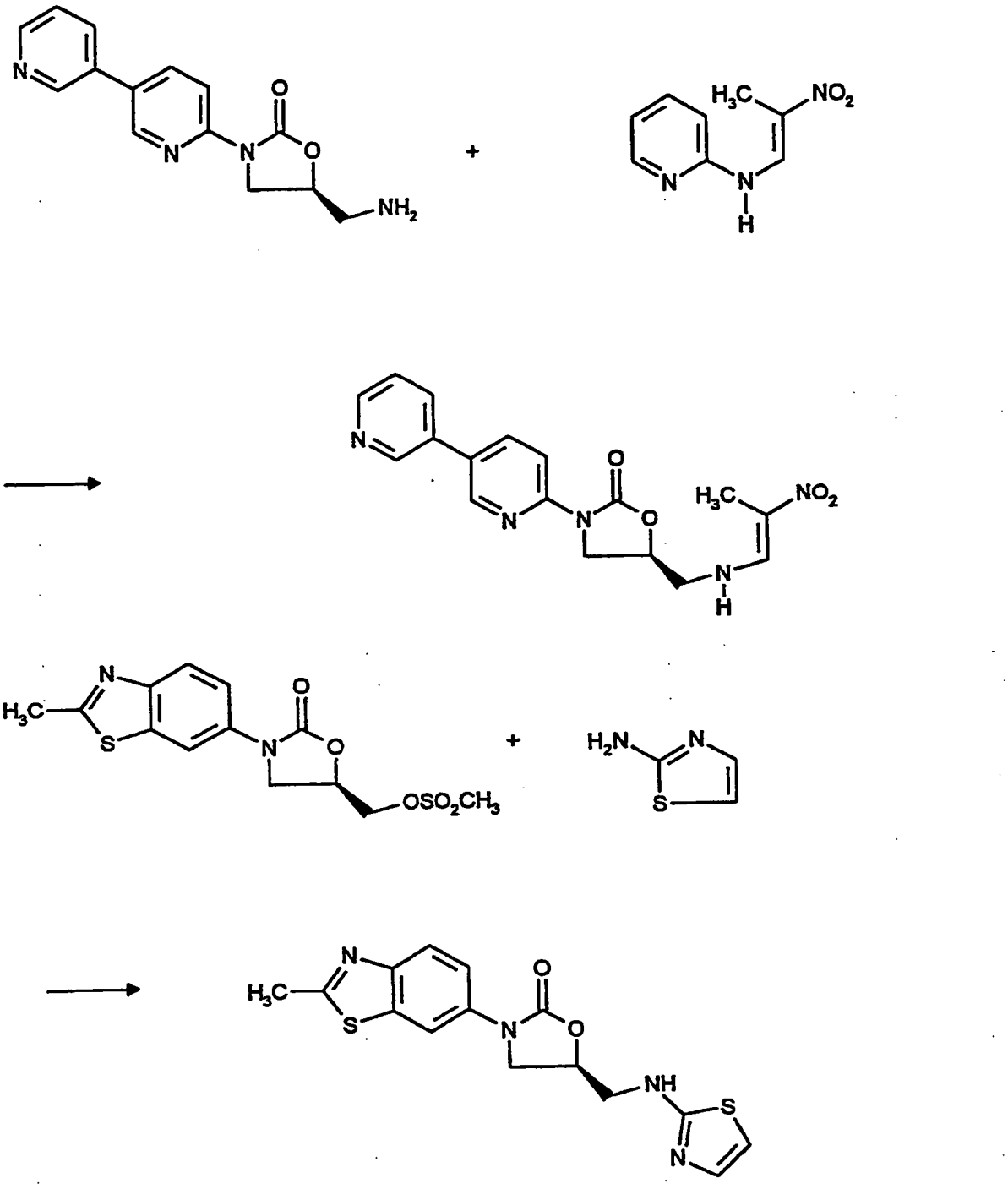
(IV)

in welcher
A die oben angegebene Bedeutung hat,
$R^{37}$ für $C_1$—$C_4$-Alkyl steht,
mit Verbindungen der allgemeinen Formel (V)

$NH_2$—$R^{1'}$ (V)

in welcher
$R^{1'}$ für einen der oben unter $R^1$ aufgeführten Heterocyclen steht,
oder mit Ethyldithioacetat in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base umsetzt,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
und gegebenenfalls weitere Substituenten oder bereits vorhandene funktionelle Gruppen nach üblichen Methoden, wie beispielsweise Alkylierung, Redoxreaktionen, Substitutionsreaktionen und/oder Verseifungen oder Ein- und Abbau von Schutzgruppen, einführt bzw. derivatisiert.

Die erfindungsgemäßen Verfahren können durch folgende Formelschemata beispielhaft erläutert werden:



Als Lösemittel eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether oder tert.Butylmethylether, oder Ketone wie Aceton oder Butanon, oder Amide wie Dimethylformamid oder Hexamethyl-phosphorsäuretriamid, oder Kohlenwasserstoffe wie Hexan, Benzol, Dichlorbenzol, Xylol oder Toluol, oder Dimethylsulfoxid, Acetonitril, Essigester, oder Halogenkohlenwasserstoffe wie Methylenchlorid, Chloroform oder Tetrachlorkohlenstoff, oder Pyridin, Picolin oder N-Methylpiperidin. Ebenso können Gemische der genannten Lösemittel verwendet werden.

Als Basen eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen anorganischen oder organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natrium- oder Kaliummethanolat, oder Natrium- oder Kaliumethanolat, oder organische Amine wie Ethyldiisopropy-

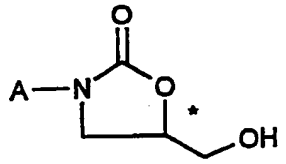
lamin, Triethylamin, Picolin, Pyridine oder N-Methylpiperidin, oder Amide wie Natriumamid oder Lithiumdiisopropylamid, oder Lithium-N-silylalkylamide, wie beispielsweise Lithium-N-(bis)triphenylsilylamid oder Lithiumalkyle wie n-Butyllithium.

Die Base wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 3 mol jeweils bezogen auf 1 mol der Verbindungen der allgemeinen Formeln (II) und (IV) eingesetzt.

Alle Umsetzungen werden im allgemeinen bei normalem, erhöhtem oder bei erniedrigtem Druck durchgeführt (z. B. 0,5 bis 5 bar). Im allgemeinen arbeitet man bei Normaldruck.

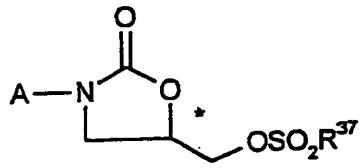
Die Verbindungen der allgemeinen Formeln (III) und (V) sind an sich bekannt oder nach üblichen Methoden herstellbar.

Die Verbindungen der allgemeinen Formel (II) sind teilweise neu und können hergestellt werden, indem man Verbindungen der allgemeinen Formel (VI)



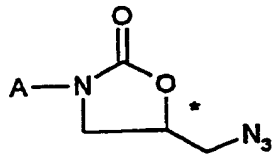
(VI)

in welcher
A die oben angegebene Bedeutung hat,
durch Umsetzung mit ($C_1$—$C_4$)-Alkyl- oder Phenylsulfonsäurechloriden in inerten Lösemitteln und in Anwesenheit einer Base in die entsprechenden Verbindungen der allgemeinen Formel (IV)



(IV)

in welcher
A und $R^{37}$ die oben angegebene Bedeutung haben
überführt,
anschließend mit Natriumazid in inerten Lösemitteln die Azide der allgemeinen Formel (VII)



(VII)



in welcher
A die oben angegebene Bedeutung hat,
herstellt,
in einem weiteren Schritt durch Umsetzung mit ($C_1$—$C_4$—O)$_3$—P oder $PPh_3$, vorzugsweise $(CH_3O)_3P$ in inerten Lösemitteln und mit Säuren in die Amine überführt.

Als Lösemittel eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether oder tert.Butylmethylether, oder Ketone wie Aceton oder Butanon, oder Amide wie Dimethylformamid oder Hexamethyl-phosphorsäuretriamid, oder Kohlenwasserstoffe wie Hexan, Benzol, Dichlorbenzol, Xylol oder Toluol, oder Dimethylsulfoxid, Acetonitril, Essigester, oder Halogenkohlenwasserstoffe wie Methylenchlorid, Chloroform oder Tetrachlorkohlenstoff, oder Pyridin, Picolin oder N-Methylpiperidin. Ebenso können Gemische der genannten Lösemittel verwendet werden.

Als Basen eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen anorganischen oder organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natrium- oder Kaliummethanolat, oder Natrium- oder Kaliumethanolat, oder organische Amine wie Ethyldiisopropylamin, Triethylamin, Picolin, Pyridine oder N-Methylpiperidin, oder Amide wie Natriumamid oder Lithiumdiisopropylamid, oder Lithium-N-silylalkylamide, wie beispielsweise Lithium-N-(bis)triphenylsilylamid oder Lithiumalkyle wie n-Butyllithium.

Die Base wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 3 mol bezogen auf 1 mol der Verbindungen der allgemeinen Formel (VI) eingesetzt.

Alle Umsetzungen werden im allgemeinen bei normalem, erhöhtem oder bei erniedrigtem Druck durchgeführt (z. B. 0,5 bis 5 bar). Im allgemeinen arbeitet man bei Normaldruck.

Die Reduktion der Azide erfolgt mit $(CH_3O)_3P$ und Salzsäure.

Die Reduktion erfolgt im allgemeinen in einem Temperaturbereich von −50°C bis zum jeweiligen Siedepunkt des Lösemittels, bevorzugt von −20°C bis +90°C.

Als Lösemittel eignen sich hierbei alle inerten organischen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, Tetrahydrofuran, Glykoldimethylether, oder Diethylenglykoldimethylether oder Amide wie Hexamethylphosphorsäuretriamid oder Dimethylformamid, oder Essigsäure. Ebenso ist es möglich, Gemische der genannten Lösemittel zu verwenden.

Die Verbindungen der allgemeinen Formeln (IV) und (VII) sind neu und können wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (VI) sind teilweise neu und können hergestellt werden, indem man

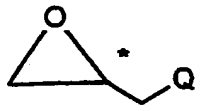
[D] Verbindungen der allgemeinen Formeln (VIII) oder (IX)

$$A-N=C=O \quad (VIII) \quad \text{oder} \quad A-CO-N_3 \quad (IX)$$

in welchen

A die oben angegebene Bedeutungen hat,

mit Lithiumbromid/$(C_4H_9)_3$ P(O) und Epoxiden der allgemeinen Formel (X)



(X)

in welcher

Q für $C_1-C_6$-Acyloxy steht,

in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base

umsetzt,

durch eine typische Esterverseifung oder durch eine typische Umesterung die Hydroxyfunktion freisetzt,

oder

[E] Verbindungen der allgemeinen Formel (XI)

$$A-NH-CO_2-X \quad (XI)$$

in welcher

A die oben angegebene Bedeutung hat

und

X für eine typische Schutzgruppe, vorzugsweise Benzyl steht,

in inerten Lösemitteln und in Anwesenheit einer Base, beispielsweise Lithiumalkylen oder Lithium-N-alkyl- oder Lithium-N-silylalkylamiden, vorzugsweise N-Butyllithium, mit Epoxiden der allgemeinen Formel (X) umsetzt,

oder

zunächst Verbindungen der allgemeinen Formel (IX) durch Abspaltung von Stickstoff in Alkoholen in die Verbindungen der allgemeinen Formel (XIa)

$$A-NH-CO_2-Y \quad (XIa)$$

in welcher

A die oben angegebene Bedeutung hat

und

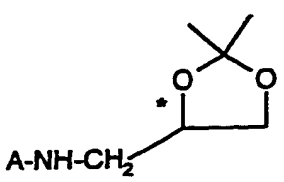
Y für geradkettiges oder verzweigtes $C_2-C_6$-Alkyl, vorzugsweise n-Butyl steht,

überführt,

und in einem zweiten Schritt wie unter [D] beschrieben in inerten Lösemitteln und in Anwesenheit einer Base, vorzugsweise Lithium-N-alkyl-oder N-Silylalkylamiden oder n-Butyllithium und Epoxiden der allgemeinen Formel (X) umsetzt,

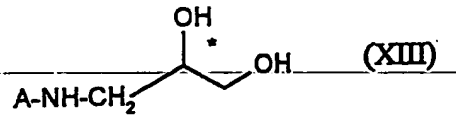
oder

[F] Verbindungen der allgemeinen Formel (XII)




(XII)

in welcher
A die oben angegebene Bedeutung hat,
entweder direkt mit Säuren und Kohlensäurediethylester
umsetzt,
oder zunächst durch Umsetzung der Verbindungen der allgemeinen Formel (XII) mit Säuren die Verbindungen der allgemeinen Formel (XIII)




(XIII)



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

Als Lösemittel eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen Lösemittel, die sich unter den Reaktionsbedingungen nicht verändern. Hierzu gehören bevorzugt Alkohole wie Methanol, Ethanol, Propanol oder Isopropanol, oder Ether wie Diethylether, Dioxan, 1,2-Dimethoxyethan, Tetrahydrofuran, Glykoldimethylether oder tert.Butylmethylether, oder Ketone wie Aceton oder Butanon, oder Amide wie Dimethylformamid oder Hexamethyl-phosphorsäuretriamid, oder Kohlenwasserstoffe wie Hexan, Benzol, Dichlorbenzol, Xylol oder Toluol, oder Dimethylsulfoxid, Acetonitril, Essigester, oder Halogenkohlenwasserstoffe wie Methylenchlorid, Chloroform oder Tetrachlorkohlenstoff, oder Pyridin, Picolin oder N-Methylpiperidin. Ebenso können Gemische der genannten Lösemittel verwendet werden.

Als Basen eignen sich in Abhängigkeit von den einzelnen Verfahrensschritten die üblichen anorganischen oder organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid, oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat, oder Alkalialkoholate wie beispielsweise Natrium- oder Kaliummethanolat, oder Natrium- oder Kaliumethanolat, oder organische Amine wie Ethyldiisopropylamin, Triethylamin, Picolin, Pyridine oder N-Methylpiperidin, oder Amide wie Natriumamid oder Lithiumdiisopropylamid, oder Lithium-N-silylalkylamide, wie beispielsweise Lithium-N-(bis)triphenylsilylamid oder Lithiumalkyle wie n-Butyllithium.

Die Base wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 3 mol bezogen auf 1 mol der Verbindungen der allgemeinen Formeln (X) und (XI) eingesetzt.

Alle Umsetzungen werden im allgemeinen bei normalem, erhöhtem oder bei erniedrigtem Druck durchgeführt (z. B. 0,5 bis 5 bar). Im allgemeinen arbeitet man bei Normaldruck.

Das Verfahren [D] erfolgt bevorzugt in Xylol oder Dichlorbenzol, gegebenenfalls in Gegenwart von Triethylamin, unter Rückfluß.

Die basenkatalysierte Umesterung wird mit einem der oben aufgeführten Alkohole, vorzugsweise Methanol, in einem Temperaturbereich von −10°C bis +40°C, vorzugsweise bei Raumtemperatur durchgeführt.

Als Basen eignen sich im allgemeinen Natriumhydrogencarbonat, Natriummethanolat, Hydrazinhydrat, Kaliumcarbonat oder Cäsiumcarbonat. Bevorzugt ist Cäsiumcarbonat.

Das Verfahren [E] erfolgt in einem der oben aufgeführten Ether mit Lithiumalkylverbindungen oder Lithium-N-silylamiden, wie beispielsweise n-Butyllithium, Lithiumdiisopropylamid oder Lithium-bistrimethylsilylamid, vorzugsweise in Tetrahydrofuran und Lithium-bis-trimethylsilylamid oder n-Butyllithium, in einem Temperaturbereich von −100°C bis +20°C, vorzugsweise von −75°C bis −40°C.

Für das Verfahren [F] eignen sich für den 1. Schritt vorzugsweise die oben aufgeführten Alkohole, im Falle der anschließenden Cyclisierung Tetrahydrofuran.

Als Basen für die Cyclisierung eignen sich vorzugsweise die oben aufgeführten Lithium-N-silylalkylverbindungen oder n-Butyllithium. Besonders bevorzugt ist n-Butyllithium.

Der erste Reaktionsschritt wird bei der Siedetemperatur des entsprechenden Alkohols, die Cyclisierung in einem Temperaturbereich von −70°C bis Raumtemperatur durchgeführt.

Die Cyclisierung [F] wird in Anwesenheit eines Hilfsmittels und/oder Anwesenheit einer Säure durchgeführt.

Als Säuren eignen sich im allgemeinen anorganische Säuren wie beispielsweise Salzsäure oder Schwefelsäure, oder organische Carbonsäuren mit 1−6 C-Atomen, gegebenenfalls substituiert durch Fluor, Chlor und/oder Brom, wie beispielsweise Essigsäure, Trifluoressigsäure, Trichloressigsäure oder Propionsäure, oder Sulfonsäuren mit $C_1$−$C_4$-Alkylresten oder Arylresten wie beispielsweise Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure oder Toluolsulfonsäure. Besonders bevorzugt ist Salzsäure.

Die Säure wird in einer Menge von 1 mol bis 10 mol, bevorzugt von 1 mol bis 2 mol, bezogen auf 1 mol der Verbindungen der allgemeinen Formel (XII) eingesetzt.

Als Hilfsmittel eignen sich die üblichen Reagenzien wie Phosgen, Carbonyldiimidazol oder Kohlensäurediethylester oder Chlorameisensäuretrichlormethylester. Bevorzugt sind Carbonyldiimidazol, Kohlensäurediethylester oder Chlorameisensäuretrichlormethylester.

Als Lösemittel eignen sich die oben aufgeführten Halogenkohlenwasserstoffe. Bevorzugt ist Methylenchlorid.

Die Verbindungen der allgemeinen Formel (IX) sind bekannt oder können nach üblichen Methoden hergestellt werden.

Die Verbindungen der allgemeinen Formel (XIII) sind größtenteils neu und können beispielsweise wie oben beschrieben hergestellt werden.

Die Verbindungen der allgemeinen Formel (VIII) sind teilweise bekannt oder neu und können dann beispiels-

weise hergestellt werden, indem man die entsprechenden Amine mit Chlorameisensäuretrichlorethylester in einem der oben aufgeführten Lösemittel, vorzugsweise Xylol bei Rückflußtemperatur umsetzt.

Die Verbindungen der allgemeinen Formel (IX) sind teilweise bekannt oder neu und können dann beispielsweise hergestellt werden, indem man ausgehend von den entsprechenen Carbonsäuren entweder mit Chlorameisensäureisobutylester/Aceton, Natriumazid/Wasser oder mit Diphenylphosphorylazid/Tetrahydrofuran oder mit Xylol oder Methylenchlorid in Gegenwart einer der oben angegebenen Basen, vorzugsweise Triethylamin, bei −10°C bis Raumtemperatur umsetzt.

Die Verbindungen der allgemeinen Formeln (XI) und (XIa) sind teilweise bekannt oder neu und können entweder durch Abspaltung von Stickstoff aus den entsprechenden Carbonsäureaziden und Umsetzung mit den entsprechenden Alkoholen oder durch Umsetzung der entsprechenden Amine mit Chlorameisensäureestern, vorzugsweise Chlorameisensäurebenzylester in einem der oben aufgeführten Lösemittel, vorzugsweise Tetrahydrofuran oder Dioxan, in einem Temperaturbereich von −10°C bis 200°C, vorzugsweise von 0°C bis 150°C, hergestellt werden.

Die minimalen Hemmkonzentrationen (MHK) wurden per Reihenverdünnungsverfahren auf Iso-Sensitest Agar (Oxoid) bestimmt. Für jede Prüfungssubstanz wurde eine Reihe von Agarplatten hergestellt, die bei jeweils doppelter Verdünnung abfallende Konzentrationen des Wirkstoffes enthielten. Die Agarplatten wurden mit einem Multipoint-Inokulator (Denley) beimpft. Zum Beimpfen wurden Übernachtkulturen der Erreger verwandt, die zuvor so verdünnt wurden, daß jeder Impfpunkt ca. $10^4$ koloniebildende Partikel enthielt. Die beimpften Agarplatten wurden bei 37°C bebrütet, und das Keimwachstum wurde nach ca. 20 Stunden abgelesen. Der MHK-Wert (µg/ml) gibt die niedrigste Wirkstoffkonzentration an, bei der mit bloßem Auge kein Wachstum zu erkennen war.



MHK-Werte (µg/ml)

| Bsp.-Nr. | Staph. 133 | Staph. 48N | Staph 25701 | Staph. 9TV | E. coli Neumann | Klebs. 57 USA | Psdm. Bonn |
|---|---|---|---|---|---|---|---|
| 11 | 0.5 | 0.5 | 0.25 | 0.25 | >64 | >64 | >64 |
| 12 | 1 | 1 | 1 | 0.5 | >64 | >64 | >64 |
| 13 | 0.25 | 0.25 | 0.25 | ≤ 0.125 | >64 | >64 | >64 |
| 14 | 1 | 1 | 1 | 0.5 | >64 | >64 | >64 |
| 15 | 0.25 | 0.5 | 0.25 | ≤ 0.125 | >64 | >64 | >64 |
| 20 | 0.25 | 0.25 | 0.25 | ≤ 0.125 | 64 | >64 | >64 |
| 23 | 0.25 | 0.5 | 0.5 | 0.25 | >64 | >64 | >64 |
| 26 | < 0.125 | 0.25 | 0.25 | ≤ 0.125 | >64 | >64 | >64 |
| 42 | < 0.125 | >0.125 | >0.125 | < 0.125 | 64 | 64 | >64 |
| 43 | 0.5 | 0.5 | 0.5 | 0.5 | >64 | >64 | >64 |

Für schnellwachsende Mykobakterien wurde die MHK-Bestimmung in Anlehnung an die von Swenson beschriebene Methode der Bouillon Mikrodilution durchgeführt [vgl. J.M. Swenson, C. Thornberry, U.A. Silcox, Rapidly growing mycobacteria. Testing of susceptibility to 34 antimicrobial agents by broth microdilution. Antimicrobial Agents and Chemotherapy Vol, 22, 186–192 (1982)].

Abweichend davon war das mit 0,1 Vol.% Tween 80 versetzte Hirn-Herzextrakt Medium.

Die verwendeten Mykobakterienstämme wurden von der DSM (Dt. Sammlung von Mikroorganismen, Braunschweig) bezogen. Sie wurden in einer feuchten Kammer bei 37°C bebrütet.

Die MHK-Werte wurden nach 2—4 Tagen abgelesen, wenn die präparatfreien Kontrollen durch Wachstum trüb waren. Der MHK-Wert definiert sich als die niedrigste Präparatkonzentration, die makroskopisch sichtbares Wachstum völlig inhibiert.

MHK-Werte: Mycotbacterium smegmatis

| Stamm: | DSM 43061 | DSM 43078 |
|---|---|---|
| Inoculum [/ml] | 2,20E+04 | 4,20E+04 |
| Bsp.-Nr. | | |
| 12 | 8 | 4 |
| 13 | 2 | 1 |
| 14 | 8 | 4 |
| 15 | 1 | 0.5 |
| 20 | 0.25 | 0.25 |
| Isoniazid | 4 | 2 |
| Strepto-mycin | 4 | 4 |

MHK-Bestimmung mit Mycoplasma pneumoniae

Mycoplasma pneumoniae Stamm PI 1428 wurde unter aeroben Bedingungen in PPLO-Medium, dem 1% Glukose, 2,5% Hefeextrakt, 20% Pferdeserum (donor horse serum) und 0,002% Phenolrot zugegeben wurde gezüchtet. MHK-Bestimmungen wurden in Anlehnung an die von ter Laak u. Mitarbeitern beschriebene Methode der Reihenmikrodilution in Flüssigmedium durchgeführt (E. A. ter Laak, A. Pijpers, J.H. Noordergraaf, E. Schoevers, J.H.M. Verheijden: Comparison of Methods for in vitro Testing of Susceptibility of Porcine Mycoplasma Species to Antimicrobial Agents; Antimicrobial Agents and Chemotherapy, Vol. 35, 228—233 (1991)). Zum Zeitpunkt des beginnenden Farbumschlags des Mediums der präparatfreien Kontrolle von rot nach gelb wurden 10 Vol% Alamar Blau zugegeben. Die Inkubation bei 37°C wurde für ca. 10 Stunden fortgesetzt und die MHK als der Wert definiert, bei dem das Medium mit der kleinsten Präparatkonzentration unverändert blau blieb.

| Bsp.-Nr. | MHK (µg / ml) |
|---|---|
| 12 | 2 |
| 13 | 2 |
| 14 | 8 |
| 23 | 4 |

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

Besonders wirksam sind die erfindungsgemäßen Verbindungen gegen Bakterien und bakterienahnliche Mikroorganismen wie Mycoplasmen. Sie sind daher besonders gut zur Prophylaxe und Chemotherapie von lokalen und systemischen Infektionen in der Human- und Tiermedizin geeignet, die durch solche Erreger hervorgerufen werden.

Zur vorliegenden Erfindung gehören pharmazeutische Zubereitungen, die neben nicht-toxischen, inerten pharmazeutisch geeigneten Trägerstoffen eine oder mehrere erfindungsgemäße Verbindungen enthalten oder die aus einem oder mehreren erfindungsgemäßen Wirkstoffen bestehen, sowie Verfahren zur Herstellung dieser Zubereitungen.

Der oder die Wirkstoffe können gegebenenfalls in einem oder mehreren der oben angegebenen Trägerstoffe auch in mikroverkapselter Form vorliegen.

Die therapeutisch wirksamen Verbindungen sollen in den oben aufgeführten pharmazeutischen Zubereitungen vorzugsweise in einer Konzentration von etwa 0,1 bis 99,5, vorzugsweise von etwa 0,5 bis 95 Gew.-%, der Gesamtmischung vorhanden sein.

Die oben aufgeführten pharmazeutischen Zubereitungen können außer den erfindungsgemäßen Verbindungen auch weitere pharmazeutische Wirkstoffe enthalten.

Im allgemeinen hat es sich sowohl in der Human- als auch in der Veterinärmedizin als vorteilhaft erwiesen, den oder die erfindungsgemäßen Wirkstoffe in Gesamtmengen von etwa 0,5 bis etwa 500, vorzugsweise 5 bis 100 mg/kg Körpergewicht je 24 Stunden, gegebenenfalls in Form mehrerer Einzelgaben, zur Erzielung der gewünschten Ergebnisse zu verabreichen. Eine Einzelgabe enthält den oder die erfindungsgemäßen Wirkstoffe vorzugsweise in Mengen von etwa 1 bis etwa 80, insbesondere 3 bis 30 mg/kg Körpergewicht.

Die erfindungsgemäßen Verbindungen können zum Zweck der Erweiterung des Wirkungsspektrums und um eine Wirkungssteigerung zu erreichen auch mit anderen Antibiotika kombiniert werden.

## Anhang zum experimentellen Teil

### Liste der verwendeten Laufmittelgemische zur Chromatographie

I Dichlormethan : Methanol
II Toluol : Ethylacetat
III in Acetonitril : Wasser
IV Ethylacetat
V Petrolether : Ethylacetat
VI $CH_2Cl_2$ : MeOH : $NH_{3(aq)}$
VII $CH_2Cl_2$ : MeOH

### Abkürzungen

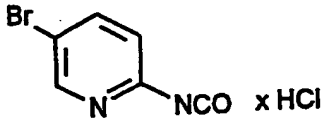
Z Benzyloxycarbonyl
Boc tert.Butoxycarbonyl
DMF Dimethylformamid
Ph Phenyl
Me Methyl
THF Tetrahydrofuran
CDI Carbonyldiimidazol
DCE Dichlorethan



### Ausgangsverbindungen

#### Beispiel I

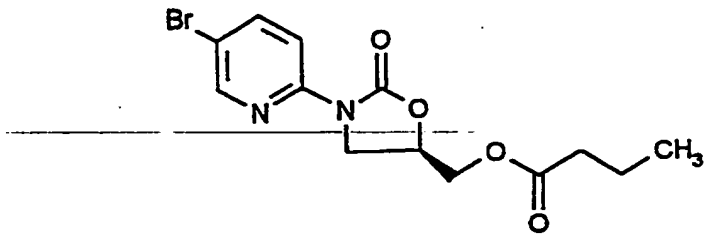
5-Brom-2-isocyanato-pyridin Hydrochlorid




Zu einer gerührten Lösung von 100 g (0,58 mol) 2-Amino-5-brompyridin in 400 ml 1,2-Dichlorethan tropft man in der Siedehitze 78,0 ml (0,64 mol) Chlorameisensäuretrichlorethylester. Nach der Zugabe wird 2h im Rückfluß gekocht, dann darf sich das Gemisch auf Raumtemperatur abkühlen. Der entstandene Niederschlag wird durch Filtration abgetrennt, mit 100 ml 1,2-Dichlorethan gut gewaschen und im Hochvakuum über Natriumhydroxid getrocknet. Man erhält 98,3 g (72%) der Titelverbindung als gelben Feststoff.
Schmp.: 248—254°C (Zers.)
$R_f$ = 0,23 (Ethylacetat)
MS (EI) m/z = 198 $(M)^+$

Beispiel II

(5R)-3-(5-Brom-pyridin-2-yl)-5-butyryloxy-methyl-oxazolidin-2-on



Eine Suspension von 2,17 g (25 mmol) Lithiumbromid und 5,46 g (25 mmol) Tributylphophinoxid in 73 ml Xylol wird 1 h am Wasserabscheider gekocht. Dazu wird in der Siedehitze ein Gemisch von 58,-5 ml (0,42 mol) Triethylamin und 66,6 g (0,42 mol) (R)-Glycidylbutyrat getropft. Gleichzeitig werden innerhalb von 20 min 98,2 g (0,42 mol) der Verbindung aus Beispiel I portionsweise zugegeben. Nach beendeter Zugabe wird noch 1 h unter Rückfluß nachgerührt. Man läßt auf Raumtemperatur abkühlen und dampft das Lösemittel im Vakuum ab. Nach Chromatographie des Rückstands an 1 kg Kieselgel (Toluol : Ethylacetat 95 : 5) erhält man 37,9 g (26%) der Titelverbindung als Öl.

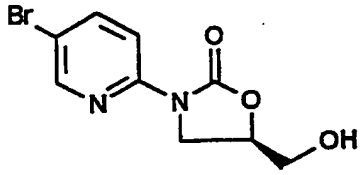
$R_f$ = 0,43 (Toluol : Ethylacetat 4 : 1)

MS (FAB) m/z = 343 $(M+H)^+$

$^1$H-NMR (250 MHz, $D_6$—DMSO): δ = 0,81 (t, J = 7 Hz, 3H, $CH_3CH_2$); 1,5 (m, 2H, $CH_3\underline{CH_2}CH_2CO$); 2,29 (t, J = 7 Hz, 2H, $CH_3CH_2\underline{CH_2}CO$); 3,91 (dd, J = 7 Hz, 10 Hz, 1H, H-4 trans); 4,25 (dd, J = 9 Hz, 10 Hz, 1H, H-4 cis); 4,36 (m, 2H, $CH_2O$); 4,97 (m, 1H, H-5); 8,08 (d, J = 1 Hz, 2H, Pyridyl H-3,4); 8,50 (d, J = 1 Hz, pyridyl H-6).

Beispiel III

(5R)-3-(5-Brom-pyridin-2-yl)-5-hydroxymethyl-oxazolidin-2-on



Eine Lösung von 19,6 g (57,3 mmol) der Verbindung aus Beispiel 1 in 125 ml wasserfreiem Methanol wird mit 185 mg (0,57 mmol) Cäsiumcarbonat versetzt und 5 h bei Raumtemperatur gerührt. Das Lösemittel wird im Vakuum abgedampft und der Rückstand wird mit 30 ml Ether verrührt. Der Niederschlag wird durch Filtration abgetrennt, mit 25 ml Wasser und 5 ml Ether gewaschen und im Hochvakuum getrocknet. Man erhält 10,73 g (69%) der Titelverbindung als helle Kristalle.

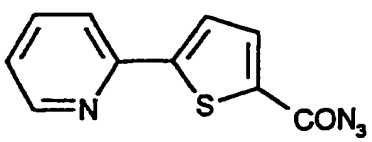
Schmp.: 0,09 (Toluol : Ethylacetat 4 : 1)

MS (DCI, $NH_3$) m/z = 273 $(M+H)^+$

$^1$H-NMR (200 MHz, $CD_3OD$) δ = 3,68 (d, J = 5,9 Hz, 1 H, $CH_2O$); 3,87 (dd, J = 4, 9 Hz, 1H, $CH_2O$); 4,06 (dd, J = 7, 10 Hz, 1H, H-4 trans); 4,26 (dd, J = 9, 10 Hz, 1H, H-4 cis); 4,75 (m, 1H, H-5); 7,92 (dd, J = 1,5 Hz, 10 Hz, 1H, Pyridyl H-3); 8,12 (d, J = 10 Hz, 1H, Pyridyl H-4); 8,40 (d, J = 1,5 Hz, 1H, Pyridyl H-6).

Beispiel IV

5-(2-Pyridyl)-thiophen-2-carbonsäureazid



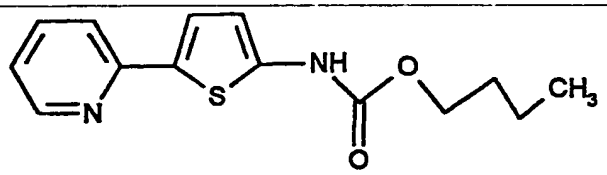


20 g (97,45 mmol) 5-(2-Pyridyl)-thiophen-2-carbonsäure werden in 200 ml Aceton gelöst, mit 15,94 ml (115 mmol) $Et_3N$ versetzt und auf 0°C gekühlt. Zu der so erhaltenen Reaktionslösung tropft man langsam unter

Rühren eine Lösung von 14,85 ml (115 mmol) Chlorameisensäureisobutylester in 88 ml Aceton. Nach 1 h bei 0°C tropft man eine Lösung von 9,5 g (146 mmol) Natriumazid in 44 ml Wasser zu, rührt 1 h bei 0°C nach und läßt auf Raumtemperatur kommen. Die Reaktionsmischung wird auf Eiswasser gekippt und abgesaugt und so weiter umgesetzt.
Ausbeute: 21 g wasserfeuchtes Pulver.

Beispiel V

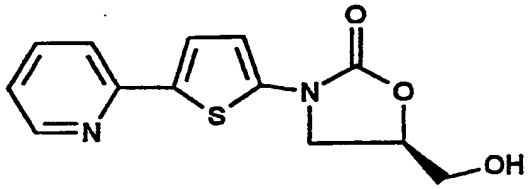
5-(2-Pyridyl)-butyloxycarbonylamino-thiophen



21 g der Verbindung aus Beispiel IV werden portionsweise in 400 ml siedendes n-Butanol eingetragen. Nach beendeter Gasentwicklung wird 15 min unter Rückfluß nachgerührt. Nach Abkühlen auf Raumtemperatur wird eingeengt, der Rückstand mit Ether verrührt, abgesaugt und bei 50°C im Umlufttrockenschrank getrocknet.
Ausbeute: 18,8 g (75% d.Th.)
$^1$H-NMR (200 MHz, $D_6$–DMSO): δ = 10,8 (s, 1H); 8,45 (d, J = 5 Hz, IH); 7,68 – 7,85 (m, 2H); 7,5 (d, J = 5 Hz, IH); 7,1–7,2 (m, 1H); 6,57 (d, J = 5 Hz, 1H); 4,14 (t, J = 7 Hz, 2H); 1,62 (q, J = 7 Hz, 2H); 1,39 (h, J = 7 Hz, 2H); 0,92 (t, J = 7 Hz, 3H).

Beispiel VI

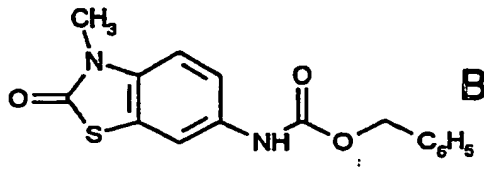
(5R)-3-(5-(2-Pyridyl)-thien-2-yl)-5-hydroxymethyl-oxazolidin-2-on



18,8 g (68 mmol) der Verbindung aus Beispiel V werden in 190 ml absolutem THF gelöst, mit 10 mg 1,10-Phenanthrolin-Hydrat versetzt und auf –70°C gekühlt. Nun werden langsam ca. 27 ml 2,5 N n-Butyllithium-Lösung in Hexan bis zum Farbumschlag nach rot zugetropft. Anschließend werden 9,6 ml (68 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf Raumtemperatur kommen, versetzt mit gesättigter Ammoniumchloridlösung, trennt die organische Phase ab und extrahiert die wäßrige Phase zweimal mit Methylenchlorid. Die vereinigten organischen Phasen werden getrocknet ($Na_2SO_4$) und eingeengt. Der Rückstand wird mit Ether verrührt und abgesaugt.
Ausbeute: 15,3 g (81,5% d.Th.)
$R_f$ = 0,06 ($CH_2Cl_2$ : $CH_3OH$ = 100 : 3)
Smp.: 191°C
$^1$H-NMR (200 MHz, $D_6$–DMSO): δ = 8,45 (d, J = 5 Hz, 1H); 7,7–7,9 (m, 2H); 7,6 (d, J = 5 Hz, 1H); 7,15–7,25 (m, 1H); 6,58 (d, J = 5 Hz, 1H); 5,28 (t, J = 7 Hz, 1H); 4,77 – 4,9 (m, 1H); 4,13 (dd, J = 10 Hz, 9 Hz, 1H); 3,86 (dd, J = 10 Hz, 6 Hz, 1H); 3,55–3,78 (m, 2H).

Beispiel VII

6-(Benzyloxycarbonylamino)-3-methyl-2-benzothiazolinon



1,76 g (8,12 mmol) 6-Amino-3-methyl-2(3H)-benzothiazolon-hydrochlorid in 17 ml Wasser, 14 ml THF und 17 ml ges. $NaHCO_3$-Lösung werden bei 0°C tropfenweise mit 1,3 ml (9,10 mmol) Chlor-ameisensäurebenzylester versetzt.

Nach 1 h werden 120 ml Wasser hinzugegeben, das THF im Vakuum abgezogen, der Niederschlag abgesaugt, dreimal mit Wasser, zweimal mit Petrolether gewaschen und bei 60°C getrocknet.

Ausbeute: 2,44 g (96%)

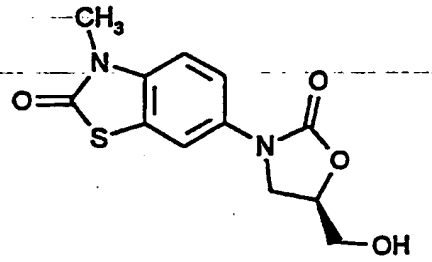
Smp.: 183°C

$R_f$ (II, 7 : 3) = 0,39

$^1$H-NMR ([D$_6$]DMSO): δ = 7,77 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,23– 7,45 (m, 6H, Ph), 7,22 (d, J = 6 Hz, 1H, Benzothiazolinon 4-H); 5,15 (s, 2H); 3,38 (s, 3H–$CH_3$).

Beispiel VIII

(5R)-3-[3-Methyl-2-benzothiazolinon-6-yl]-5-(hydroxymethyl)-oxazolidin-2-on




Methode A

26,76 g (85,12 mmol) der Verbindung aus Beispiel VII werden in 400 ml THF gelöst, mit 10 mg 1,10-Phenanthrolin-Hydrat versetzt und auf –70°C gekühlt. Nun werden langsam ca. 34 ml 2,5 N n-Butyllithium-Lösung in Hexan bis zum Farbumschlag nach rot zugetropft. Anschließend werden 12 ml (85,12 mmol) (R)-Glycidylbutyrat zugetropft. Man läßt auf RT kommen, versetzt mit gesättigter Ammoniumchloridlösung und zieht im Vakuum das THF ab. Der entstandene Niederschlag wird abgesaugt, mit Wasser und Ether gewaschen und im Hochvakuum getrocknet.

Ausbeute: 17,93 g (75%)

Smp.: 166°C

$R_f$ (II, 1:1) = 0,09

MS (EI): m/z = 280 ($M^+$)

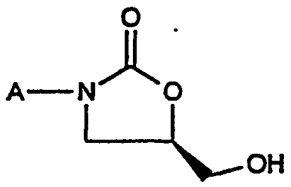
$^1$H-NMR ([D$_6$]DMSO): δ = 7,80 (d, J = 1 Hz, 1H, Benzothiazolinon 7-H); 7,60 (dd, J = 6, J = 1 Hz, 1H, Benzothiazolinon 5-H); 7,32 (d, J = 6 Hz, 1H, Benzthiazolinon 4-H); 5,23 (t, J = 6 Hz, 1H, OH); 4,62 – 4,80 (m, 1H, 5-H); 4,10 (t, J = 9 Hz, 1H, 4-H); 3,85 (dd, J = 9, J = 5 Hz, 1H, 4-H); 3,48–3,75 (m, 2H, $CH_2O$); 3,40 (s, 3H, $CH_3$).

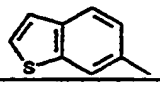
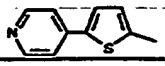
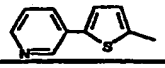
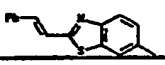
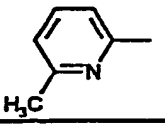
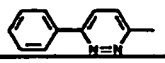
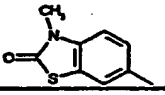
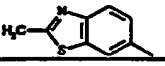
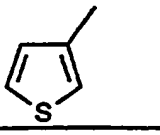
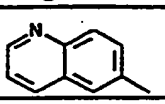
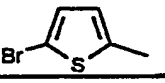
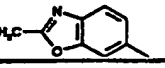
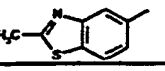
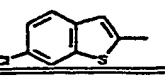
Methode B

9,3 g (0,03 mol) der Verbindung aus Beispiel VII werden in 150 ml THF gelöst und auf –70°C gekühlt. Anschließend werden 4 ml (0,01 mol) 2,5 M n-Butyllithiumlösung in Hexan zugetropft. Danach werden gleichzeitig langsam nochmals 8 ml (0,02 mol) n-Butyllithium und 4,23 ml (0,03 mol) (R)-Glycidylbutyrat zugetropft. Man läßt auf Raumtemperatur kommen und rührt drei Stunden nach. Die Aufarbeitung erfolgt wie für Methode A beschrieben Ausbeute: 6 g (72%).

Analog den Vorschriften der Beispiele I bis VIII werden die in Tabelle I aufgeführten Verbindungen dargestellt:

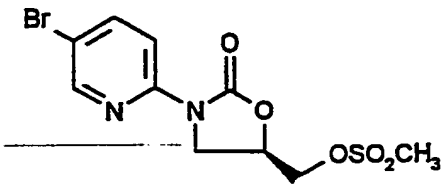
Tabelle I



| Bsp.-Nr. | A | Smp. (°C) | $R_f$ / Laufmittel (Verhältnis) | Ausbeute (% d.Th.) |
|---|---|---|---|---|
| IX |  | 162 | - | 63 |
| X |  | 209 u.Z. | - | 61 |
| XI |  | 185 | - | 71 |
| XII |  | 188 | 0,52, I (9:1) | 76 |
| XIII |  | 144 | 0,32, I (95:5) | 78 |
| XIV |  | 158 | 0,29, II (1:1) | 28 |
| XV |  | 166 | 0,09, II (1:1) | 82 |
| XVI |  | - | 0,05, II (1:1) | 57 |
| XVI |  | 132 | - | 79 |
| XVII |  | 165 | 0,1, V (1:4) | 45 |
| XVIII |  | 156 | 0,24, V (4:1) | 67 |
| XIX |  | 109 | - | 24 |
| XX |  | - | 0,47, II (1:1) | 68 |
| XXI |  | - | 0,05, II (1:1) | 57 |
| XXII |  | 200 u.Z. | - | 98 |

Beispiel XXIII

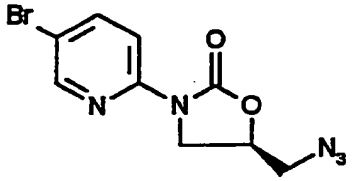
(5R)-3-(5-Brom-pyridin-2-yl)-5-methansulfonyloxy-methyl-oxazolidin-2-on



Eine auf 0°C gekühlte, gerührte Lösung von 10,5 g (38,44 mmol) der Verbindung aus Beispiel III und 6,40 ml (46,14 mmol) Triethylamin in 36 ml wasserfreiem Dichlormethan wird langsam mit 3,27 ml (42,28 mmol) Methansulfonsäurechlorid versetzt. Man rührt 10 min. bei 0—5°C nach und rührt das Gemisch in 50 ml Eiswasser ein. Die organische Phase wird abgetrennt, mit 20 ml gesättigter $NaHCO_3$-Lösung und 20 ml Eiswasser gewaschen und über $MgSO_4$ getrocknet. Das Lösemittel wird im Vakuum eingedampft und der Rückstand mit 50 ml Ether verrührt, abgesaugt und im Hochvakuum getrocknet. Man erhält 12,8 g (95%) der Titelverbindung als farblose Kristalle.
Schmp.: 138—138,5°C
$R_f$ = 0,65 (Dichlormethan : Methanol 95 : 5)
MS (DCI, $NH_3$) m/z = 351 $(M+H)^+$
$^1$H-NMR (250 MHz, $D_6$-DMSO) δ = 3,25 (s, 3H, $OSO_2CH_3$); 3,91 (dd, J = 7, 10 Hz, 1H, H-4 trans); 4,27 (dd, J = 10, 10 Hz, 1H, H-4 cis); 4,52 (m, 2H, $CH_2O$); 5,02 (m, 1H, H-5); 8,09 (s, 2H, Pyridyl H-3,4); 8,52 (s, 1H, Pyridyl H-6).

Beispiel XXIV

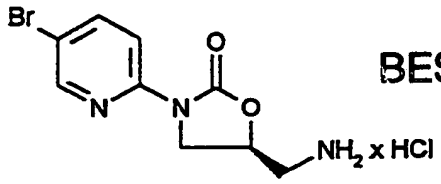
(5R)-3-1-(5-Brom-pyridin-2-yl)-5-azidomethyl-oxazolidin-2-on



Eine gerührte Lösung von 12,5 g (35,6 mmol) der Verbindung aus Beispiel XXIII in 48 ml wasserfreiem DMF wird mit 3,01 g (46,28 mmol) Natriumazid versetzt und 3 h bei 70°C gerührt. Man läßt auf Raumtemperatur abkühlen und rührt in 100 ml Eiswasser ein. Der entstandene Niederschlag wird durch Filtration abgetrennt, mit 50 ml Wasser und 20 ml Petrolether gewaschen und an der Luft getrocknet. Man erhält 10,1 g (95%) der Titelverbindung als helle Kristalle.
Schmp.: 64—67°C
$R_f$ = 0,63 (Toluol : Ethylacetat 2 : 3)
MS (DCI, $NH_3$) m/z = 298 $(M+H)^+$
$^1$H-NMR (250 MHz, $D_6$—DMSO) δ = 3,73 (m, 2H, $CH_2N_3$); 3,87 (dd, J = 6, 8 Hz, 1H, H-4 trans); 4,22 (dd, J = 8, 8 Hz, 1H, H-4 cis); 4,92 (m, 1H, H-5); 8,08 (s, 2H, Pyridyl H-3,4); 8,51 (s, 1H, Pyridyl H-6).

Beispiel XXV

(5S)-3-(5-Brom-pyridin-2-yl)-5-aminomethyl-oxazolidin-2-on Hydrochlorid





Eine gerührte Lösung von 10,1 g (33,9 mmol) der Verbindung aus Beispiel XXIV in 16,5 ml 1,2-Dimethoxyethan wird auf 50°C erwärmt. Man tropft langsam 4,68 ml (4,70 mmol) Trimethylphosphit zu (Gasentwicklung) und

rührt nach beendeter Zugabe nach 2 h bei 90°C nach. Nun tropft man 6,6 ml 6 N HCl zu und rührt nochmals 2 h bei 90°C nach. Man läßt auf Raumtemperatur abkühlen, trennt den Niederschlag durch Filtration ab, wäscht mit 2 × 10 ml 1,2-Dimethoxyethan und trocknet im Hochvakuum über NaOH. Man erhält 8,9 g (85%) der Titelverbindung als farblose Kristalle.

Schmp.: 260—262°C

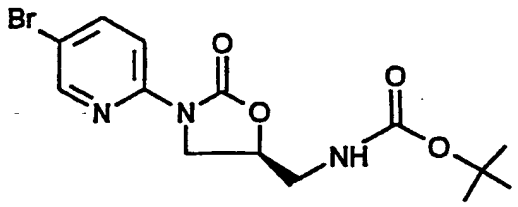
$R_f$ = 0,53 (Acetonitril : Wasser 4 : 1)

MS (EI) m/z = 271 ($M^+$)

$^1$H-NMR (250 MHz, $D_6$—DMSO) δ = 3,28 (m, 2H, $CH_2NH_2$); 3,93 (dd, J 7, 9 Hz, 1H, H-4 trans); 4,28 (dd, J = 9, 9 Hz, 1H, H-4 cis); 5,00 (m, 1H, H-5); 8,05 (s, 2H, Pyridyl H-3,4); 8,5 (m, 3H, NH2, Pyridyl H-6).

Beispiel XXVI

(5S)-3-(5-Brom-pyridin-2-yl)-5-((tert.butyloxy)carbonyl)aminomethyl-oxazolidin-2-on



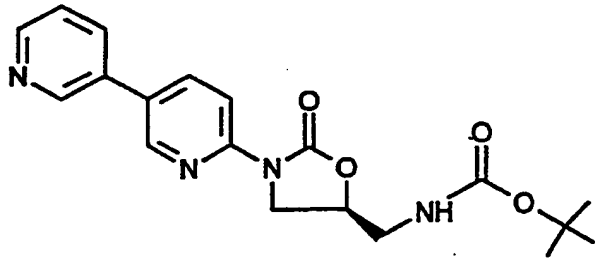

Man suspendiert 4,7 g (15 mmol) der Verbindung aus Beispiel XXV in 100 ml $CH_2Cl_2$. Anschließend fügt man 2,2 ml (16 mmol) Triethylamin zu, wobei eine Lösung entsteht. Man kühlt auf 0°C ab. Nun addiert man 3,5 g (16 mmol) Boc-Anhydrid so zu, daß die Temperatur +5°C nicht übersteigt und läßt bei Raumtemperatur über Nacht nachrühren. Man wäscht die organische Phase mit ges. NaCl-Lösung, trocknet über $MgSO_4$ und engt ein. Man erhält 5,4 g (97% d.Th.) des Produktes als weißen Feststoff.

Fp.: 184°C

$R_f$-Wert (Petrolether : Essigester = 10 : 4) = 0,30

Beispiel XXVII

((5S)-3-(5-[3-Pyridyl]-pyridin-2-yl)-5-((tert.butyloxy)carbonyl)aminomethyloxazolidin-2-on




Unter Argon legt man 5,3 g (14,24 mmol) der Verbindung aus Beispiel XXVI und 2,81 g Diethyl-(3-pyridyl)-boran in 100 ml abs. THF vor. Man addiert eine Lösung von 0,5 g (0,43 mmol) [($PPh_3$)$_4$Pd] in 90 ml THF und 4,9 ml (9,83 mmol) 2 M Natriumcarbonatlösung. Man läßt den Ansatz 5 Tage bei Rückfluß rühren. Nach dem Abkühlen auf RT gibt man 10 g Kieselgur zu und engt ein. Der Rückstand wird auf eine mit Kieselgel gefüllte Säule aufgetragen und mit Essigester eluiert.

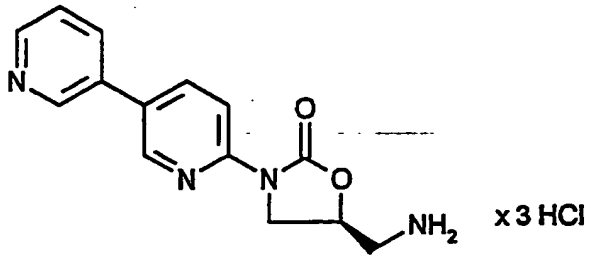
Man erhält 4 g (76% d.Th.) der Titelverbindung

Fp.: 163°C

$R_f$-Wert = 0,36 ($CH_2Cl_2$ : MeOH = 100 : 5)

Beispiel XXVIII

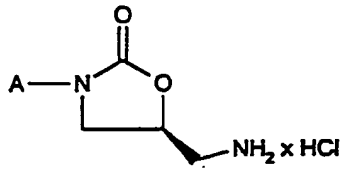
(5S)-3-(5-[3-Pyridyl]-pyridin-2-yl)-5-aminomethyl-oxazolidin-2-on Trihydrochlorid

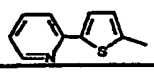
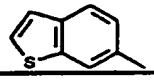
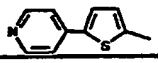
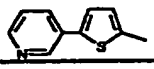
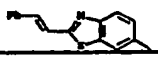
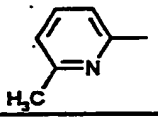
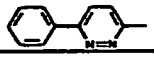
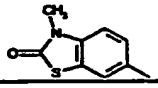
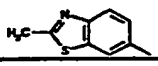
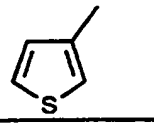
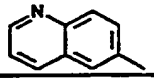
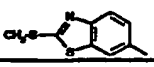
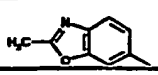
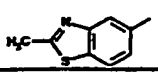
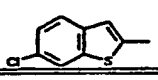



3,8 g (10,3 mmol) der Verbindung aus Beispiel XXVII werden in 25 ml Dioxan suspendiert. Man addiert 32,1 ml einer 4 M HCl-Lösung in Dioxan und läßt über Nacht bei Raumtemperatur rühren. Man engt ein und rührt den Rückstand mit Ether aus. Anschließend wird der Feststoff durch eine Fritte abgesaugt und mit Ether nachgewaschen. Man trocknet am Hochvakuum und erhält 3,7 g (95% d.Th.) der Titelverbindung.
Fp.: >250°C
MS (EI): 271 ($M^+$), 172
$^1$H-NMR (200 MHz, DMSO-$d_6$): δ = 9,35 (sb, 1H); 8,93 (m, 3H); 8,6 (breit, 3H); 8,42 (dd, J = 9, J = 3, 1H); 8,24 (d, J = 9, 1H); 8,11 (dd, J = 7,5, J = 6,5, 1H); 6,7 – 5,3 (breit, 2H); 5,06 (m, 1H); 4,38 (tr, J = 10, 1H); 4,03 (dd, J = 10, J = 7,5, 1H); 3,29 (m, 2H).

Analog den Vorschriften der Beispiele XXIII bis XXVIII wurden die in Tabelle II aufgeführten Verbindungen dargestellt:

Tabelle II

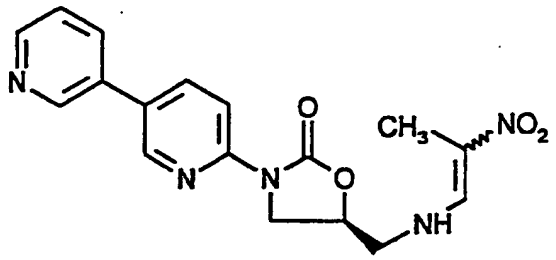



| Bsp.-Nr. | A | Smp. (°C) | $R_f$ / Laufmittel (Verhältnis) | Ausbeute (% d.Th.) |
|---|---|---|---|---|
| XXIX |  | - | - | 95 |
| XXX |  | - | - | 87 |
| XXXI |  | - | - | 94 |
| XXXII |  | - | - | 94 |
| XXXIII |  | 303 | 0,19, III (9:1) | 94 |
| XXXIV |  | - | 0,21, III (9:1) | 75 |
| XXXV |  | 273 | 0,24, III (4:1) | 75 |
| XXXVI |  | 259 u.Z. | 0,09, III (9:1) | 75 |
| XXXVII |  | 264 u.Z. | 0,16, III (9:1) | 94 |
| XXXVIII |  | 272 u.Z. | 0,13, III (9:1) | 61 |
| XXXIX |  | 80 | 0,12, II (4:1) | 87 |
| XL |  | - | 0,27, VI (100:10:4) | 26 |
| XLI |  | 258 u.Z. | - | 58 |
| XLII |  | 188 | 0,13, II (1:4) | 80 |
| XLIII |  | - | 0,05, II (1:1) | 57 |
| XLIV |  | - | 0,5, I (100:3) | 79 |

## Herstellungsbeispiele

### Beispiel 1

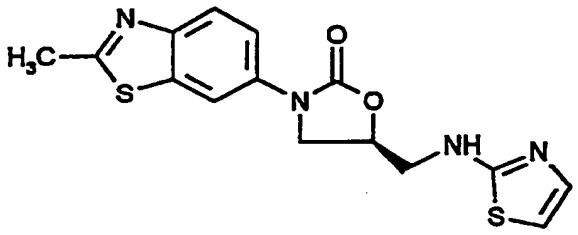
(5S)-3-(5-[3-Pyridyl]-pyridin-2-yl)-5-(2-nitro-prop-1-en-1-yl-aminomethyl)-oxazolidin-2-on



Unter Argon läßt man 100 mg (0,37 mmol) der Verbindung aus Beispiel XXVIII (freie Base; hergestellt durch Lösen in Wasser, $NH_{3(aq)}$-Zugabe bis pH 11, Extraktion mit $CH_2Cl_2$, Trocknen über $MgSO_4$ und Einengen) in 1 ml DMF und gibt 200 mg (1,11 mmol) 2-(2-Nitro-prop-1-en-1-yl-amino)-pyridin zu und läßt über Nacht rühren. Man versetzt mit Wasser, extrahiert 3 × mit Essigester, wäscht die organische Phase mit ges. NaCl-Lösung und trocknet über $MgSO_4$. Man engt ein und reinigt durch Säulenchromatographie an Kieselgel (Laufmittel $CH_2Cl_2$: MeOH = 100 : 5). Man erhält 126 mg (96% d.Th.) der Titelverbindung.
Fp.: 207°C
$R_f$-Wert: ($CH_2Cl_2$ : MeOH = 10 : 1) 0,57
MS (DCI): 356 $(M+H)^+$
$^1$H-NMR (200 MHz, DMSO-$d_6$): δ = 8,95 (d, J = 2, 1H); 8,79 (d, J = 2, 1H); 8,60 (dd, J = 5, J = 2, 1H); 8,4 — 7,9 und 7,6 — 7,4 (m, insgesamt 6H); 4,9 (m, 1H); 4,3 (m, 1H); 4,05 (m, 1H); 3,7 (m, 2H); 1,95 und 1,93 (s; insgesamt 3H).

### Beispiel 2

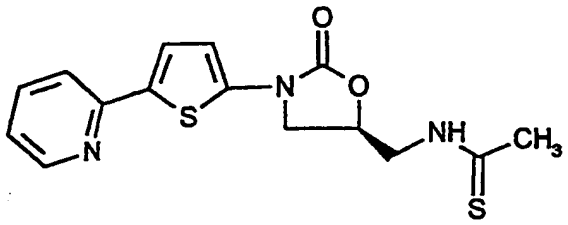
(5R)-3-(2-Methyl-benzo[4,5-d]thiazol-6-yl)-5-(2-thiazolyl-aminomethyl)-oxazolidin-2-on



Unter Argon werden 292 mg (2,92 mmol) 2-Aminothiazol in 5 ml abs. THF vorgelegt und bei −78°C mit 1,33 ml (2,92 mmol) 2,2 M n-BuLi-Lösung versetzt. Man läßt 30 Minuten bei −78°C rühren. Man addiert 0,5 g (1,46 mmol) (5R)-3-(2-Methyl-benzo[4, 5-d]thiazol-6-yl)-5-methoxysulfonyloxymethyl-oxazolidin-2-on, gelöst in 5 ml abs. THF, und läßt 1 h bei −78°C rühren. Man entfernt das Kühlbad und läßt über Nacht rühren. Man addiert $NH_4Cl$-Lösung und HCl-Lösung (auf pH 3), extrahiert mit Chloroform, trocknet über $MgSO_4$ und engt ein. Die Substanz wird säulenchromatographisch an Kieselgel gereinigt (Laufmittel $CH_2Cl_2$ : MeOH = 100 : 1 bis 100 : 3). Man erhält 193 mg (38% d.Th.) der Titelverbindung.
Fp.: 207°C
$R_f$ = 0,47 ($CH_2Cl_2$ : MeOH = 10 : 1)

Beispiel 3

(5R)-3-(5-(2-Pyridyl)-thien-2-yl)-5-thioacetylamino-methyl-oxazolidi-n-2-on



3,48 mg (1 mmol) der Verbindung aus Beispiel XXIX werden mit 4 ml THF und 0,24 ml (1,7 mmol) Triethylamin versetzt. Zu der so erhaltenen Reaktionsmischung gibt man unter Rühren 152 µl (1,1 mmol) Dithioessigsäureethylester und hält 24 h bei Raumtemperatur. Nach Einengen wird mit Methylenchlorid/Methanol (100 : 2) an Kieselgel chromatographiert.

Ausbeute: 100 mg (36% d.Th.)

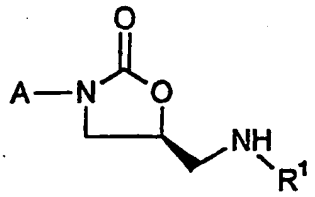
Smp.: 181°C n.Z.

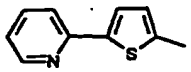
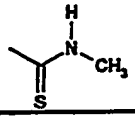
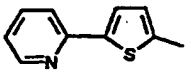
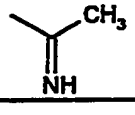
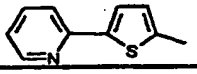
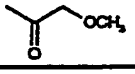
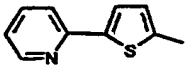
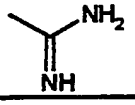
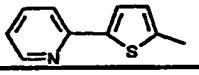
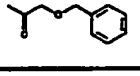
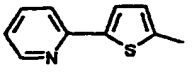
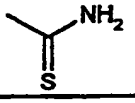
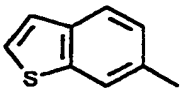
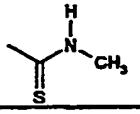
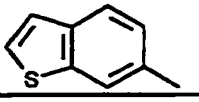
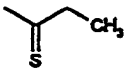
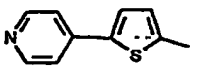
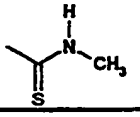
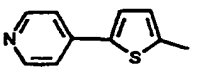
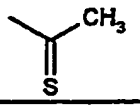
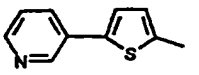
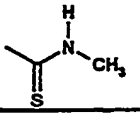
$R_f$: 0,36 (I; 100 : 5)

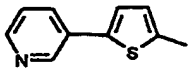
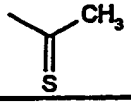
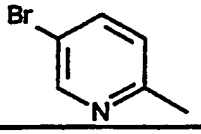
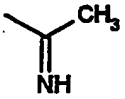
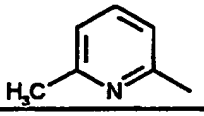
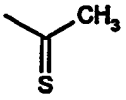
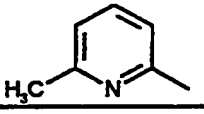
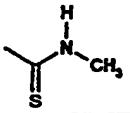
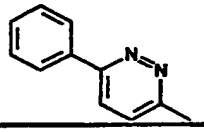
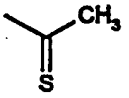
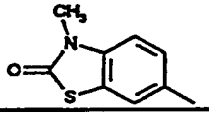
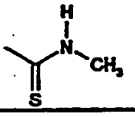
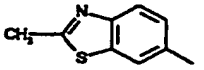
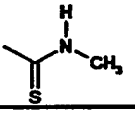
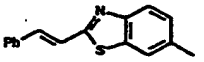
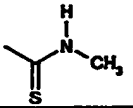
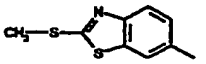
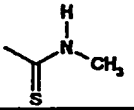
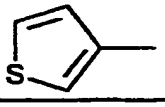
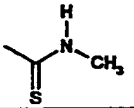
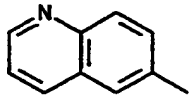
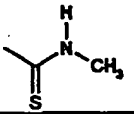
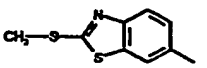
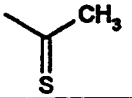
$^1$H-NMR ($D_6$—DMSO, 300 MHz): δ = 10,37 (br, 1H); 8,47 (d, J = 5 Hz, 1H); 7,75 —7,88 (m, 2H); 7,62 (d, J = 5 Hz, 1H); 7,2 (m, 1H); 6,58 (d, J = 5 Hz, 1H); 5,03— 5,13 (m, 1H); 4,21 (dd, J = 10 Hz, 9 Hz, 1H); 3,95 (t, J = 6 Hz, 2H); 3,85 (dd, J = 10 Hz, 6 HZ, 1H); 2,45 (s, 3H).

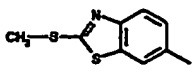
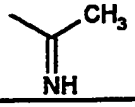
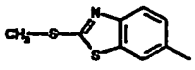
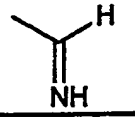
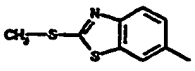
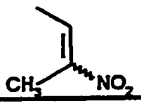
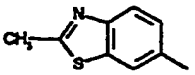
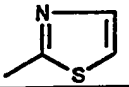
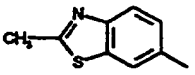
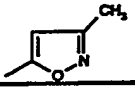
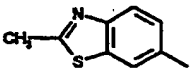
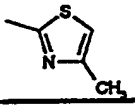
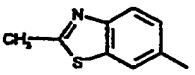
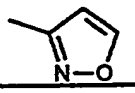
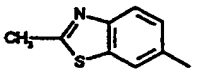
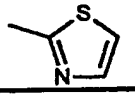
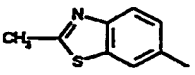
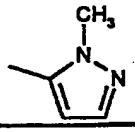
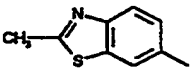
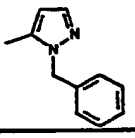
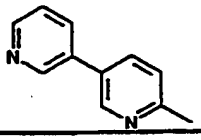
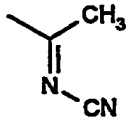
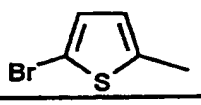
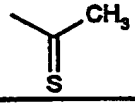
Analog den Vorschriften der Beispiele 1 bis 3 werden die in Tabelle 1 aufgeführten Verbindungen dargestellt:

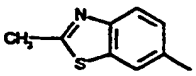
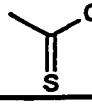
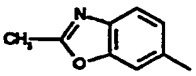
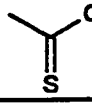
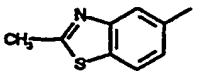
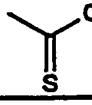
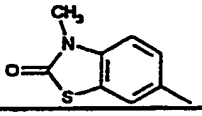
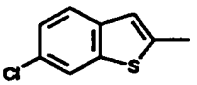
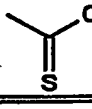
Tabelle 1



| Bsp.-Nr. | A | $R^1$ | Smp. (°C) | $R_f$ | Ausbeute (% d.Th.) |
|---|---|---|---|---|---|
| 4 |  |  | 160 u.Z. | 0,23, I (100:5) | 50 |
| 5 |  |  | 214 u.Z. | 0,02, I (100:5) | 40 |
| 6 |  |  | 127 | 0,29, I (100:5) | 80 |
| 7 |  |  | 212 u.Z. | | 13 |
| 8 |  |  | 152 | 0,32, I (100:5) | 79 |
| 9 |  |  | 137 u.Z. | | 25 |
| 10 |  |  | 143 u.Z. | | 99 |
| 11 |  |  | 142 u.Z. | 0,48, I (100:5) | 76 |
| 12 |  |  | 153 | 0,52, I (10:1) | 24 |
| 13 |  |  | 159 | 0,57, I (10:1) | 30 |
| 14 |  |  | | 0,48, I (10:1) | 5 |

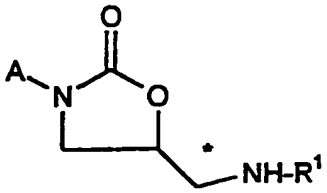
| Bsp.-Nr. | A | $R^1$ | Smp. (°C) | $R_f$ | Ausbeute (% d.Th.) |
|---|---|---|---|---|---|
| 15 |  |  | 160 u.Z. | 0,58, I (10:1) | 28 |
| 16 |  |  | 160 | 0,11, I (85:15) | 54 |
| 17 |  |  | - | 0,11, I (97:3) | 58 |
| 18 |  |  | 91 | 0,59, I (9:1) | 39 |
| 19 |  |  | 189 | 0,53, I (9:1) | 48 |
| 20 |  |  | 190 | 0,44, I. (9:1) | 63 |
| 21 |  |  | 160 | 0,48, I (9:1) | 72 |
| 22 |  |  | 182 | 0,12, I (95:5) | 75 |
| 23 |  |  | 152 | 0,31, I (9:1) | 52 |
| 24 |  |  | 77 | 0,55, I (9:1) | 70 |
| 25 |  |  | 115 | 0,51, I (9:1) | 71 |
| 26 |  |  | 163 u.Z. | 0,32, II (100:3) | 38 |

| Bsp.-Nr. | A | $R^1$ | Smp. (°C) | $R_f$ | Ausbeute (% d.Th.) |
|---|---|---|---|---|---|
| 27 |  |  | 184 | - | 27 |
| 28 |  |  | 203 | 0,08, VI (100:5:2) | 32 |
| 29 |  |  | 206 | 0,58 VII (10:1) | 68 |
| 30 |  |  | 207 | 0,47, I (10:1) | 38 |
| 31 |  |  | 211 | 0,34, I (100:5) | 35 |
| 32 |  |  | 201 | 0,49, I (100:5) | 29 |
| 33 |  |  | 184 | 0,42, I (100:5) | 39 |
| 34 |  |  | 223 | 0,39, I (100:5) | 18 |
| 35 |  |  | 214 | 0,29, I (100:5) | 25 |
| 36 |  |  | 218 | 0,39, I (100:5) | 39 |
| 37 |  |  | 229 | 0,28, I (100:5) | 37 |
| 38 |  |  | 133 u.Z. | 0,58, I (100:3) | 58 |

| Bsp.-Nr. | A | $R^1$ | Smp. (°C) | $R_f$ | Ausbeute (% d.Th.) |
|---|---|---|---|---|---|
| 39 |  |  | 224 | | 5 |
| 40 |  |  | 183 | | 33 |
| 41 |  |  | 180 u.Z. | 0,31, I (100:3) | 45 |
| 42 |  |  | 203 u.Z. | 0,31, I (100:3) | 53 |
| 43 |  |  | 176 u.Z. | 0,45, I (100:3) | 22 |

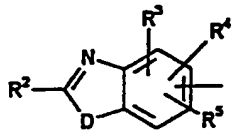
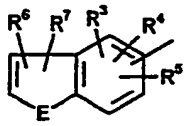
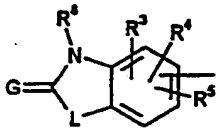
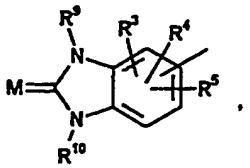
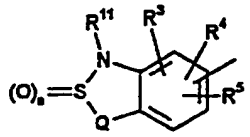
## Patentansprüche

1. Substituierte Oxazolidinone der allgemeinen Formel (I)



(I)

in welcher
A für einen über ein Kohlenstoffatom direkt gebundenen 5-gliedrigen aromatischen Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der zusätzlich einen annellierten Benzol- oder Naphthylring besitzen kann, oder
für einen über ein Kohlenstoffatom direkt gebundenen 6-gliedrigen, aromatischen Heterocyclus mit mindestens einem Stickstoffatom steht, oder
für einen über ein Kohlenstoffatom direkt gebundenen, jeweils 6-gliedrigen, bi- oder tricyclischen aromatischen Rest mit mindestens einem stickstoffhaltigen Ring steht, oder
für β-Carbolin-3-yl oder für über den 6-Ring direkt gebundenes Indolizinyl steht, wobei die Cyclen gegebenenfalls jeweils bis zu 3-fach gleich oder verschieden durch Carboxy, Halogen, Cyano, Mercapto, Formyl, Pyridyl, Phenyl, Trifluormethyl, Nitro, geradkettiges oder verzweigtes Alkoxy, Alkoxycarbonyl, Alkylthio oder Acyl mit jeweils bis zu 6 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen substituiert sind, die ihrerseits durch Phenyl substituiert sein können, oder
für einen Rest der Formel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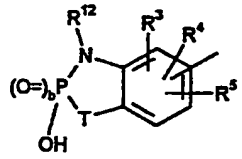
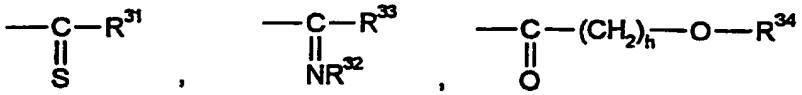
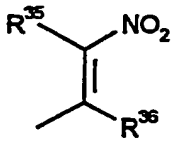


steht, worin
$R^3$, $R^4$, $R^5$, $R^6$ und $R^7$ gleich oder verschieden sind und Wasserstoff oder Carboxy, Halogen, Cyano, Formyl, Trifluormethyl, Nitro, für geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder für eine Gruppe der Formel $-CO-NR^{13}R^{14}$ stehen,
worin
$R^{13}$ und $R^{14}$ gleich oder verschieden sind und Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Phenyl bedeuten,
$R^2$, $R^8$, $R^9$, $R^{10}$, $R^{11}$ und $R^{12}$ gleich oder verschieden sind und Wasserstoff, Cycloalkylcarbonyl oder Cycloalkyl mit jeweils 3 bis 6 Kohlenstoffatomen, oder geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen bedeuten, oder geradkettiges oder verzweigtes Alkyl mit bis zu 10 Kohlenstoffatomen bedeuten, das gegebenenfalls durch Cyano, Trifluormethyl, Halogen, Phenyl, Hydroxy, Carboxyl, geradkettiges oder verzweigtes Alkoxycarbonyl mit bis zu 6 Kohlenstoffatomen, Aryl mit 6 bis 10 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen und/oder durch eine Gruppe der Formel $-(CO)_c-NR^{15}R^{16}$, $R^{17}-N-SO_2-R^{18}$, $R^{19}R^{20}-N-SO_2-$ oder $R^{21}-S(O)_d$ substituiert ist,
worin
c eine Zahl 0 oder 1 bedeutet,
$R^{15}$, $R^1$ und $R^{17}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
oder gemeinsam mit dem Stickstoffatom einen 5- bis 6-gliedrigen, gesättigten Heterocyclus mit gegebenenfalls einem weiteren Heteroatom aus der Serie N, S und/oder O bilden, der seinerseits gegebenenfalls, auch an einem weiteren Stickstoffatom, durch geradkettiges oder verzweigtes Alkyl oder Acyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,
$R^1$ und $R^{20}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
d eine Zahl 0, 1 oder 2 bedeutet,
$R^1$ und $R^{21}$ gleich oder verschieden sind und geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Benzyl, Phenyl oder Tolyl bedeuten,
oder
geradkettiges oder verzweigtes Acyl mit bis zu 6 Kohlenstoffatomen bedeuten, das gegebenenfalls Trifluormethyl, Trichlormethyl oder durch eine Gruppe der Formel $-OR^{22}$ substituiert ist,
worin
$R^{22}$ Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet, das gegebenenfalls durch Aryl mit bis zu 10 Kohlenstoffatomen substituiert ist,
oder
eine Gruppe der Formel $-(CO)_e-NR^{23}R^{24}$, $-NR^{25}-SO_2R^{26}$, $R^{27}R^{28}-NSO_2-$ oder $R^{29}-S(O)_f$ bedeuten,
worin
e die oben angegebene Bedeutung von c hat und mit dieser gleich oder verschieden ist,
$R^{23}$ und $R^{24}$ und $R^{25}$ jeweils die oben angegebene Bedeutung von $R^{15}$, $R^{16}$ und $R^{17}$ haben und mit dieser gleich oder verschieden sind,
$R^{27}$ und $R^{28}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
f die oben angegebene Bedeutung von d hat und mit dieser gleich oder verschieden ist,
$R^{26}$ und $R^{29}$ die jeweils oben angegebene Bedeutungen von $R^{18}$ und $R^{21}$ haben und mit dieser gleich oder verschieden sind,
D ein Sauerstoffatom oder einen Rest der Formel $-S(O)_g$ bedeutet,
worin

g eine Zahl 0, 1 oder 2 bedeutet,
E und L gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom bedeuten,
G, M, T und Q gleich oder verschieden sind und ein Sauerstoff- oder ein Schwefelatom, oder eine Gruppe der Formel —$NR^{30}$ bedeuten,
worin
$R^{30}$ Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
a und b gleich oder verschieden sind und eine Zahl 1 oder 2 bedeuten,
$R^1$ für einen Rest der Formel

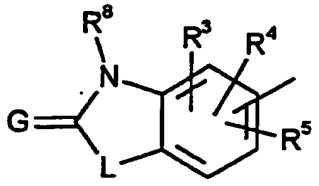


oder



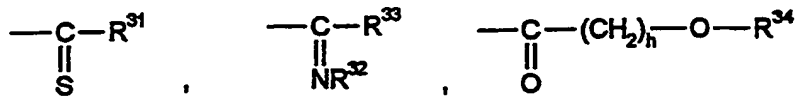
steht, worin
$R^{31}$ geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder eine Gruppe der Formel —$NR^{38}R^{39}$ bedeutet,
worin
$R^{38}$ und $R^{39}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
$R^{32}$ Wasserstoff, Cyano, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen bedeutet,
$R^{33}$ Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 7 Kohlenstoffatomen, Phenyl, Cycloalkyl mit 3 bis 6 Kohlenstoffatomen oder eine Gruppe der Formel —$NR^{40}R^{41}$ bedeutet,
worin
$R^{40}$ und $R^{41}$ die oben angegebene Bedeutung von $R^{13}$ und $R^{14}$ haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
$R^{34}$ geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen oder Benzyl bedeutet,
$R^{35}$ und $R^{36}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeuten,
oder
$R^1$ für Cyano oder für einen 5- bis 7-gliedrigen, gesättigten, partiell ungesättigten oder ungesättigten Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe S, N und/oder O steht, der gegebenenfalls auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Halogen oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen substituiert ist,
als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

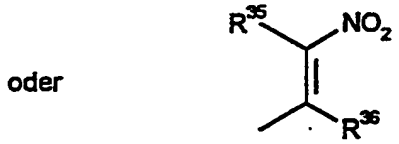
2. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1,
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 3-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 4 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 4 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder für einen Rest der Formel



steht, worin
G ein Sauerstoff- oder Schwefelatom bedeutet,
L ein Sauerstoff- oder Schwefelatom bedeutet,
$R^8$ geradkettiges oder verzweigtes Alkyl mit bis zu 6 Kohlenstoffatomen bedeutet,

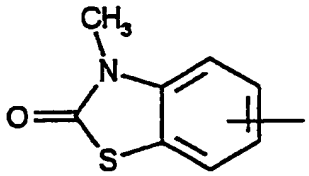
$R^3$, $R^4$ und $R^5$ gleich oder verschieden sind und Wasserstoff, Fluor, Chlor oder Brom bedeuten,
$R^1$ für einen Rest der Formel



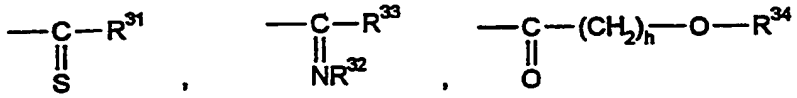


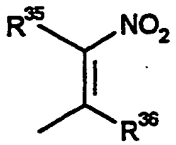
steht, worin
$R^{31}$ geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
$R^{38}$ und $R^{39}$ gleich oder verschieden sind und Wasserstoff, Methyl oder Ethyl bedeuten,
$R^{32}$ Wasserstoff, Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen bedeutet,
$R^{33}$ Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 5 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
$R^{40}$ und $R^{41}$ die oben angegebene Bedeutung von $R^{38}$ und $R^{39}$ haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
$R^{34}$ geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen oder Benzyl bedeutet,
$R^{35}$ und $R^{36}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeuten,
oder
$R^1$ für Cyano oder für Thienyl, Oxazolyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls, auch über eine N-Funktion, bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sind,
als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

3. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1,
in welcher
A für jeweils über ein Kohlenstoffatom gebundenes Chinolyl, Benzothiophen, Benzthiazolyl, Benzoxazolyl, Pyridyl, Pyridazyl oder Thienyl steht, die gegebenenfalls bis zu 2-fach gleich oder verschieden durch Fluor, Chlor, Brom, Pyridyl, Phenyl oder durch geradkettiges oder verzweigtes Alkyl oder Alkylthio mit jeweils bis zu 3 Kohlenstoffatomen oder durch geradkettiges oder verzweigtes Alkenyl mit bis zu 3 Kohlenstoffatomen substituiert sind, das seinerseits durch Phenyl substituiert sein kann, oder
für einen Rest der Formel



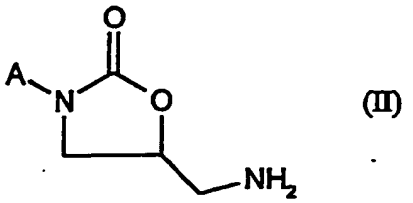
steht,
$R^1$ für einen Rest der Formel



oder 

steht, worin
$R^{31}$ geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder eine Gruppe der Formel $-NR^{38}R^{39}$ bedeutet,
worin
$R^{38}$ und $R^{39}$ gleich oder verschieden sind und Wasserstoff oder Methyl bedeuten,
$R^{32}$ Wasserstoff, Cyano, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenyl oder geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen bedeutet,
$R^{33}$ Wasserstoff, geradkettiges oder verzweigtes Alkyl mit bis zu 4 Kohlenstoffatomen, Phenyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder eine Gruppe der Formel $-NR^{40}R^{41}$ bedeutet,
worin
$R^{40}$ und $R^{41}$ die oben angegebene Bedeutung von $R^{38}$ und $R^{39}$ haben und mit dieser gleich oder verschieden sind,
h eine Zahl 1, 2, 3 oder 4 bedeutet,
$R^{34}$ geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen oder Benzyl bedeutet,
$R^{35}$ und $R^{36}$ gleich oder verschieden sind und Wasserstoff oder geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen bedeuten,
oder
$R^1$ für Cyano oder für Thienyl, Thiazolyl, Isoxazolyl oder Pyrazolyl steht, die gegebenenfalls auch über eine N-Funktion bis zu 2-fach gleich oder verschieden durch Benzyl, Fluor, Chlor, Brom oder durch geradkettiges oder verzweigtes Alkyl mit bis zu 3 Kohlenstoffatomen substituiert sein kann,
als reine Stereoisomere oder als Stereoisomerengemisch,
und deren Salze.

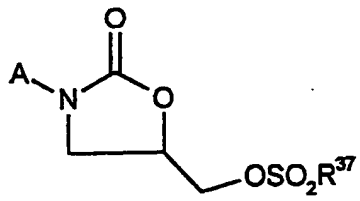
4. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, dadurch gekennzeichnet, daß man
[A] Verbindungen der allgemeinen Formel (II)

 (II)

in welcher
A die in Anspruch 1 angegebene Bedeutung hat,
mit Verbindungen der allgemeinen Formel (III)

$R^1-Y$ (III)

in welcher
$R^1$ die in Anspruch 1 angegebene Bedeutung hat,
und
Y in Abhängigkeit von $R^1$ für Wasserstoff, Halogen oder für $C_1-C_4$ geradkettiges oder verzweigtes Alkoxy oder Oxyalkoxycarbonyl steht,
oder
[B] Verbindungen der allgemeinen Formel (IV)



(IV)

in welcher
A die oben angegebene Bedeutung hat,
$R^{37}$ für $C_1-C_4$-Alkyl steht,
mit Verbindungen der allgemeinen Formel (V)

$NH_2-R^{1'}$ (V)

in welcher
$R^{1'}$ für einen der oben unter $R^1$ aufgeführten Heterocyclen steht,
oder mit Ethyldithioacetat in inerten Lösemitteln, gegebenenfalls in Anwesenheit einer Base umsetzt,
und im Fall der S-Oxide eine Oxidation nach üblicher Methode durchführt,
und gegebenenfalls weitere Substituenten oder bereits vorhandene funktionelle Gruppen nach üblichen Methoden einführt bzw. derivatisiert,
und gegebenenfalls die Stereoisomere nach üblichen Methoden trennt.

5. Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1 zur Verwendung bei der Bekämpfung von Krankheiten.

6. Verwendung von Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1 zur Herstellung von Arzneimitteln.

7. Arzneimittel enthaltend Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1.

BM

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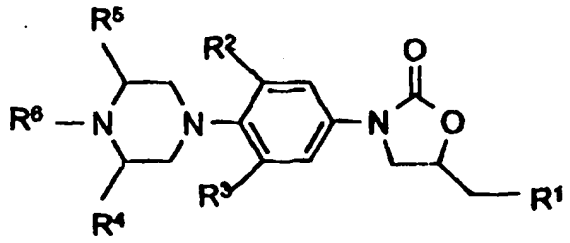
(57) Abstract



(I)

The invention concerns a compound of formula (I) wherein, for example: $R^1$ is of the formula -NHC(=O)$R^a$ wherein $R^a$ is for example (1-4C)alkyl; $R^2$ and $R^3$ are independently hydrogen or fluoro; $R^4$ and $R^5$ are independently hydrogen or methyl; $R^6$ is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, and optionally substituted by substituents selected from (1-4C)alkyl (optionally substituted), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro; pharmaceutically-acceptable salts, suitable N-oxides and in-vivo-hydrolysable esters thereof; processes for their preparation; pharmaceutical compositions containing them and their use as antibacterial agents.

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# SUBSTITUTED PIPERAZINYL-PHENYL-OXAZOLIDINONE DERIVATIVES AND THEIR USE AS ANTI-BACTERIAL AGENTS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing an oxazolidinone ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly good activity against such pathogens.

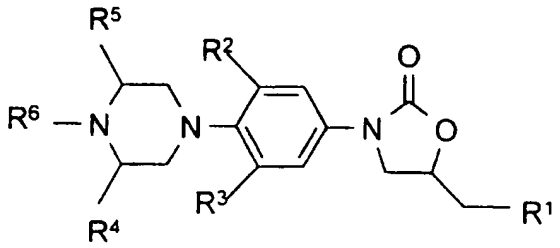
Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant streptococcus pneumoniae and multiply resistant Enterococcus faecium.

The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with nephrotoxicity and ototoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens.

The present inventors have discovered a class of antibiotic compounds containing an oxazolidinone ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams.

We have now discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics. In comparison with compounds described in the art (for example Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165) the compounds also possess a favourable toxicological profile.

Accordingly the present invention provides a compound of the formula (I)



(I)

wherein:

$R^1$ is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, or of the formula -NHC(=O)$R^a$ wherein $R^a$ is hydrogen, (1-4C)alkoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or $R^1$ is of the formula -N(Me)C(=O)$R^b$ wherein $R^b$ is hydrogen, methyl or methoxy or $R^1$ is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2;

$R^2$ and $R^3$ are independently hydrogen or fluoro;

$R^4$ and $R^5$ are independently hydrogen or methyl;

$R^6$ is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl (optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2),

(1-4C)alkylS(O)$_n$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; and suitable N-oxides thereof.

In this specification the term "alkyl" includes straight chained and branched structures. For example, (1-6C)alkyl includes propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only.

In this specification a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, includes pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine.

Examples of (1-4C)alkyl include methyl, ethyl, propyl, isopropyl and tert-butyl; examples of halo include fluoro, chloro, bromo and iodo; examples of N-(1-4C)alkylcarbamoyl include methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl; examples of di-(N-(1-4C)alkyl)carbamoyl include di-(methyl)carbamoyl and di-(ethyl)carbamoyl; examples of the (1-4C)alkyl group or groups in N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl being optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl include 2-hydroxyethylaminocarbonyl, bis-(2-hydroxyethyl)aminocarbonyl, 2-methoxyethylaminocarbonyl and methoxycarbonylmethylaminocarbonyl; examples of (1-4C)alkylS(O)$_n$ include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of (1-4C)alkylS(O)$_n$amino include methylsulfonylamino and ethylsulfonylamino; examples of (2-4C)alkenyl include allyl and vinyl; examples of (1-4C)alkoxy include methoxy, ethoxy and propoxy; examples of (1-4C)alkanoylamino include formamido, acetamido and propionylamino; examples of (2-4C)alkanoylamino include acetamido and propionylamino; examples of N-(1-4C)alkylamino include methylamino and ethylamino; examples of di-(N-(1-

4C)alkyl)amino include di-N-methylamino, di-(N-ethyl)amino and N-ethyl-N-methylamino; examples of (1-4C)alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, n- and tert-butoxycarbonyl ; examples of (1-4C)alkanesulfonyloxy include methanesulfonyloxy and ethanesulfonyloxy; and examples of (1-4C)alkylaminocarbonyloxy include methylaminocarbonyloxy and ethylaminocarbonyloxy.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

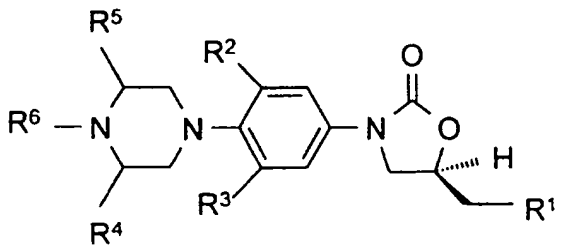
In this specification a suitable N-oxide refers to the N-oxides which may be formed on an available nitrogen atom in either the piperazine ring or in the heteroaryl ring $R^b$. A suitable N-oxide may be optionally in the form of a pharmaceutically-acceptable salt.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the formula (I).

An in-vivo hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An in-vivo hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino or piperazino linked from a ring nitrogen atom via methylamino to the 3- or 4-position of the benzoyl ring.

The compounds of the present invention have a chiral centre at the C-5 position of the oxazolidinone ring. The pharmaceutically active enantiomer is of the formula (IA):



(IA)

The present invention includes the pure enantiomer depicted above or mixtures of the 5R and 5S enantiomers, for example a racemic mixture. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted above could be either 5R or 5S depending upon the value of $R^1$. For example, when $R^1$ is acetamido, the enantiomer depicted above is the 5S enantiomer and when $R^1$ is hydroxy, the enantiomer depicted above is the 5R enantiomer.

Furthermore, some compounds of the formula (I) may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereo-isomers that possess antibacterial activity.

The invention relates to all tautomeric forms of the compounds of the formula (I) that possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

In a further aspect of the invention there is provided a compound of the formula (I) wherein:

$R^1$ is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, or $R^1$ is of the formula $-NHC(=O)R^a$ wherein $R^a$ is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or $R^1$ is of the formula $-NHSO_2$(1-4C)alkyl

$R^2$ and $R^3$ are independently hydrogen or fluoro;

$R^4$ and $R^5$ are independently hydrogen or methyl;

$R^6$ is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl [optionally substituted by carboxy or (1-4C)alkoxycarbonyl], (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; and suitable N-oxides thereof.

In another further aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, as defined in the above aspects of the invention, except that suitable N-oxides are excluded.

In a yet further aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, as defined anywhere above, except that the following optional substituents on $R^6$, namely (1-4C)alkoxy, (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino and those N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl substituents with the (1-4C)alkyl group or groups substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl, are excluded; and the number of optional substituents on $R^6$ is restricted to one or two. For the avoidance of doubt, in the preceding yet further aspect of the invention suitable N-oxides are optionally excluded.

In a preferred aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, wherein the substituents $R^1$ to $R^6$ and other optional substituents mentioned above have the values disclosed hereinbefore, or any of the following values :

(a) Preferably $R^1$ is hydroxy, chloro, fluoro, methanesulfonyloxy, amino, azido, methoxy, methylthio, methylaminocarbonyloxy, or of the formula -NHC(=O)$R^a$ wherein $R^a$ is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or $R^1$ is of the formula -N(Me)C(=O)$R^b$ wherein $R^b$ is hydrogen, methyl or methoxy or $R^1$ is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(b) More preferably $R^1$ is hydroxy, chloro, fluoro, methanesulfonyloxy, or of the formula -NHC(=O)$R^a$ wherein $R^a$ is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or $R^1$ is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(c) Yet more preferably $R^1$ is hydroxy, or of the formula -NHC(=O)$R^a$ wherein $R^a$ is (1-4C)alkyl or $R^1$ is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(d) When $R^1$ is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2, n is preferably 2.

(e) Yet more preferably $R^1$ is of the formula -NHC(=O)(1-4C)alkyl.

(f) Most preferably $R^1$ is acetamido.

(g) In another aspect $R^1$ is hydroxy.

(h) Preferably one of $R^2$ and $R^3$ is hydrogen and the other is fluoro.

(i) Preferably at least one of $R^4$ and $R^5$ is hydrogen.

(j) Preferably $R^4$ and $R^5$ are both hydrogen.

(k) Preferably the heteroaryl ring in $R^6$ is pyrimidine, pyridazine or pyrazine.

(l) Yet more preferably the heteroaryl ring in $R^6$ is pyrimidine or pyrazine.

(m) Still more preferably the heteroaryl ring in $R^6$ is pyrimidin-2-yl or pyrazin-2-yl.

(n) Most preferably the heteroaryl ring in $R^6$ is pyrimidin-2-yl.

(o) Preferably optional substituents on the heteroaryl ring are not positioned in the 2-position relative to the ring carbon atom which is attached to the piperazine ring.

(p) Preferably the optional substituents on the heteroaryl ring are independently selected from (1-4C)alkyl (optionally substituted by (1-4C)alkoxy or (2-4C)alkanoylamino), (1-4C)alkylthio, halo, carboxy, (1-4C)alkoxycarbonyl, and carbamoyl.

(q) More preferably the optional substituents on the heteroaryl ring are independently selected from methyl or ethyl (each optionally substituted by methoxy, ethoxy or acetamido), methylthio, ethylthio, chloro, bromo, carboxy, methoxycarbonyl, ethoxycarbonyl and carbamoyl.

(r) Yet more preferably the optional substituents on the heteroaryl ring are independently selected from methyl, ethyl, methoxymethyl, 2-(acetamido)ethyl, methylthio, chloro, bromo, carboxy, methoxycarbonyl and carbamoyl.

(s) Most preferably the optional substituents on the heteroaryl ring are independently selected from (1-4C)alkyl (preferably methyl), halo (preferably chloro), nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

(t) Preferably the heteroaryl ring is unsubstituted or substituted by one substituent.

(u) Most preferably the heteroaryl ring is unsubstituted.

Therefore, especially preferred compounds of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, are those defined above wherein

$R^1$ is acetamido, one of $R^2$ and $R^3$ is hydrogen and the other is fluoro. $R^4$ and $R^5$ are both hydrogen. $R^6$ is pyrimidine or pyrazine and the optional substituents on the heteroaryl ring are independently selected from methyl, chloro, nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

Particular compounds of the present invention include :

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

Further particular compounds of the present invention include :

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(3-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

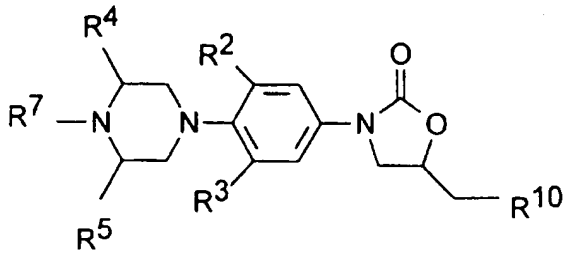
Especially preferred compounds of the invention include

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

In a further aspect the present invention provides a process for preparing a compound of the formula (I), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof. The compounds of the formula (I), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof may be prepared by deprotecting a compound, containing at least one protecting group, of the formula (II), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof :



(II)

wherein $R^2$, $R^3$, $R^4$ and $R^5$ are as hereinabove defined. $R^7$ is $R^6$ or protected $R^6$ and $R^{10}$ is $R^1$ or protected $R^1$ and thereafter if necessary forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, tert-butyl); lower alkoxy lower alkyl groups (eg methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (eg allyl); lower alkanoyl groups (eg acetyl); lower alkoxycarbonyl groups (eg tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (eg trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl); aryl lower alkyl groups (eg benzyl) groups; and triaryl lower alkyl groups (eg triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, eg p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (eg tert-butoxycarbonyl); lower alkenyloxycarbonyl (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (eg trimethylsilyl and tert-butyldimethylsilyl); alkylidene (eg methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, metal- or enzymically-catalysed hydrolysis, for groups such as o-nitrobenzyloxycarbonyl, photolytically and for groups such as silyl groups, fluoride.

Examples of protecting groups for amide groups include aralkoxymethyl (eg. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (eg. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (eg. trimethylsilyl, tert-butyldimethylsilyl,

by reacting the amide with the appropriate chloride and removing with acid, or in the case of the silyl containing groups fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

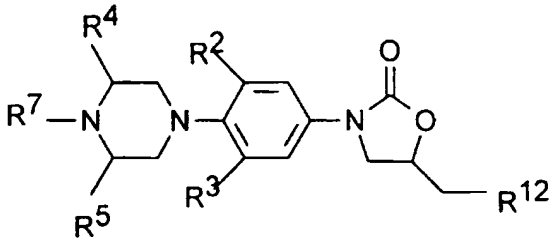
For further examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons).

In another aspect of the present invention the compounds of the formulae (I) and (II), pharmaceutically-acceptable salts, suitable N-oxides and in-vivo hydrolysable esters thereof can be prepared:

(a) by modifying a substituent in or introducing a substituent into another compound of formula (I) or (II);

(b) when $R^1$ or $R^{10}$ is of the formula - $NHS(O)_n$(1-4C)alkyl, wherein n is 1 or 2, by oxidising a compound of the formula (I) wherein n is 0 or, when n is 2 by oxidising a compound of the formula (I) or (II) wherein n is 1;

(c) when $R^1$ or $R^{10}$ is azido, by reacting a compound of the formula (III) with a source of azide:



(III)

(d) when $R^1$ or $R^{10}$ is amino, by reducing a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is azido;

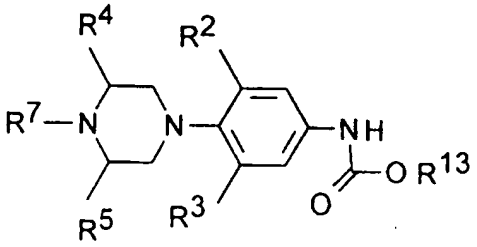
(e) when $R^1$ or $R^{10}$ is of the formula -$NHC(=O)R^a$, by introducing -$C(=O)R^a$ into a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino;

(f) when $R^1$ or $R^{10}$ is of the formula -$NHS(O)_n$ (1-4C)alkyl by introducing -$S(O)_n$ (1-4C)alkyl into a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino:

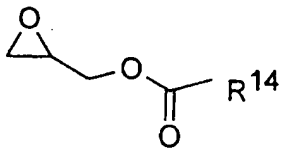
(g) when $R^1$ or $R^{10}$ is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is hydroxy;

(h) when $R^1$ or $R^{10}$ is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (III);

(i) when $R^1$ or $R^{10}$ is hydroxy, by reacting a compound of the formula (IV) with a compound of the formula (V):

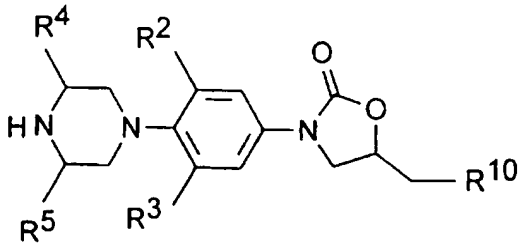


(IV)



(V)

(j) by reacting a compound of the formula (VI) with a compound of the formula (VII):



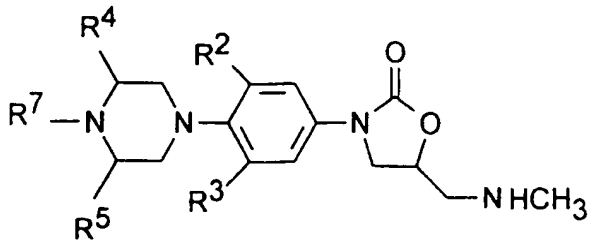
(VI)

$R^7$-$L^1$

(VII)

(k) when $R^{10}$ is of the formula -N($CO_2R^{15}$)CO(1-4C)alkyl; from a compound of the formula (I) and (II) wherein $R^1$ or $R^{10}$ is hydroxy;

(l) when $R^1$ or $R^{10}$ is of the formula -N(Me)C(=O)$R^b$, by introducing the group -C(=O)$R^b$ into a compound of the formula (VIII):



(VIII)

and

(m) when a suitable N-oxide is required, by preparation directly from a corresponding parent compound of the formula (I) or (II), or by assembly from suitable N-oxide starting materials;

wherein $R^2$ - $R^5$ and $R^7$ and $R^{10}$ are as hereinabove defined. $R^{12}$ is mesyloxy or tosyloxy, $R^{13}$ is (1-6C)alkyl or benzyl. $R^{14}$ is (1-6C)alkyl. $R^{15}$ is (1-4C)alkyl or benzyl and $L^1$ is a leaving goup and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester.

Methods for converting substituents into other substituents are known in the art. For example, an alkylthio group may be oxidised to an alkylsulfinyl or alkysulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, an amino group converted to an acetamido or sulfonamido group, a hydroxy group alkylated to a methoxy group, a carboxy group converted to a carbamoyl group, an N-(1-4C)alkylcarbamoyl or di-(N-(1-4C)alkyl)carbamoyl group, or a bromo group converted to an alkylthio group. Also for example, a chloro group may be introduced at an unsubstituted position in $R^7$, or a chloro group may be removed from $R^7$ (by, for example, hydrogenation as in Examples 9 and 31).

Compounds of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is $-NHS(O)_n$(1-4C)alkyl can be prepared by oxidising a compound of the formula (I) or (II) with standard reagents known in the art for the oxidation of a thio group to a sulfinyl or sulfonyl group. For example, a thio group may be oxidised to a sulfinyl group with a peracid such as m-chloroperoxybenzoic acid and oxidising agents such as potassium permanganate will

convert a thio group to a sulfonyl group. Compounds of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is -NHS(1-4C)alkyl can be prepared by reacting compounds of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino with a reagent such as (1-4C)alkylSCl.

A compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is azido may be prepared, for example, by reacting a compound of the formula (III) with sodium azide in an inert solvent such as DMF in a temperature range of ambient to 100°C, normally in the region of 75°C - 85°C. A compound of the formula (III) may be prepared by converting the hydroxy group in a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is hydroxy into a tosyloxy or mesyloxy group by standard methods known in the art. For example, by reacting the compound of the formula (I) or (II) with tosyl chloride or mesyl chloride in the presence of a mild base such as triethylamine, or pyridine.

Suitable reducing agents for reducing azido to amino in a compound of the formula (I) or (II) include triethylamine/hydrogen sulfide, triphenylphosphine or phosphite ester, or hydrogen in the presence of a catalyst. More specifically the reduction of the azido group may be carried out by heating it in an aprotic solvent, such as 1,2-dimethoxyethane, in the presence of $P(OMe)_3$ and subsequently heating in 6N aqueous hydrochloric acid, or reacting it with hydrogen in the presence of palladium on carbon in a solvent such as DMF or ethyl acetate. For further details on the reduction of azides to amines see USP 4,705,799. The azido compound may be reduced and converted to a compound of the formula (I) or (II), wherein $R^1$ or $R^{10}$ is acetamido, in situ using acetic anhydride in DMF.

When $R^a$ is (1-4C)alkyl, the group -C(=O)(1-4C)alkyl may be introduced into a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino by standard acetylation procedures. For example, the amino group may be acetylated to give an acetamido group using the Schotten-Baumann procedure i.e. reacting the compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino with acetic anhydride in aqueous sodium hydroxide and THF in a temperature range of 0°C to ambient temperature. Preferably the acylation is carried out in situ following the catalytic hydrogenation of a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is azido, by performing the hydrogenation in the presence of acetic anhydride (for example using similar methods to those used in Example 15).

When $R^a$ is hydrogen, the -CHO group may be introduced into the compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino (amino compound) by reacting the latter

compound with formic acetic anhydride, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature, or by reacting it with ethyl formate in an inert organic solvent in the temperature range of 50-100°C.

When $R^a$ is (1-4C)alkoxy, the -COO(1-4C)alkyl group may be introduced into the amino compound by reacting the latter compound with (1-4C)alkyl chloroformate, in the presence of an organic base such as triethylamine, in an organic solvent such as dichloromethane and in a temperature range of 0°C to ambient temperature.

When $R^a$ is amino, the $-CONH_2$ group may be introduced into the amino compound by reacting the latter compound either with potassium cyanate in aqueous acid (eg hydrochloric acid) in a temperature range of ambient temperature to 40°C or with phenyl carbamate in glyme at reflux.

When $R^a$ is chloromethyl, dichloromethyl, cyanomethyl or methoxymethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with the appropriate acid chloride under standard conditions. The acid chloride may be prepared from the appropriate acid. When $R^a$ is acetylmethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with diketene, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature.

Alternatively, the amino compound may be reacted with the appropriate acid anhydride, in dichloromethane or THF, in the presence of an organic base such as triethylamine and in a temperature range of 0°C to ambient temperature, or the amino compound may be reacted with the appropriate acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and an organic base such as triethylamine, in an organic solvent such as dichloromethane, in a temperature range of 0°C to ambient temperature.

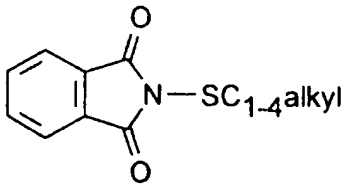
When $R^a$ is methylamino, the -CONHMe group may be introduced into the amino compound by reacting the latter compound with methyl isocyanate in an organic solvent such as THF or acetonitrile, in a temperature range of 0°C to ambient temperature.

When $R^a$ is dimethylamino, the $-CONMe_2$ group may be introduced into the amino compound my reacting the latter compound with dimethylcarbamoyl chloride and triethylamine in an organic solvent such as THF or acetonitrile, in a temperature range of 0°C to ambient temperature.

Standard reaction conditions for the conversion of a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino to a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is sulfonamido are known in the art. For example, a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino could for example be converted to a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is (1-4C)alkylSO$_2$NH- by reacting the former compound with a sulfonyl chloride, for example, mesyl chloride, in a mild base such as pyridine.

Alternatively compounds of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is (1-4C)alkylSO$_2$NH- or (1-4C)alkylSONH- may be prepared by reacting a compound of the formula (I) or (II) wherein $R^1$ is amino with a compound of the formula (1-4C)alkylSO$_2$L$^2$ or (1-4C)SOL$^2$ wherein L$^2$ is a phthalimido group.

The phthalimido compound may be prepared by oxidising a compound of the formula (IX):




(IX)

with standard oxidising agents known for the conversion of a thio group to a sulfinyl or sulfonyl group.

Compounds of the formula (IX) can be prepared by reacting phthalimide with an alkylthiochloride ((1-4C)alkylSCl).

A compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is fluoro may be prepared by reacting a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is hydroxy (hydroxy compound) with a fluorinating agent such as diethylaminosulfur trifluoride in an organic solvent such as dichloromethane in the temperature range of 0°C to ambient temperature.

When $R^1$ or $R^{10}$ is chloro, the compound of the formula (I) or (II) may be formed by reacting the hydroxy compound with a chlorinating agent. For example, by reacting the hydroxy compound with thionyl chloride in a temperature range of ambient temperature to reflux, optionally in a chlorinated solvent such as dichloromethane or by reacting the hydroxy compound with carbon tetrachloride/triphenyl phosphine in dichloromethane, in a temperature range of 0°C to ambient temperature.

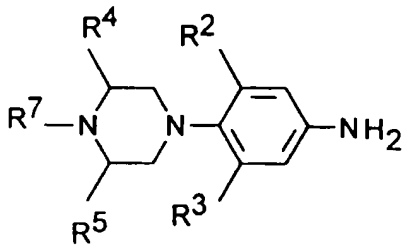
The (1-4C)alkanesulfonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkanesulfonyl chloride in the presence of a mild base such as triethylamine or pyridine.

The (1-4C)alkylaminocarbonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkyl cyanate in an organic solvent such as THF or acetonitrile, in the presence of triethylamine, in a temperature range of 0°C to 50°C.

A compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is chloro may also be prepared from a compound of the formula (III), by reacting the latter compound with lithium chloride and crown ether, in a suitable organic solvent such as THF, in a temperature range of ambient temperature to reflux. A compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is (1-4C)alkylthio or (1-4C)alkoxy may be prepared by reacting the compound of the formula (III) with sodium thio(1-4C)alkoxide or sodium (1-4C)alkoxide respectively, in an alcohol or THF, in a temperature range of 0°C to reflux.

Compounds of the formulae (IV) and (V) are conveniently reacted together in the presence of a strong base such as butyl lithium, lithium bistrimethylsilylamide, sodium hydride, lithium tert-butoxide or lithium diisopropylamide. The reaction is conveniently carried out in an inert solvent such as tetrahydrofuran (THF), dimethylformamide (DMF), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidone in a temperature range of -78°C to -50°C for the deprotonation and cyclisation. Suitable values for $R^{13}$ include ethyl and benzyl and suitable values for $R^{14}$ include ethyl and n-propyl, preferably n-propyl.

A compound of the formula (IV) is conveniently prepared by reacting a chloroformate of the formula ($ClCOOR^{13}$) with a compound of the formula (IVA):

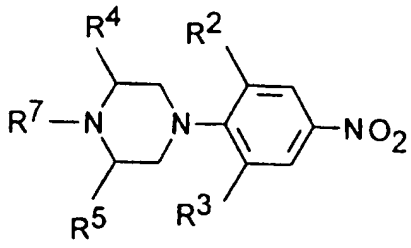



(IVA)

wherein $R^2$ - $R^5$ and $R^7$ are as hereinabove defined. The reaction is conveniently carried out in the presence of an inorganic or organic base such as sodium bicarbonate or an amine base

such as dimethylaniline, the former in a solvent such as acetone/water and the latter in an organic solvent such as THF, toluene, DMF or acetonitrile.

A compound of the formula (IVA) may be prepared by reducing a compound of the formula (IVB):

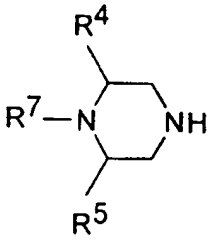


(IVB)

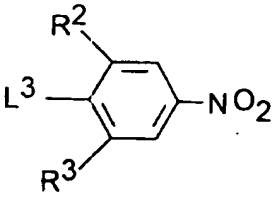
wherein $R^2$ - $R^5$ and $R^7$ are as hereinabove defined.

Many reduction methods suitable for the reduction of a nitro to an amino group are known in the art, for example catalytic hydrogenation, metal reductions or with reducing agents such as sodium hydrosulfite. Suitable catalysts in catalytic hydrogenation include Raney nickel, platinum metal and its oxide, rhodium, palladium-on-charcoal and Wilkinson's catalyst $RhCl(Ph_3P)_3$. Catalyst hydrogenation is conveniently carried out in the temperature range 0°C - 150°C, but preferably at ambient temperature at slightly above atmospheric pressure.

A compound of the formula (IVB) is conveniently prepared by reacting together compounds of the formulae (X) and (IVC):



(X)



(IVC)

wherein $R^2$ - $R^5$ and $R^7$ are as hereinabove defined and $L^3$ is a leaving group, preferably halo and in particular fluoro.

The reaction between compounds of the formulae (X) and (IVC) is carried out in the presence of an organic or inorganic base such as sodium bicarbonate, potassium carbonate or an amine base such as diisopropylethylamine, in an inert solvent such as acetonitrile, DMF, DMPU or N-methylpyrrolidone, in a temperature range of 50°C - 150°C.

Compounds of the formula (X) are conveniently prepared by reacting the appropriate piperazine ring with a compound of the formula (VII) using similar conditions to those described (see later) for the reaction between compounds of the formulae (VI) and (VII). It may be advantageous to protect one of the ring nitrogen atoms in the piperazine ring prior to the reaction with a compound of the formula (VII) and remove the protecting group thereafter. For compounds of the formula VII in which $L^1$ is not activated for displacement, more vigorous reaction conditions may be necessary, for example the Buchwald reaction using a strong base (such as potassium tert-butoxide or lithium bistrimethylsilylamide) and a catalyst (such as Pd(0)), as illustrated in Example 15. It is within the ordinary skill of an organic chemist to recognise when such reaction conditions are necessary.

Alternatively, a compound of the formula (IVB) may be formed by reacting the appropriate piperazine ring in which one of the ring nitrogen atoms is protected (with for example a (1-4C)alkoxycarbonyl group) with a compound of the formula (IVC). The ring nitrogen-protecting group may then be removed and $R^7$ introduced onto the ring nitrogen by reacting the product of the deprotection with a compound of the formula (VII).

Compounds of the formula (VII) may be prepared by introducing substituents into or modifying substituents in a known optionally substituted heteroaryl ring. Such conversions are well known to the skilled chemist, for example a cyano group may be hydrolysed to a carboxy group which in turn may be converted to a carbamoyl or alkoxycarbonyl group or reduced to a hydroxymethyl group; an amino group may be acylated to an alkanoylamino group; a thio group may be alkylated to an alkylthio group which in turn may be oxidised to an alkylsulfinyl or alkylsulfonyl group and a hydroxyalkyl group may be alkylated to an alkoxyalkyl group.

The reaction between compounds of the formulae (VI) and (VII) is conveniently carried out in the presence of a base, in an aprotic polar solvent; preferably one with a high boiling point, such as acetonitrile or dimethylformamide. Suitable bases include amine bases

such as triethylamine. The reaction is preferably carried out in the temperature range 50°C - 150°C. Suitable leaving groups for this reaction include halo, (1-4C)alkylthio, (1-4C)alkanesulfinyl, (1-4C)alkanesulfonyl or phenoxy. Preferably the leaving group is fluoro, chloro or (1-4C)alkanesulfonyl such as methanesulfonyl.

A compound of the formula (II) wherein $R^{10}$ is of the formula $-N(CO_2R^{15})CO(1\text{-}4C)alkyl$ is conveniently prepared by reacting a compound of the formula (I) and (II) wherein $R^1$ or $R^{10}$ is hydroxy with an amide of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ under Mitsunobu conditions. For example, in the presence of tri-n-butylphosphine and 1,1'-(azodicarbonyl)dipiperidine in an organic solvent such as THF, and in the temperature range 0°C - 60°C, but preferably at ambient temperature. Details of analogous Mitsunobu reactions are contained in Tsunoda et al. Tet. Letts., 34, 1639, (1993). Amides of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ may be prepared by standard procedures of organic chemistry which are within the ordinary skill of an organic chemist.

The group $-C(=O)R^b$ may be introduced into a compound of the formula (VIII) to give the appropriate compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is of the formula $-N(Me)C(=O)R^b$ using similar methods to those described for the introduction of the appropriate $-C(=O)R^a$ group into the compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino.

The compound of the formula (VIII) may be prepared by reacting a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino with formaldehyde and sodium borohydride or sodium cyanoborohydride, in an alcholic solvent such as ethanol or isopropanol, in a temperature range of 0°C to ambient temperature.

Suitable N-oxides of compounds of the formula (I) or (II) may be prepared directly from a corresponding parent compound of the formula (I) or (II) using techniques well known to the ordinary skilled organic chemist, such as, for example, using a peracid (such as m-chloroperbenzoic acid) or perphthalic acid in a suitable solvent (such as dioxan or a mixture of water and THF) at a suitable temperature (such as ambient temperature). Example 36 also illustrates possible suitable reagents and conditions for preparing suitable N-oxides. The preparation of suitable N-oxides by assembly from suitable N-oxide starting materials and the

use of the processes described in this specification is within the skill of the ordinary skilled organic chemist, and is illustrated by, for example, Example 18.

It is also possible to convert one $R^7$ group into another $R^7$ group as a final step in the preparation of a compound of the formula (I) or (II) (see the specific examples).

When an optically active form of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using an optically active starting material, or by resolution of a racemic form of the compound or intermediate using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof for the therapeutic treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered with one or more known drugs selected from other clinically useful antibacterial agents (for example ß-lactams or aminoglycosides). These may include penicillins, for example oxacillin or flucloxacillin and carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness against methicillin-resistant staphylococci. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein product (BPI) or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100mg and 1g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of the compound of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

Antibacterial Activity

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive

organisms. which are used to screen for activity against pathogenic bacteria. Notably. the pharmaceutically-acceptable compounds of the present invention show activity against enterococci. pneumococci and methicillin resistant strains of S. aureus and coagulase negative staphylococci. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The antibacterial properties of the compounds of the invention may also be demonstrated in-vivo in conventional tests. No overt toxicity or other untoward effects are observed when compounds of the formula I are so tested at conventional daily dose levels.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of $10^4$ CFU/spot.

Staphylococci were tested on agar. using an inoculum of $10^4$ CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood. an inoculum of $10^4$ CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms.

| Organism | | MIC (µg/ml) Example 1 |
|---|---|---|
| Staphylococcus aureus: | | |
| | Oxford | 0.5 |
| | Novb. Res | 1.0 |
| | MRQR | 1.0 |
| Coagulase Negative Staphylococci | | |
| | MS | 0.25 |
| | MR | 0.5 |
| Streptococcus pyogenes | | |
| | C203 | 1.0 |

| | |
|---|---|
| Enterococcus faecalis | 1.0 |
| Bacillus subtilis | 0.25 |

Novb. Res = Novobiocin resistant

MRQR = methicillin resistant quinolone resistant

MR = methicillin resistant

MS = methicillin sensitive

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-26°C and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of end-products of the formula I were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected];

(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis; and

(vii) in which :-

| | |
|---|---|
| ® | is a Trademark |
| DMF | is N,N-dimethylformamide |
| DMA | is N,N-dimethylacetamide |
| TLC | is thin layer chromatography |
| DMSO | is dimethylsulfoxide |
| $CDCl_3$ | is deuterated chloroform |
| MS | is mass spectroscopy |
| ESP | is electrospray |
| THF | is tetrahydrofuran |
| TFA | is trifluoroacetic acid |
| NMP | is N-methylpyrrolidone |
| dba | is dibenzylideneacetone |
| DMPU | is N,N-dimethylpropyleneurea. |

**Example 1 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 1.5 trifluoroacetate salt (500 mg, 1 mM) was dissolved in ethanol (20 ml). 2-Chloropyrimidine (125 mg, 1.1 mM) was added, followed by triethylamine (0.36 ml, 2.6 mM) and water (2 ml, to aid solubility), and the solution stirred at ambient temperature for 24 hours. Further 2-chloropyrimidine (62 mg, 0.5 mM) was added, and the mixture refluxed for 16 hours. The solution was evporated to dryness, water (20 ml) added to the residue, and the pH adjusted to 12 with 1N sodium hydroxide solution. The solution was extracted with ethyl acetate (2 x 20 ml), and the combined organic layers dried over magnesium sulfate, and evaporated. The white residue was chromatographed on silica, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (270 mg).

MS (ESP): 415 ($MH^+$)

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.03 (t, 4H); 3.40 (t, 2H); 3.70 (dd, 1H); 3.87 (t, 4H); 4.08 (t, 1H); 4.69 (m, 1H); 6.65 (t, 1H); 7.09 (t, 1H); 7.17 (dd, 1H); 7.49 (dd, 1H); 8.19 (t, 1H); 8.38 (d, 2H).

The N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 1.5 trifluoroacetate salt starting material was prepared as follows :-

N-[(5S)-3-(3-Fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (PCT patent application WO 93/23384 Example 1 (j), 1 g, 2.3 mM) was dissolved in dichloromethane (50 ml) under argon, and cooled in an ice-bath. TFA (12.7 ml) was added, and the mixture stirred at 0°C for 30 minutes. Solvent was evaporated, and the residue treated four times by evaporation with 30 ml portions of ethyl acetate to remove TFA. The required starting material as a remaining solid analysed for 1.5 moles of residual TFA.

MS (ESP ): 337 ($MH^+$).

NMR (DMSO-D6 + $CD_3COOD$) δ: ~1.8 (obscured by solvent); 3.21 (t, 4H); 3.28 (t, 4H); 3.45 (t, 2H); 3.74 (dd, 1H); 4.19 (t, 1H); 4.73 (m, 1H); 7.12 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H).

**Example 2 : N-[(5S)-3-(3-Fluoro-4-(4-(5-chloropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (6.73 g, 15 mM) was dissolved in DMA (100 ml). Triethylamine (4.37 ml, 31.4 mM) was added, and the whole mixture stirred at ambient temperature under argon for 10 minutes. 2,5-Dichloropyrimidine (2.23 g, 15 mM) was added, and the solution heated to 100°C for 8 hours. After cooling, solvent was evaporated, and the residue slurried with water for 1 hour. Solid was filtered, washed with water (2 x 100 ml) and dried. The residue was chromatographed twice on silica by dry flash chromatography, eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (3.04 g).

Microanalysis: Found: C, 53.4; H, 4.8; N, 18.6%.

Required for $C_{20}H_{22}ClFN_6O_3$: C, 53.6; H, 4.9; N, 18.7%.

MS (ESP): 449 ($MH^+$) for $C_{20}H_{22}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.02 (t, 4H); 3.39 (t, 2H); 3.69 (dd, 1H); 3.86 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.19 (t, 1H); 8.43 (s, 2H).

The N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt starting material was prepared as follows :-

N-[(5S)-3-(3-Fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (PCT patent application WO 93/23384, 34 g, 78 mM) was dissolved in dichloromethane (500 ml), and cooled in an ice-bath. TFA (50 ml) was added, and the mixture stirred at 0°C for 1.5 hours. Solvent was evaporated, and the residual oil dissolved in ethyl acetate (40 ml). Diethyl ether was added to turbidity (~75 ml), and the solution left to crystallise. Filtration gave product as the mono trifluroacetate salt (32.5 g).

Microanalysis: Found : C, 47.5; H, 5.0; N, 11.8

$C_{18}H_{22}F_4N_4O_5$ requires : C, 48.0; H, 4.9; N, 12.4

**Example 3 : N-[(5S)-3-(3-Fluoro-4-(4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (90 mg, 0.2 mM) was dissolved in DMA (3 ml). Triethylamine (58 µL, 0.42 mM) was stirred in, then 2-chloro-4,6-dimethylpyrimidine (28.5 mg, 0.2 mM) was added, and the solution heated under argon at 160°C for 5 hours. After cooling, solvent was evaporated, and the residue chromatographed on a 5 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 3% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (50 mg).

MS (ESP): 443 ($MH^+$) for $C_{22}H_{27}FN_6O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 2.31 (s, 6H); 3.09 (t, 4H); 3.60-3.71 (m, 2H); 3.75 (dd, 1H); 3.99 (t, 4H); 4.02 (t, 1H); 4.76 (m, 1H); 6.09 (brt, 1H); 6.29 (s, 1H); 6.95 (t, 1H); 7.08 (dd, 1H); 7.44 (dd, 1H).

**Example 4 : N-[(5S)-3-(3-Fluoro-4-(4-(3,5-dichloropyridazin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) was dissolved in DMA (15 ml). Triethylamine (306 µL, 2.2 mM) was stirred in, then 3,4,5-trichloropyridazine (184mg, 1 mM) was added, and the solution heated to 100°C for 16 hours. After cooling, the mixture was diluted with water (50 ml) and extracted weith ethyl acetate (2 x 25 ml). The combined extracts were dried over magnesium sulfate, evaporated, and the residue chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (280 mg).

MS (ESP): 483 ($MH^+$) for $C_{20}H_{21}Cl_2FN_6O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.13 (t, 4H); 3.39 (t, 2H); 3.57 (t, 4H); 3.69 (dd, 1H); 4.06 (t, 1H); 4.70 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 8.21 (brt, 1H); 9.01 (s, 1H).

**Example 5 : N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (0.9 g, 2 mM) was dissolved in NMP (25 ml), triethylamine (0.28 ml, 2 mM) and 3,6-dichloropyridazine (298 mg, 2 mM) were added, and the solution heated to 110°C for 24 hours. After cooling, solvent was evaporated, and the residue chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (165 mg).

MS (ESP): 449 ($MH^+$) for $C_{20}H_{22}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.06 (t, 4H); 3.39 (t, part obscured, 2H); 3.73 (t + m, 5H); 4.07 (t, 1H); 4.68 (m, 1H); 7.09 (t, 1H); 7.17 (dd, 1H); 7.42 (d, 1H); 7.48 (dd, 1H); 7.54 (d, 1H); 8.21 (t, 1H).

**Example 6 : N-[(5S)-3-(3-Fluoro-4-(4-(pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (247 mg, 0.55 mM) was dissolved in ethanol (25 ml), and treated with triethylamine (77 µL, 0.55 mM). Palladium catalyst (10% on charcoal, 100 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 2.5% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (79 mg).

MS (ESP): 415 ($MH^+$) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.06 (t, 4H); 3.38 (t, 2H); 3.70 (br, 5H); 4.06 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.16 (dd, 1H); 7.29 (d, 1H); 7.38 (dd, 1H); 7.49 (dd, 1H); 8.18 (brt, 1H); 8.55 (d, 1H).

**Example 7 : N-[(5S)-3-(3-Fluoro-4-(4-(6-carbamoylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (225mg, 0.5 mM) was dissolved in DMA (15 ml), triethylamine (101 mg, 1 mM) was added, and the whole mixture stirred at ambient temperature under argon for 15 minutes. 3-Chloropyridazine-6-carboxamide (Heterocycles, 1992, 34, 225; 79 mg, 0.5 mM) was added, and the solution heated to 120°C for 6 hours. After cooling, solvent was evaporated, the residue dissolved in dichloromethane, and washed with saturated sodium bicarbonate solution. The organic layer was dried (magnesium sulfate) and evaporated, and the residue chromatographed on silica, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (150 mg).

MS (ESP): 458 ($MH^+$) for $C_{21}H_{24}FN_7O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.08 (t, 4H); 3.37 (t, 2H); 3.69 (dd, 1H); 3.86 (t, 4H); 4.07 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.39 (d, 1H); 7.50 (dd, 1H); 7.53 (brs, 1H); 7.86 (d, 1H); 8.14 (brs, 1H); 8.21 (brt, 1H).

**Example 8 : N-[(5S)-3-(3-Fluoro-4-(4-(6-*n*-butyloxycarbonylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

Using the method and scale of Example 7, but replacing the 3-chloropyridazine-6-carboxamide

with n-butyl 3-chloropyridazine-6-carboxylate (PCT patent application WO 96/03380; 108 mg, 0.5 mM), the title product (162 mg) was obtained after chromatography as in Example 7.

MS (ESP): 515 ($MH^+$) for $C_{25}H_{31}FN_6O_5$

NMR (DMSO-D6) δ: 0.92 (t, 3H); 1.40 (hextet, 2H); 1.68 (quintet, 2H); 1.81 (s, 3H); 3.09 (t, 4H); 3.38 (t, 2H); 3.69 (dd, 1H); 3.89 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.20 (dd, 1H); 7.33 (d, 1H); 7.50 (dd, 1H); 7.82 (d, 1H); 8.20 (brt, 1H).

**Example 9 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(4-(3-chloropyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 25, 0.67 g, 1.5 mM) was dissolved in a mixture of ethanol (100 ml) and DMF (50 ml), and treated with triethylamine (208 µL, 1.5 mM). Palladium catalyst (10% on charcoal, 100 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue azeotroped dry with toluene (100 ml). The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (235 mg).

MS (ESP): 415 ($MH^+$) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.06 (t, 4H); 3.39 (t, 2H); 3.71 (t + m, 5H); 4.07 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 7.85 (d, 1H); 8.10 (t, 1H); 8.20 (brt, 1H); 8.39 (d, 1H).

**Examples 10-14**

Examples 10-14 were all prepared using the following procedure :-

Triethylamine (2 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in DMA (20 ml) under argon. The resultant mixture was stirred at room temperature for 15 minutes, and the appropriate halo-heterocycle (1 mM) added. The mixture was heated with stirring at 110°C for 6 hours. After cooling the solvent was removed by centrifugal evaporation. The residue was mixed with water and the solid filtered. The crude solids were dissolved or slurried in dichloromethane and purified by silica Mega Bond Elut® chromatography, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. The relevant fractions were combined and the solvent evaporated to give the following compounds :-

**Example 10 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylaminocarbonylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

MS (ESP): 472 ($MH^+$) for $C_{22}H_{26}FN_7O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.79 (d, 3H); 3.08 (t, 4H); 3.38 (t, 2H); 3.69 (dd, 1H); 3.84 (t, 4H); 4.06 (t, 1H); 4.69 (m, 1H); 7.09 (t, 1H); 7.18 (dd, 1H); 7.38 (d, 1H); 7.50 (dd, 1H); 7.85 (d, 1H); 8.19 (brt, 1H); 8.77 (brq, 1H).

The appropriate halo-heterocycle, 3-chloro-6-methylaminocarbonylpyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (429 mg, 2 mM) was dissolved in ethanol (10 ml), and a solution of methylamine in ethanol (2M, 4 ml) added. The mixture was stirred at ambient temperature for 1 hour, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 3% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (304 mg).

NMR (DMSO-D6) δ: 2.81 (d, 3H); 8.06 (d, 1H); 8.20 (d, 1H); 9.17 (brs, 1H).

**Example 11 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(2-methoxyethylaminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

MS (ESP): 516 ($MH^+$) for $C_{24}H_{30}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.09 (t, 4H); 3.26 (s, 3H); 3.39 (t, 2H); 3.47 (m, 4H); 3.69 (dd, 1H); 3.88 (t, 4H); 4.08 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.50 (dd, 1H); 7.86 (d, 1H); 8.20 (brt, 1H); 8.70 (brs, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(2-methoxyethylaminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (429 mg, 2 mM) was dissolved in ethanol (10 ml), and 2-methoxyethylamine (150 mg, 2 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent then removed. The residue was chromatographed on a

10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (76 mg).

MS (ESP): 216 ($MH^+$) for $C_8H_{10}ClN_3O_2$

NMR (DMSO-D6) δ: 3.26 (s, 3H); 3.49 (m, 4H); 8.08 (d, 1H); 8.21 (d, 1H); 9.14 (brs, 1H).

**Example 12 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(2-hydroxyethylaminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

MS (ESP): 502 ($MH^+$) for $C_{23}H_{28}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.08 (t, 4H); 3.37 (m, 4H); 3.51 (q, 2H); 3.69 (dd, 1H); 3.85 (t, 4H); 4.07 (t, 1H); 4.67 (m, 1H); 4.74 (t, 1H); 7.09 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.49 (dd, 1H); 7.86 (d, 1H); 8.20 (t, 1H); 8.67 (t, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(2-hydroxyethylaminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and 2-hydroxyethylamine (488 mg, 8 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (637 mg).

MS (ESP): 202 ($MH^+$) for $C_7H_8ClN_3O_2$

NMR (DMSO-D6) δ: 3.39 (q, 2H); 3.55 (q, 2H); 4.75 (t, 1H); 8.08 (d, 1H); 8.21 (d, 1H); 9.08 (brt, 1H).

**Example 13 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(*bis*-(2-hydroxyethyl)aminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

MS (ESP): 546 ($MH^+$) for $C_{25}H_{33}FN_7O_6$

$^1$H NMR (DMSO - D6) : 1.83 (s, 3H); 3.08 (t, 4H); 3.40 (t, 2H); 3.49 (t, 2H); 3.55 (overlapping, 8H); 3.69 (dd, 1H); 3.81 (t, 3H); 4.08 (t, 1H); 4.69 (m, 1H); 4.78 (t, 1H); 7.12 (t, 1H); 7.19 (t, 1H); 7.38 (d, 1H); 7.51 (dd, 1H); 7.55 (t, 1H); 8.19 (t, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(*bis*-(2-hydroxyethyl)aminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and bis-(2-hydroxyethyl)amine (488 mg, 8 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (637 mg).

MS (ESP): 202 ($MH^+$) for $C_7H_8ClN_3O_2$

NMR (DMSO-D6) δ: 3.39 (q, 2H); 3.55 (q, 2H); 4.75 (t, 1H); 8.08 (d, 1H); 8.21 (d, 1H); 9.08 (brt, 1H).

**Example 14 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methoxycarbonylmethylaminocarbonyl)-pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

MS (ESP): 530 ($MH^+$) for $C_{24}H_{28}FN_7O_6$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.10 (t, 4H); 3.37 (t, 2H); 3.63 (s, 3H); 3.69 (dd, 1H); 3.87 (t, 4H); 4.03 (d, 2H); 4.07 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.50 (dd, 1H); 7.86 (d, 1H); 8.20 (t, 1H); 9.13 (t, 1H).

The appropriate haloheterocycle, 3-chloro-6-methoxycarbonylmethylaminocarbonyl-pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and glycine methyl ester hydrochloride (1 g, 8 mM), and triethylamine (808 mg, 8 mM) added. The mixture was stirred at ambient temperature for 18 hours, and solvent removed. The residue was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a

gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (85 mg).
NMR (DMSO-D6) δ: 3.65 (s, 3H); 4.08 (d, 2H); 8.13 (d, 1H); 8.23 (d, 1H); 9.58 (brt, 1H).

**Example 15 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

(5R)-5-Azidomethyl-3-(3-fluoro-4-(4-pyrimid-5-ylpiperazin-1-yl)phenyl)oxazolidin-2-one (430 mg, 1.08 mM) was dissolved in DMF (25 ml) and the solution purged with argon. Palladium (10% on carbon, 50 mg) was added, followed by acetic anhydride (240 µL, 2.16 mM) and the mixture hydrogenated at ambient temperature under hydrogen confined in a balloon for 6 hours. The mixture was filtered through celite, evaporated to dryness, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (340 mg).

MS (ESP): 415 ($MH^+$) for $C_{20}H_{23}FN_6O_3$
NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.08 (t, 4H); 3.39 (m, 6H); 3.68 (dd, 1H); 4.07 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 8.20 (t, 1H); 8.53 (s, 2H); 8.61 (s, 1H).

The (5R)-5-azidomethyl-3-(3-fluoro-4-(4-pyrid-2-ylpiperazin-1-yl)phenyl)oxazolidin-2-one used as starting material was prepared as follows :-

Tris(dba)dipalladium (1.0 g, 1.09 mM) was added to a degassed, stirred solution of 5-bromopyrimidine (12.19 g, 77 mM), *N*-benzylpiperazine (40.5 g, 0.23 M), and tri-*o*-tolylphosphine (1.29 g, 4.24 mM) in toluene (500 ml) under argon. A solution of lithium bis(trimethylsilylamide) (1M in THF, 230 ml) was added dropwise with stirring at ambient temperature. The mixture was then heated with stirring at 100°C for 5 hours. After cooling, the mixture was partitioned between dilute hydrochloric acid (2N, 500ml) and diethyl ether (500 ml). The aqueous phase was separated, made basic with aqueous sodium hydroxide, and extracted with diethyl ether (3 x 500 ml). The combined organic extracts were washed with brine (250 ml), dried over magnesium sulfate, filtered and evaporated to dryness. The residue

was chromatographed on silica by dry flash chromatography, eluting with a gradient increasing in polarity from 0 to 2.5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 1-benzyl-4-(pyrimid-5-yl)piperazine as an oil (5.15 g), which the NMR spectrum showed to be contaminated with 1-benzyl-4-(pyrimid-2-yl)piperazine. The mixture was used without further purification.

MS (ESP): 254 ($MH^+$) for $C_{15}H_{18}N_4$

NMR (DMSO-D6) δ: 2.62 (t, 4H); 3.35 (t, 4H); 7.32 (m, 5H); 8.34 (s, 2H); 8.68 (s, 1H).

Crude 1-benzyl-4-(pyrimid-5-yl)piperazine (5.3 g, 20 mM) and ammonium formate (5.26 g, 0.08 M) were dissolved in a mixture of methanol (100 ml) and water (0.5 ml), and treated with palladium (10% on carbon, 1.3 g) under argon. The mixture was heated to reflux for 3 hours, cooled, filtered through celite, and evaporated to dryness. The residue was treated with aqueous sodium carbonate (2M, 50 ml), and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (magnesium sulfate) and evaporated, to give an oil containing 1-(pyrimid-5-yl)piperazine, mixed with 1-(pyrimid-2-yl)piperazine (3.35 g). The mixture was used as such in the next stage.

MS (ESP): 165 ($MH^+$) for $C_8H_{12}N_4$

3,4-Difluoronitrobenzene (1.53 ml, 1.38 mM) was dissolved in acetonitrile (60 ml). N,N-diisopropylethylamine (6.93 ml, 40 mM), and the above mixture of piperazines (2.72 g, 16.6 mM) added, and the mixture heated to reflux for 18 hours. Solvent was evaporated, and the residue rougly purified by chromatography on silica by dry flash chromatography, eluting with dichloromethane. Relevant fractions were combined and evaporated. This residue was split into three equal portions (500 mg) which were further purified by chromatography on a 90 g Biotage Kiloprep® silica column, eluting with 2.5% methanol in dichloromethane. Relevant fractions were combined to give 3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)nitrobenzene (1.2 g).

MS (ESP): 304 ($MH^+$) for $C_{14}H_{14}FN_5O_2$

NMR (DMSO-D6) δ: 3.43 (s, 8H); 7.23 (t, 1H); 8.02 (m, 2H); 8.53 (s, 2H); 8.61 (s, 1H).

3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)nitrobenzene (2.08 g, 6.8 mM) was dissolved in a mixture of ethyl acetate (300 ml) and DMF (20 ml), and the solution flushed with argon. Palladium (10% on carbon, 125 mg) was added, and the mixture hydrogenated at ambient temperature and pressure to greater than the theoretical uptake of gas. The mixture was filtered through celite, washed with water (2 x 150 ml), then brine (100 ml), dried (magnesium sulfate) and evaporated to dryness, to give 5-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluoro-benzene as a solid (1.7 g), which was used as such in the next stage.

MS (ESP): 274 ($MH^+$) for $C_{14}H_{16}FN_5$

NMR (DMSO-D6) δ: 2.96 (t, 4H); 3.36 (t, 4H); 4.98 (s, 2H); 6.31 (dd, 1H); 6.36 (dd, 1H); 6.80 (t, 1H); 8.50 (s, 2H); 8.58 (s, 1H).

5-Amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.7 g, 6.2 mM) was dissolved in dry dichloromethane (40 ml) under argon, and cooled to -4°C. Pyridine (0.63 ml, 7.79 mM) was added, followed by benzyl chloroformate (0.98 ml, 6.85 mM). The mixture was stirred for 72 hours at ambient temperature. The resulting suspension was diluted with 5% methanol in dichloromethane (100 ml), washed with water (2 x 50 ml), dried (magnesium sulfate), and evaporated to dryness. The residue was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 2.5% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 5-benzyloxycarbonyl-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.31 g).

MS (ESP): 408 ($MH^+$) for $C_{22}H_{22}FN_5O_2$

NMR (DMSO-D6) δ: 3.34 (m, 8H); 5.13 (s, 2H); 7.01 (t, 1H); 7.16 (d, 1H); 7.35 (complex, 6H); 8.52 (s, 2H); 8.59 (s, 1H); 9.92 (s, 1H).

tert-Butanol (0.354 g, 3.19 mM) and dry THF (25 ml) were stirred under argon, and cooled to -10°C. n-Butyl lithium (1.6 M in *iso*hexane, 2.39 ml, 3.83 mM) was added dropwise, the mixture was stirred 10 minutes, then cooled to -70°C. A solution of 5-benzyloxycarbonyl-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.3 g, 3.19 mM) dissolved in dry DMPU (20 ml) was added dropwise. After stirring for 10 minutes, a solution of (R)-glycidyl-butyrate (0.55 g, 3.83 mM) in dry THF (10 ml) was added, and stirring continued at -78°C for 30 minutes. The temperature was allowed to rise to ambient over 16 hours, the mixture

treated with methanol (10 ml), and stirred for 10 minutes. The reaction was diluted with saturated aqueous sodium bicarbonate (20 ml) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated. The residue, still containing DMPU, was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give (5R)-3-(4-(4-(pyrimid-5-yl)piperazin-1-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (0.70 g).

MS (ESP): 374 ($MH^+$) for $C_{18}H_{20}FN_5O_3$

NMR (DMSO-D6) δ: 3.10 (m, 4H); 3.40 (m, 4H); 3.53 (m, 1H); 3.65 (m, 1H); 3.77 (t, 1H); 4.03 (t, 1H); 4.66 (m, 1H); 5.19 (t, 1H); 7.10 (t, 1H); 7.21 (d, 1H); 7.54 (d, 1H); 8.21 (s, 2H); 8.60 (s, 1H).

(5R)-3-(4-(4-(pyrimid-5-yl)piperazin-1-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (0.654 g, 1.75 mM) was dissolved in pyridine (15 ml), and cooled under argon to 0°C. Triethylamine (0.292 ml, 2.1 mM) and methanesulfonyl chloride (0.163 ml, 2.1 mM) were added, and stirring continued at 0°C for 10 minutes, before allowing the temperature to reach ambient over 2 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (50 ml). The solution was washed with water (3 x 40 ml), brine (25 ml), dried (magnesium sulfate) and evaporated. The solid residue was triturated with diethyl ether (20 ml), and (5R)-3-(3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one filtered off (0.65 g).

MS (ESP): 452 ($MH^+$) for $C_{19}H_{22}FN_5O_5S$

NMR (DMSO-D6) δ: 3.13 (m, 4H); 3.23 (s, 3H); 3.42 (m, 4H); 3.80 (dd, 1H); 4.16 (t, 1H); 4.47 (m, 2H); 4.98 (m, 1H); 7.14 (t, 1H); 7.22 (dd, 1H); 7.50 (dd, 1H); 8.54 (s, 2H); 8.61 (s, 1H).

(5R)-3-(3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one (0.6 g, 1.33 mM) was dissolved in dry DMF (15 ml), sodium azide (520 mg, 8 mM) was added, and the mixture was heated at 80°C under argon for 7 hours. Solvent was evaporated, and the residue partitioned between ethyl acetate (50 ml) and water (50 ml). The organic layer was separated, reextracted with ethyl acetate (2 x 25 ml), dried (magnesium

sulfate) and evaporated. to give (5R)-5-azidomethyl-3-(3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)oxazolidin-2-one as a solid (0.46 g).

MS (ESP): 399 ($MH^+$) for $C_{18}H_{19}FN_8O_2$

NMR (DMSO-D6) δ: 3.12 (t, 4H); 3.41 (t, 4H); 3.66 (dd, 1H); 3.73 (complex, 2H); 4.11 (t, 1H); 4.86 (m, 1H); 7.11 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H); 8.53 (s, 2H); 8.61 (s, 1H).

**Examples 16-26**

Examples 16-26 (all of which are (5S) chiral compounds are summarised in Table 1 below) were prepared using the following procedure which employed a Zymark robotic system for multiple parallel synthesis :-

Triethylamine (2 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in DMA (15 ml) under argon. The resultant mixture was stirred at room temperature for 10 minutes. This solution was then added to the appropriate halo-heterocycle (1 mM) and the mixture heated with stirring at 110°C for 6 hours. After cooling the solvent was removed by centrifugal evaporation (SAVANT AES2000) with radiant heating for 5 hours. The residue was mixed with water and the solid filtered. The purity at this stage was assessed by TLC. Impure materials were dissolved in a mixture of dichloromethane and methanol and purified by silica Mega Bond Elut® chromatography, using a suitable mixture of the two solvents, as determined from the TLC. The relevant fractions were combined and the solvent removed by centrifugal evaporation (SAVANT AES2000 ) on medium heat for 3 hours. Compounds so prepared were generally characterised by the presence of the correct molecular ion for $MH^+$ in their electrospray mass spectra, and by their HPLC retention time (in minutes), using the following system and elution parameters.

Column HYPERSIL ODS 5m

Flow rate 1.0 ml/min

Detector Wavelength 254l

Solvent A 1 mMol TFA/$H_2O$

Solvent B 1 mMol TFA/$CH_3CN$

| *Time* | *% Solvent A* | *% Solvent B* |
|---|---|---|
| 0 | 95 | 5 |
| 3 | 95 | 5 |
| 17 | 5 | 95 |
| 18 | 95 | 5 |
| 20 | 95 | 5 |

Table 1

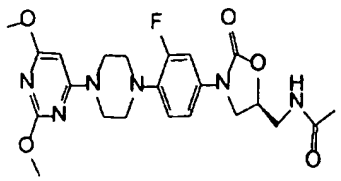
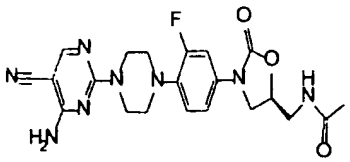
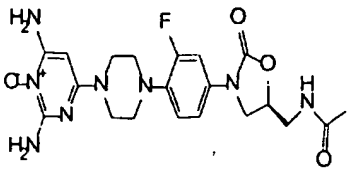
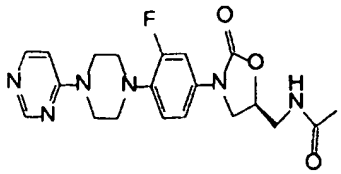
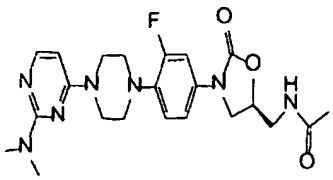
| Example | Structure | Starting Material | HPLC RT | Mass ion | Notes |
|---|---|---|---|---|---|
| 16 | CHIRAL  | 6-Chloro-2.4-dimethoxypyrimidine | 17.6 | 475.2 | 2.3 |
| 17 | CHIRAL  | 4-Amino-2-chloro-5-cyanopyrimidine | 16.9 | | 2.4 |
| 18 | CHIRAL  | 2,6-Diamino-4-chloro-pyrimidine-1-oxide | 15.3 | 461.4 | 1 |
| 19 | CHIRAL  | 4-Chloro-pyrimidine | 14.7 | 415.3 | 1.7 |
| 20 | CHIRAL  | 4-Chloro-2-dimethylamino-pyrimidine | 16.6 | 458.3 | 1 |

Table 1 continued

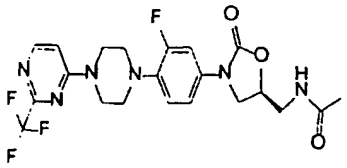
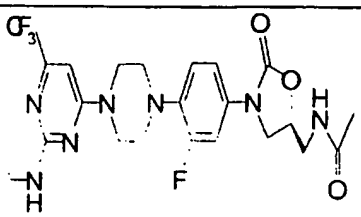
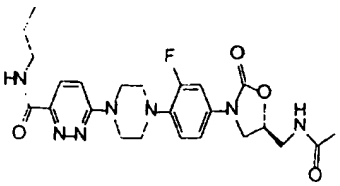
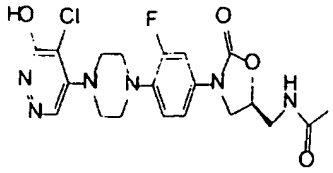
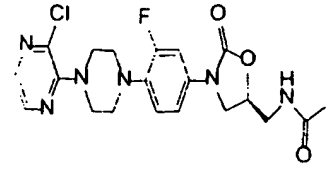
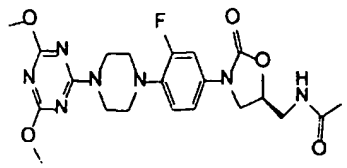
| Example | Structure | Starting Material | HPLC RT | Mass ion | Notes |
|---|---|---|---|---|---|
| 21 | CHIRAL  | 4-Chloro-2-trifluoromethyl-pyrimidine | 20.8 | 483.2 | 1.8 |
| 22 |  | 2-Ethylamino-4-chloro-6-trifluoromethyl-pyrimidine | 19.9 | 526.3 | 1.11 |
| 23 | CHIRAL  | N-(n-Propyl)-3-chloro-pyridazine-6-carboxamide | 17.7 | 500.3 | 1.9 |
| 24 | CHIRAL  | 4,5-Dichloro-3-hydroxy-pyridazine | 16.5 | 465.2 | 1.10 |
| 25 | CHIRAL  | 2,3-Dichloropyrazine | 20.3 | 449.2 | 1.5 |

**Table 1 continued**

| Example | Structure | Starting Material | HPLC RT | Mass ion | Notes |
|---|---|---|---|---|---|
| 26 | CHIRAL  | 2-Chloro-4.6-dimethoxy-1.3.5-triazine | | | 2.6 |

Notes

1. Further purified by chromatography on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity in the range from 0% to 10% methanol in dichloromethane.

2. Obtained pure directly from reaction.

3. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(2,4-dimethoxypyrimid-6-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.51 (dd, 1H); 3.67 (t, 4H); 3.79 (2 x s, 6H); 4.06 (t, 1H); 4.68 (m, 1H); 5.77 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.21 (t, 1H).

4. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimid-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.00 (t, 4H); 3.39 (t, 2H); 3.69 (dd, 1H); 3.89 (t, 4H); 4.08 (t, 1H); 4.70 (m, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.29 (br, 2H); 7.49 (dd, 1H); 8.08 (d, 1H); 8.21 (t, 1H); 8.28 (s, 1H).

5. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(3-chloropyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.13 (t, 4H); 3.39 (t, 2H); 3.52 (t, 4H); 3.70 (dd, 1H); 3.89 (t, 4H); 4.08 (t, 1H); 4.70 (m, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.29 (br, 2H); 7.49 (dd, 1H); 8.08 (d, 1H); 8.21 (t, 1H); 8.28 (s, 1H).

6. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(4,6-dimethoxy-1,3,5-triazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 3.13 (t, 4H); 3.55-3.70 (m, 2H); 3.76 (dd, 1H); 3.97 (s, 6H); 4.02 (t + m, 5H); 4.77 (m, 1H); 6.10 (brt, 1H); 6.95 (t, 1H); 7.09 (dd, 1H); 7.46 (dd, 1H).

7. Preparation of starting material: J. Chem. Soc., 1951, 1218.

8. The appropriate haloheterocycle, 2-trifluoromethyl-4-chloropyrimidine, was prepared as follows :-

2-Trifluoromethyl-4-hydroxypyrimidine (1.06 g, 6.5 mM) was dissolved in thionyl chloride (10 ml) and DMF (10 drops) added. The mixture was heated to reflux for 1 hour, cooled, and solvent evaporated. The residue was partitioned between aqueous 2N potassium carbonate solution (50 ml) and dichloromethane (50 ml). The organic layer was separated, dried over sodium sulfate and evaporated to give the desired product, slightly contaminated with DMF (0.9 g).

NMR ($CDCl_3$) δ: 7.57 (d, 1H); 8.80 (d, 1H).

9. The appropriate haloheterocycle, N-(n-propyl)-3-chloropyridazine-6-carboxamide, was prepared as follows :-

Ethyl 3-chloropyridazine-6-carboxylate (Ref: Bull.Soc.Chim.France 1959, p 1793; 4.2 g, 22.6 mM) was dissolved in dry 1,2-dimethoxyethane (25 ml), n-propylamine (5 ml, 61 mM) added, and the mixture stirred at ambient temperature for 3 days. Solvent was removed, and the residue purified by dry column chromatography, using diethyl ether as eluant. Relevant

fractions were combined and evaporated, and the residue recrystallised from a mixture of diethyl ether and petrol. to give the desired product. mp 128.5°C-129.5°C (1.71 g).

Microanalysis: Found: C, 48.1; H, 5.4; N, 21.3; Cl, 18.1%

$C_8H_8ClNO_2$ requires: C, 48.1; H, 5.0; N, 21.1; Cl, 17.8%

10. Preparation of starting material: J. Amer. Chem. Soc., 1953, 75, 1909.

11. Characterised by NMR and MS

N-[(5S)-3-(3-Fluoro-4-(4-(2-ethylamino-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 526 (MH+) for $C_{23}H_{27}F_4N_7O_3$

NMR (DMSO-D6) δ: 1.07 (t, 3H); 1.81 (s, 3H); 3.00 (t, 4H); 3.23 (q, 2H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.77 (t, 4H); 4.06 (t, 1H); 4.65 (m, 1H); 6.42 (s, 1H); 7.07 (t, 1H); 7.10 (br, 1H); 7.17 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

**Example 27 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(*bis*(2-hydroxyethylamino)carbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

Using the method and scale of Examples 10-14, the title product (248 mg) was obtained after chromatography.

MS (ESP): 546 ($MH^+$) for $C_{25}H_{33}FN_7O_6$

NMR (DMSO-D6) δ: 1.85 (s, 3H); 3.09 (t, 4H); 3.39 (t, 2H); 3.55 (m, 8H); 3.70 (dd, 1H); 3.83 (t, 4H); 4.08 (t, 1H); 4.68 (m, 1H); 4.77 (t, 2H); 7.12 (t, 1H); 7.18 (dd, 1H); 7.37 (d, 1H); 7.51 (dd, 1H); 7.55 (d, 1H); 8.19 (t, 1H).

The appropriate haloheterocycle, 3-chloro-6-(bis(2-hydroxyethyl)aminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and bis(2-hydroxyethyl)amine (841 mg, 8 mM) added. The mixture was stirred at ambient temperature for 24 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient from 0% to 10% methanol in

dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (896 mg).

NMR (DMSO-D6) δ: 3.43 (s, 4H); 3.58 (q, 2H); 3.64 (q, 2H); 4.63 (t, 1H); 4.82 (t, 1H); 7.84 (d, 1H); 8.01 (d, 1H).

**Example 28 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (0.9 g, 2 mM) was dissolved in DMA (10 ml), and triethylamine (0.556 ml, 4 mM) added. 3-Chloro-6-methylpyridazine (257 mg, 2 mM) was added and the mixture heated to 100°C for 18 hours. Solvent was evaporated, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 1% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired product (61 mg), slightly contaminated with N-[(5S)-3-(3-fluoro-4-(4-formylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 429 ($MH^+$) for $C_{21}H_{25}N_6FO_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.42 (s, 3H); 3.06 (t, 4H); 3.37 (t, 2H); 3.66 (t overlapping m, 5H); 4.06 (t, 1H); 4.68 (m, 1H); 7.05 (t, 1H); 7.15 (dd, 1H); 7.23 (d, 1H); 7.29 (d, 1H); 7.48 (dd, 1H); 8.19 (t, 1H).

**Example 29 : N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (1.35 g, 3 mM) was dissolved in DMA (30 ml), and triethylamine (606 mg, 6 mM) added under argon. 2,4-Dichloro-6-methylpyrimidine (489 mg, 3 mM) was added and the mixture heated to 110°C for 6 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (100 ml). The solution was washed with water (50 ml), dried over magnesium sulfate and evaporated. The residue was purified by chromatography on a

90 g Biotage Kiloprep® silica column. Elution with 2.5% methanol in dichloromethane gave N-[(5S)-3-(3-fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (312 mg) - Example 29A.

MS (ESP): 463 ($MH^+$) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.27 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.83 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 6.65 (s, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Further elution with 5% methanol in dichloromethane gave N-[(5S)-3-(3-fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (838 mg) - Example 29B.

MS (ESP): 463 ($MH^+$) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.80 (s, 3H); 2.23 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.72 (t, 4H); 4.05 (t, 1H); 4.68 (m, 1H); 6.76 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.18 (t, 1H).

**Example 30 : N-[(5S)-3-(3-Fluoro-4-(4-(2-methyl-6-chloropyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (1.35 g, 3 mM) was dissolved in DMA (30 ml), and triethylamine (606 mg, 6 mM) added under argon. 4,6-Dichloro-2-methylpyrimidine (489 mg, 3 mM) was added and the mixture heated to 110° for 6 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (100 ml). The solution was washed with water (50 ml), dried over magnesium sulfate and evaporated to give the desired product plus residual DMA.

MS (ESP): 463 ($MH^+$) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.34 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.76 (t, 4H); 4.05 (t, 1H); 4.67 (m, 1H); 6.79 (s, 1H); 7.06 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

**Example 31 : N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 29A, 153 mg, 0.33 mM) was dissolved in a mixture of ethanol (40 ml) and DMF (10 ml). Triethylamine (92 µL, 0.66 mM) and palladium catalyst (10% on charcoal, 100 mg) were added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated. The residue was dissolved in dichloromethane (200 ml), washed with water, dried over magnesium sulfate and evaporated to give the title product (90 mg).

MS (ESP): 429 ($MH^+$) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.26 (s, 3H); 2.98 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.84 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 6.52 (d, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H); 8.21 (d, 1H).

**Example 32 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

Using the same technique as Example 31, but starting with N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 29B, 692 mg, 1.5 mM) the title product was obtained (470mg).

MS (ESP): 429 ($MH^+$) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.25 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.67 (dd, 1H); 3.73 (t, 4H); 4.05 (t, 1H); 4.68 (m, 1H); 6.73 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.18 (t, 1H); 8.37 (s, 1H).

**Example 33 : N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

Using the same technique as Example 31, but starting with N-[(5S)-3-(3-Fluoro-4-(4-(2-methyl-6-chloropyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 30, 1.34 g, 2.69 mM) the title product was obtained (690mg).

MS (ESP): 429 ($MH^+$) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.36 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.72 (t, 4H); 4.07 (t, 1H); 4.68 (m, 1H); 6.66 (d, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.48 (dd, 1H); 8.08 (d, 1H); 8.19 (t, 1H).

**Example 34 : N-[(5S)-3-(3-Fluoro-4-(4-(1,2,4-triazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

Triethylamine (0.5 ml, 3.6 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (157 mg, 0.34 mM) in acetonitrile (5 ml), and 3-methylsulfinyl-1,2,4-triazine (50 mg, 0.34 mM) added. The resultant mixture was heated with stirring at 75°C for 18 hours. After cooling the solvent was evaporated, the residue dissolved in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (106 mg).

MS (ESP): 416 ($MH^+$) for $C_{19}H_{22}FN_7O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.06 (t, 4H); 3.38 (t, 2H); 3.69 (t, 1H); 3.94 (t, 4H); 4.07 (t, 1H); 4.69 (m, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.50 (dd, 1H); 8.18 (t, 1H); 8.34 (d, 1H); 8.63 (d, 1H).

The 3-methylsulfinyl-1,2,4-triazine used as starting material was prepared as follows :-

3-Methylthio-1,2,4-triazine (J. Het. Chem., 1970, 7, 767; 254 mg, 2 mM) was dissolved in dichloromethane (5 ml) and stirred at ambient temperature. 3-Chloroperoxybenzoic acid (50% strength, 690 mg, 2 mM) was added in portions over 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate (5 ml), dried (magnesium sulfate), and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 3-methylsulfinyl-1,2,4-triazine as a gum (60 mg).

MS (ESP): 144 ($MH^+$) for $C_4H_5N_3OS$

NMR (DMSO-D6) δ: 2.97 (s, 3H); 9.05 (d, 1H); 9.58 (d, 1H).

**Example 35 : N-[(5S)-3-(3-Fluoro-4-(4-(1,3,5-triazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

Triethylamine (0.21 ml, 1.5 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in 1,4-dioxane (20 ml), and 2-phenoxy -1,3,5-triazine (J. Amer. Chem. Soc., 1975, 97, 1851; 173 mg, 1 mM) added. The resultant mixture was heated to reflux for 4 hours. After cooling the solvent was evaporated, the residue dissolved in 5% methanol in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 3% to 11% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the product contaminated with phenol, which was rechromatographed as above eluting with a gradient increasing in polarity from 0% to 7% methanol in dichloromethane to give a pure sample (38 mg).

MS (ESP): 416 ($MH^+$) for $C_{19}H_{22}FN_7O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.02 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.92 (t, 4H); 4.07 (t, 1H); 4.68 (m, 1H); 7.08 (t, 1H); 7.19 (dd, 1H); 7.50 (dd, 1H); 8.23 (t, 1H); 8.58 (s, 2H).

**Example 36 : N-[(5S)-3-(3-Fluoro-4-(1-oxo-4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 1, 207 mg, 0.5 mM) was dissolved in a mixture of methanol (10 ml) and dichloromethane (5 ml), and magnesium monoperoxyphthalate.$6H_2O$ (90%, 279 mg, 0.51 mM) was added. After stirring for 4 hours, precipitated phthalic acid was filtered off, and solvents removed. Solvent was evaporated, the residue preabsorbd on silica, and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 5% to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (38 mg) slightly contaminated with phthalic acid.

MS (ESP): 431 ($MH^+$) for $C_{20}H_{23}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.05 (d, 2H); 3.39 (t, 2H); 3.75 (dd, 1H); 3.92 (quintet, 4H); 4.13 (t, 1H); 4.62 (d, 2H); 4.74 (m, 1H); 6.72 (t, 1H); 7.42 (dd, 1H); 7.64 (dd, 1H); 8.22 (t, 1H); 8.42 (d, 2H); 8.63 (t, 1H).

**Example 37 : N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide**

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide trifluoroacetate salt (900 mg, 2 mM) was dissolved in DMA (20 ml), and triethylamine (610 mg, 6 mM) added. 2,4-Dichloro-5-methylpyrimidine (326 mg, 2 mM) was added and the mixture heated to 100°C for 18 hours. Solvent was evaporated, and the residue partitioned between dichloromethane (40 ml) and water (20 ml). The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by dry column chromatography on silica eluting with a gradient increasing in polarity from 0% to 7% methanol in dichloromethane. The minor, less polar component (13 mg) was N-[(5S)-3-(3-fluoro-4-(4-(4-chloro-5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37A).

MS (ESP): 463 ($MH^+$) for $C_{21}H_{24}ClFN_6O_3$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 2.17 (s, 3H); 3.09 (t, 4H); 3.56-3.71 (m, 2H); 3.75 (dd, 1H); 3.93 (t, 4H); 4.03 (t, 1H); 4.76 (m, 1H); 6.04 (t, 1H); 6.94 (t, 1H); 7.08 (dd, 1H); 7.46 (dd, 1H); 8.10 (s, 1H).

The major, more polar component (400 mg) was N-[(5S)-3-(3-fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37B).

MS (ESP): 463 ($MH^+$) for $C_{21}H_{24}ClFN_6O_3$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 2.24 (s, 3H); 3.14 (t, 4H); 3.57-3.69 (m, 2H); 3.74 (t overlapping m, 5H); 4.03 (t, 1H); 4.78 (m, 1H); 6.24 (t, 1H); 6.94 (t, 1H); 7.08 (dd, 1H); 7.45 (dd, 1H); 7.97 (s, 1H).

**Example 38 : N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide**

N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37B; 380 mg, 0.82 mM) was dissolved in methanol (30 ml), and treated with triethylamine (230 µL, 1.7 mM). Palladium catalyst (10% on charcoal, 40 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue partitioned between dichloromethane (20 ml) and water (10 ml). The organic layer was dried over magnesium sulfate and evaporated to give the title product (290 mg).

MS (ESP): 429.4 ($MH^+$) for $C_{21}H_{25}FN_6O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 2.26 (s, 3H); 3.17 (t, 4H); 3.63 (t overlapping m, 6H); 3.76 (dd, 1H); 4.03 (t, 1H); 4.77 (m, 1H); 6.29 (t, 1H); 6.96 (t, 1H); 7.09 (dd, 1H); 7.45 (dd, 1H); 8.16 (s, 1H); 8.63 (s, 1H).

**Example 39**

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

| (a) | Tablet I | mg/tablet |
|---|---|---|
| | Compound X | 100 |
| | Lactose Ph.Eur | 179 |
| | Croscarmellose sodium | 12 |
| | Polyvinylpyrrolidone | 6 |
| | Magnesium stearate | 3 |

| (b) | Tablet II | mg/tablet |
|---|---|---|
| | Compound X | 50 |
| | Lactose Ph.Eur | 229 |
| | Croscarmellose sodium | 12 |
| | Polyvinylpyrrolidone | 6 |
| | Magnesium stearate | 3 |

| (c) | Tablet III | mg/tablet |
|---|---|---|
| | Compound X | 1 |
| | Lactose Ph.Eur | 92 |
| | Croscarmellose sodium | 4 |
| | Polyvinylpyrrolidone | 2 |
| | Magnesium stearate | 1 |

| (d) | Capsule | mg/capsule |
|---|---|---|
| | Compound X | 10 |
| | Lactose Ph.Eur | 389 |
| | Croscarmellose sodium | 100 |
| | Magnesium stearate | 1 |

| (e) | Injection I | (50 mg/ml) |
|---|---|---|
| | Compound X | 5.0% w/v |
| | Isotonic aqueous solution | to 100% |

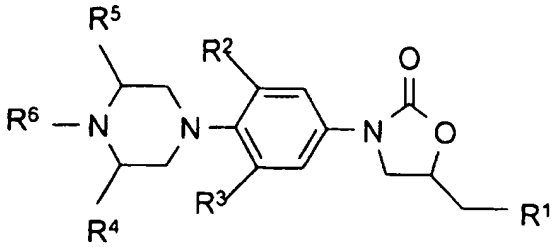
Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

## CLAIMS

1. A compound of the formula (I)



(I)

wherein:

$R^1$ is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, or of the formula -NHC(=O)$R^a$ wherein $R^a$ is hydrogen, (1-4C)alkoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or $R^1$ is of the formula -N(Me)C(=O)$R^b$ wherein $R^b$ is hydrogen, methyl or methoxy or $R^1$ is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2;

$R^2$ and $R^3$ are independently hydrogen or fluoro;

$R^4$ and $R^5$ are independently hydrogen or methyl;

$R^6$ is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl (optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; suitable N-oxides thereof and in-vivo-hydrolysable esters thereof.

2. A compound of the formula (I), as claimed in claim 1, wherein:

$R^1$ is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, or $R^1$ is of the formula $-NHC(=O)R^a$ wherein $R^a$ is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or $R^1$ is of the formula $-NHSO_2$(1-4C)alkyl;

$R^2$ and $R^3$ are independently hydrogen or fluoro;

$R^4$ and $R^5$ are independently hydrogen or methyl;

$R^6$ is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl [optionally substituted by carboxy or (1-4C)alkoxycarbonyl], (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; suitable N-oxides thereof and in-vivo-hydrolysable esters thereof.

3. A compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1 and 2, except that the following optional substituents on $R^6$, namely (1-4C)alkoxy, (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino and those N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl substituents with the (1-4C)alkyl group or groups substituted by hydroxy, (1-4C)alkoxy or

(1-4C)alkoxycarbonyl, are excluded; and the number of optional substituents on R$^6$ is restricted to one or two.

4. A compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof as claimed in claims 1-3, wherein :

R$^1$ is acetamido, one of R$^2$ and R$^3$ is hydrogen and the other is fluoro, R$^4$ and R$^5$ are both hydrogen, R$^6$ is pyrimidine or pyrazine and the optional substituents on the heteroaryl ring are independently selected from methyl, chloro, nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

5. A compound of the formula (I), as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

and pharmaceutically-acceptable salts and suitable N-oxides thereof.

6. A compound of the formula (I), as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(3-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

7. A compound of the formula (I), or a pharmaceutically-acceptable salt or suitable

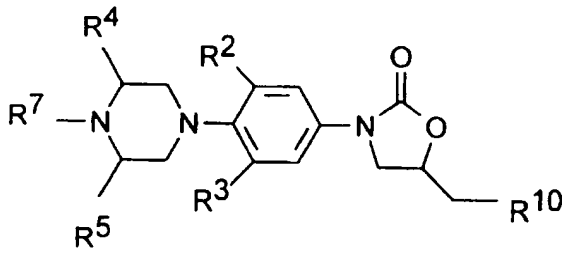
N-oxide thereof, as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide.

8. A process for the preparation of a compound of the formula (I), as claimed in claim 1, which comprises :-

(a) the deprotection of a compound, containing at least one protecting group, of the formula (II), a pharmaceutically-acceptable salt , suitable N-oxide or in-vivo hydrolysable ester thereof :

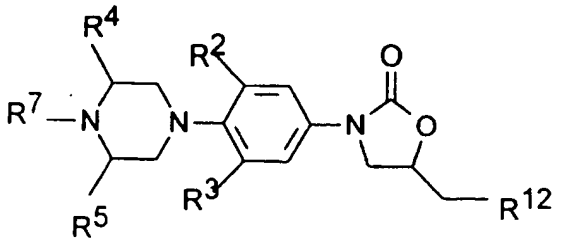


(II)

(b) the modification of a substituent in or the introduction of a substituent into another compound of formula (I) or (II);

(c) when $R^1$ or $R^{10}$ is of the formula - $NHS(O)_n$(1-4C)alkyl, wherein n is 1 or 2, the oxidation of a compound of the formula (I) wherein n is 0 or, when n is 2 the oxidation of a compound of the formula (I) or (II) wherein n is 1;

(d) when $R^1$ or $R^{10}$ is azido, the reaction of a compound of the formula (III) with a source of azide:



(III)

(e) when $R^1$ or $R^{10}$ is amino, the reduction of a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is azido;

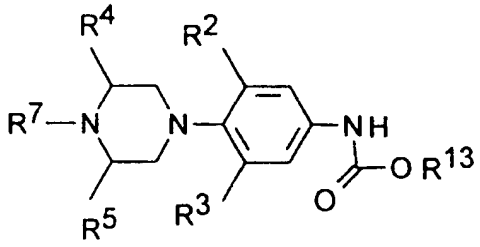
(f) when $R^1$ or $R^{10}$ is of the formula $-NHC(=O)R^a$, the introduction of $-C(=O)R^a$ into a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino;

(g) when $R^1$ or $R^{10}$ is of the formula $-NHS(O)_n$ (1-4C)alkyl the introduction of $-S(O)_n$ (1-4C)alkyl into a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is amino;

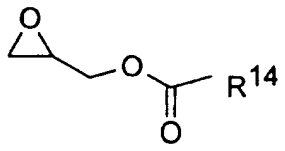
(h) when $R^1$ or $R^{10}$ is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein $R^1$ or $R^{10}$ is hydroxy;

(i) when $R^1$ or $R^{10}$ is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (III);

(j) when $R^1$ or $R^{10}$ is hydroxy, the reaction of a compound of the formula (IV) with a compound of the formula (V):

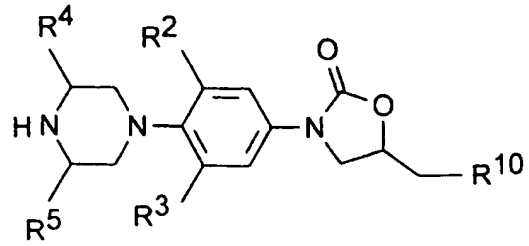


(IV)



(V)

(k) the reaction of a compound of the formula (VI) with a compound of the formula (VII):

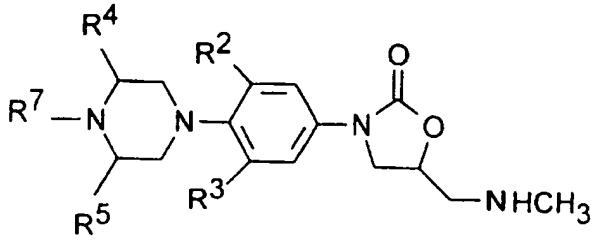


$R^7$-$L^1$

(VI) (VII)

(l) when $R^{10}$ is of the formula -N($CO_2R^{15}$)CO(1-4C)alkyl: from a compound of the formula (I) and (II) wherein $R^1$ or $R^{10}$ is hydroxy;

(m) when $R^1$ or $R^{10}$ is of the formula -N(Me)C(=O)$R^b$, by the introduction of the group -C(=O)$R^b$ into a compound of the formula (VIII):




(VIII)

and

(n) when a suitable N-oxide is required, by preparation directly from a corresponding parent compound of the formula (I) or (II), or by assembly from suitable N-oxide starting materials:

wherein $R^2$, $R^3$, $R^4$ and $R^5$ are as hereinabove defined, $R^7$ is $R^6$ or protected $R^6$, $R^{10}$ is $R^1$ or protected $R^1$, $R^{12}$ is mesyloxy or tosyloxy, $R^{13}$ is (1-6C)alkyl or benzyl, $R^{14}$ is (1-6C)alkyl, $R^{15}$ is (1-4C)alkyl or benzyl and $L^1$ is a leaving goup and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester;

and when an optically active form of a compound of the formula (I) is required it may be obtained by carrying out one of the above procedures using an optically active starting material, or by resolution of a racemic form of the compound or intermediate using a standard procedure.

9. A pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7 and a pharmaceutically-acceptable diluent or carrier.

10. A method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7.

11. The use of a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

# INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/GB 97/01767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/12 A61K31/495 A61K31/53

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 93 23384 A (THE UPJOHN COMPANY ) 25 November 1993 see claims --- | 1-4,9-11 |
| Y | WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 see claims --- | 1-4,9-11 |
| Y | WO 95 14684 A (THE UPJOHN COMPANY ) 1 June 1995 see claims --- | 1-4,9-11 |
| P,X | WO 97 21708 A (PHARMACIA & UPJOHN COMPANY ) 19 June 1997 see the whole document ----- | 1-11 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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1

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 September 1997 | 26.09.97 |

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# INTERNATIONAL SEARCH REPORT

Ir...national application No.
PCT/GB 97/01767

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Remark: Although claim(s) 10
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/GB 97/01767

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| WO 9721708 A | 19-06-97 | AU 1407797 A | 03-07-97 |

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 263/20, 417/12, 413/10, 413/04, A61K 31/42, C07D 261/04, 307/32, 471/10 // (C07D 471/10, 235:00, 221:00)

A1

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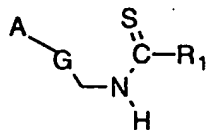
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HESTER, Jackson, B., Jr. [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). NIDY, Eldon, George [US/US]; 3103 Morgan Street, Kalamazoo, MI 49001 (US). PERRICONE, Salvatore, Charles [US/US]; 7011 Division Avenue, Delton, MI 49046 (US). POEL, Toni-Jo [US/US]; 304 Anderson, Wayland, MI 49348 (US).

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

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY




(I)

(57) Abstract

The present invention provides compounds of Formula (I) or pharmaceutical acceptable salts thereof wherein A, G and $R_1$ are as defined in the claims which are antibacterial agents.

*FOR THE PURPOSES OF INFORMATION ONLY*

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# OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY

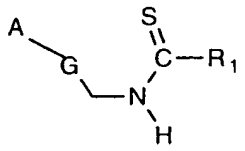
## BACKGROUND OF THE INVENTION

The present invention relates to new and useful oxazolidinone compounds and their preparations, and more particularly to oxazolidinone compounds in which the carbonyl functionality of -NH-C(O)-R is converted to a thiocarbonyl functionality, such as a thiourea -NH-C(S)-$NH_2$, an alkyl thiourea -NH-C(S)-NH-($C_{1-4}$ alkyl), thioamide -NH-C(S)-($C_{1-4}$ alkyl) or -NH-C(S)-H.

Replacement of the oxygen atom with a sulfur atom has unexpectedly improved the antimicrobial properties of the compounds. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, Gram-negative organisms such as H. *influenzae* and M. *catarrahlis* as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. The compounds are particularly useful because they are effective against the latter organisms which are known to be responsible for infection in persons with AIDS.

## SUMMARY OF THE INVENTION

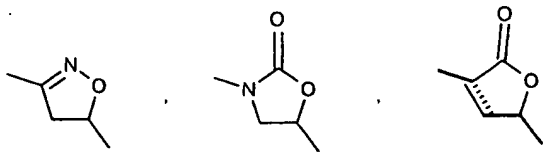
In one aspect the subject invention is a compound of the Formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



$R_1$ is

a) H,

b) $NH_2$,

c) NH-$C_{1-4}$ alkyl,

d) $C_{1-4}$ alkyl,

e) -O$C_{1-4}$ alkyl,

f) -S $C_{1-4}$ alkyl,

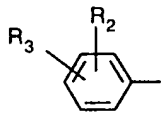
g) $C_{1-4}$ alkyl substituted with 1-3 F, 1-2 Cl, CN or -COO$C_{1-4}$ alkyl,

h) $C_{3-6}$ cycloalkyl,

i) N($C_{1-4}$ alkyl)$_2$ or

j) $N(CH_2)_{2-5}$;

A is

a) 

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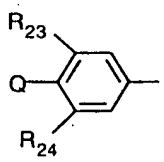
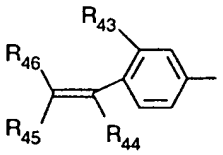
b) 

,

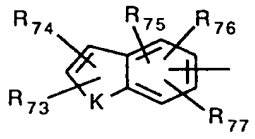
c) 

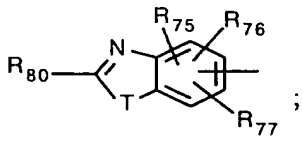
,

d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O,
wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,
wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,
wherein the heteroaromatic moiety is optionally substituted with one to three $R_{48}$,

e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,
wherein the heteroaromatic moiety is bonded via a carbon atom,
wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,
wherein the heteroaromatic moiety is optionally substituted with one to three $R_{55}$,

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

g)  , or

h)  ;

wherein $R_2$ is

a) H,
b) F,
c) Cl,
d) Br,
e) $C_{1-3}$ alkyl,
f) $NO_2$, or
g) $R_2$ and $R_3$ taken together are -O-$(CH_2)_h$-O-;

$R_3$ is

a) -S(=O)$_i$ $R_4$,
b) -S(=O)$_2$-N=S(O)$_j$$R_5$$R_6$,
c) -SC(=O)$R_7$,
d) -C(=O)$R_8$,
e) -C(=O)$R_9$,
f) -C(=O)N$R_{10}$$R_{11}$,

g) $-C(=NR_{12})R_8$,
h) $-C(R_8)(R_{11})-OR_{13}$,
i) $-C(R_9)(R_{11})-OR_{13}$,
j) $-C(R_8)(R_{11})-OC(=O)R_{13}$,
k) $-C(R_9)(R_{11})-OC(=O)R_{13}$,
l) $-NR_{10}R_{11}$,
m) $-N(R_{10})-C(=O)R_7$,
n) $-N(R_{10})-S(=O)_iR_7$,
o) $-C(OR_{14})(OR_{15})R_8$,
p) $-C(R_8)(R_{16})-NR_{10}R_{11}$, or
q) $C_{1-8}$ alkyl substituted with one or more =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{10}R_{11}$, $C_{2-5}$ alkenyl, or $C_{2-5}$ alkynyl;

$R_4$ is

a) $C_{1-4}$ alkyl optionally substituted with one or more halos, OH, CN, $NR_{10}R_{11}$, or $-CO_2R_{13}$,
b) $C_{2-4}$ alkenyl,
c) $-NR_{16}R_{18}$,
d) $-N_3$,
e) $-NHC(=O)R_7$,
f) $-NR_{20}C(=O)R_7$,
g) $-N(R_{19})_2$,
h) $-NR_{16}R_{19}$, or
i) $-NR_{19}R_{20}$,

$R_5$ and $R_6$ at each occurrence are the same or different and are

a) $C_{1-2}$ alkyl, or
b) $R_5$ and $R_6$ taken together are $-(CH_2)_k-$;

$R_7$ is $C_{1-4}$ alkyl optionally substituted with one or more halos;

$R_8$ is

a) H, or
b) $C_{1-8}$ alkyl optionally substituted with one or more halos, or $C_{3-8}$ cycloalkyl;

$R_9$ is $C_{1-4}$ alkyl substituted with one or more

a) $-S(=O)R_{17}$,
b) $-OR_{13}$,
c) $-OC(=O)R_{13}$,
d) $-NR_{10}R_{11}$, or

e) $C_{1-5}$ alkenyl optionally substituted with CHO;

$R_{10}$ and $R_{11}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-4}$ alkyl, or

c) $C_{3-8}$ cycloalkyl;

$R_{12}$ is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

$R_{13}$ is

a) H, or

b) $C_{1-4}$ alkyl;

$R_{14}$ and $R_{15}$ at each occurrence are the same or different and are

a) $C_{1-4}$ alkyl, or

b) $R_{14}$ and $R_{15}$ taken together are $-(CH)_l-$;

$R_{16}$ is

a) H,

b) $C_{1-4}$ alkyl, or

c) $C_{3-8}$ cycloalkyl;

$R_{17}$ is

a) $C_{1-4}$ alkyl, or

b) $C_{3-8}$ cycloalkyl;

$R_{18}$ is

a) H,

b) $C_{1-4}$ alkyl,

c) $C_{2-4}$ alkenyl,

d) $C_{3-4}$ cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

$R_{19}$ is

a) Cl,

b) Br, or

c) I;

$R_{20}$ is a physiologically acceptable cation;

$R_{21}$ and $R_{22}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-4}$ alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein $R_{23}$ and $R_{24}$ at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) $C_{1-2}$ alkyl,

e) CN

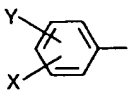
f) OH,

g) $C_{1-2}$ alkoxy,

h) nitro, or

i) amino;

Q is

a) 

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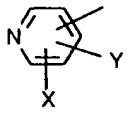
b) 

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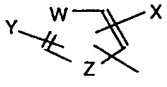
c) 

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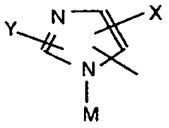
d) 

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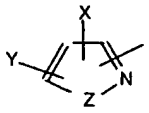
e) 

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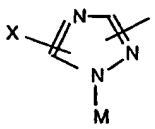
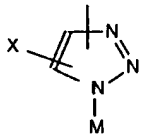
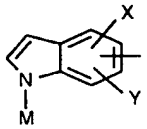
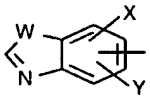
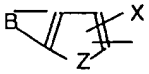
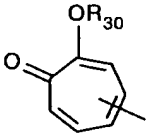
f)  ,

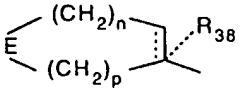
g)  ,

h)  ,

i)  ,

j) 

k)  ,

l)  ,

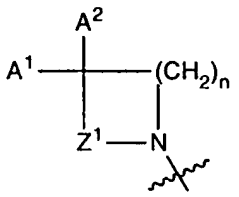
m) a diazinyl group optionally substituted with X and Y,

n) a triazinyl group optionally substituted with X and Y,

o) a quinolinyl group optionally substituted with X and Y,

p) a quinoxalinyl group optionally substituted with X and Y,

q) a naphthyridinyl group optionally substituted with X and Y,

r) 

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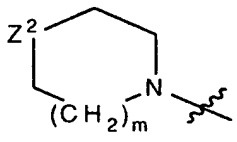
s) 

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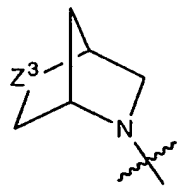
t) 

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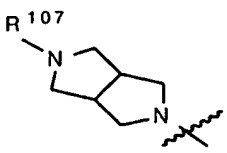
u) 

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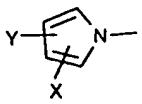
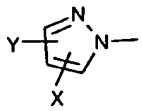
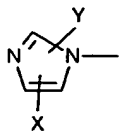
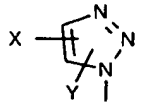
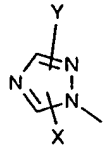
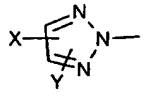
v)  ,

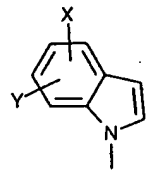
w)  ,

x)  ,

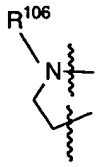
y)  ,

z)  ,

aa)  ,

bb)  or,

Q and $R_{24}$ taken together are



wherein $Z^1$ is

a) $-CH_2-$,
b) $-CH(R^{104})-CH_2-$,
c) -C(O)-, or
d) $-CH_2CH_2CH_2-$;

wherein $Z^2$ is

a) $-O_2S-$,
b) -O-,
c) $-N(R^{107})-$,
d) -OS-, or
e) -S-;

wherein $Z^3$ is

a) $-O_2S-$,
b) -O-,
c) -OS-, or
d) -S-;

wherein $A^1$ is

a) H-, or
b) $CH_3$;

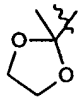
wherein $A^2$ is

a) H-,
b) HO-,
c) $CH_3-$,
d) $CH_3O-$,
e) $R^{102}O-CH_2-C(O)-NH-$
f) $R^{103}O-C(O)-NH-$,
g) $(C_1-C_2)$alkyl-O-C(O)-,
h) $HO-CH_2-$,
i) $CH_3O-NH-$,
j) $(C_1-C_3)$alkyl-$O_2C-$

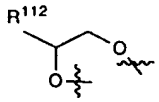
k) $CH_3$-C(O)-,

l) $CH_3$-C(O)-$CH_2$-,

m)  , or

n)  ,

$A^1$ and $A^2$ taken together are:

a)  ,

b)  , or

c)  ;

wherein $R^{102}$ is

a) H-,

b) $CH_3$-,

c) phenyl-$CH_2$-, or

d) $CH_3C(O)$-;

wherein $R^{103}$ is

a) ($C_1$-$C_3$)alkyl-, or

b) phenyl-;

wherein $R^{104}$ is

a) H-, or

b) HO-;

wherein $R^{105}$ is

a) H-,

b) $(C_1-C_3)$alkyl-,

c) $CH_2 = CH-CH_2$-, or

d) $CH_3-O-(CH_2)_2$-;

wherein $R^{106}$ is

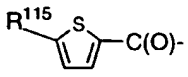
a) $CH_3-C(O)$-,

b) H-C(O)-,

c) $Cl_2CH-C(O)$-,

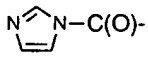
d) $HOCH_2-C(O)$-,

e) $CH_3SO_2$-,

f) 

,

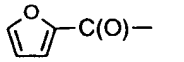
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C-C(O)-O-CH_2-C(O)$-,

j) $H-C(O)-O-CH_2-C(O)$-,

k) 

,

l) $HC\equiv C-CH_2O-CH_2-C(O)$-, or

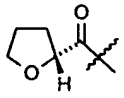
m) phenyl-$CH_2-O-CH_2-C(O)$-;

wherein $R^{107}$ is

a) $R^{102}O-C(R^{110})(R^{111})-C(O)$-,

b) $R^{103}O-C(O)$-,

c) $R^{108}-C(O)$-,

d) 

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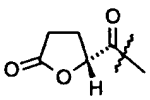
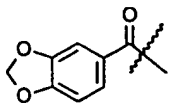
e) 

,

f) $H_3C-C(O)-(CH_2)_2-C(O)$-,

g) $R^{109}-SO_2$-,

h) 

i) $HO\text{-}CH_2\text{-}C(O)\text{-}$,

j) $R^{116}\text{-}(CH_2)_2\text{-}$,

k) $R^{113}\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)\text{-}$,

l) $(CH_3)_2N\text{-}CH_2\text{-}C(O)\text{-}NH\text{-}$,

m) $NC\text{-}CH_2\text{-}$, or

n) $F_2\text{-}CH\text{-}CH_2\text{-}$;

wherein $R^{108}$ is

a) H-,

b) $(C_1\text{-}C_4)$alkyl,

c) aryl $\text{-}(CH_2)_p$,

d) $ClH_2C\text{-}$,

e) $Cl_2HC\text{-}$,

f) $FH_2C\text{-}$,

g) $F_2HC\text{-}$, or

h) $(C_3\text{-}C_6)$cycloalkyl;

wherein $R^{109}$ is

a) $\text{-}CH_3$,

b) $\text{-}CH_2Cl$

c) $\text{-}CH_2CH{=}CH_2$,

d) aryl, or

e) $\text{-}CH_2CN$;

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

a) H-,

b) $CH_3\text{-}$; or

wherein $R^{112}$ is

a) H-,

b) $CH_3O\text{-}CH_2O\text{-}CH_2\text{-}$, or

c) $HOCH_2\text{-}$;

wherein $R^{113}$ is

a) $CH_3\text{-}$,

b) $HOCH_2\text{-}$,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N\text{-}CH_2\text{-}$;

wherein $R^{114}$ is

a) HO-,

b) $CH_3O$-,

c) $H_2N$-,

d) $CH_3O$-C(O)-O-,

e) $CH_3$-C(O)-O-$CH_2$-C(O)-O-,

f) phenyl-$CH_2$-O-$CH_2$-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) $CH_3O$-$CH_2$-O-$(CH_2)_2$-O-, or

i) $CH_3O$-$CH_2$-O-;wherein $R^{113}$ is

a) $CH_3$-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-$CH_2$-;

wherein $R^{115}$ is

a) H-, or

b) Cl-;

wherein $R^{116}$ is

a) HO-

b) $CH_3O$-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) $C_{1-8}$ alkyl,

c) $C_{3-8}$ cycloalkyl,

d) -$(CH_2)_m$$OR_{13}$, or

e) -$(CH_2)_h$-$NR_{21}R_{22}$;

Z is

a) O,

b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

Y is

a) H,
b) F,
c) Cl,
d) Br,
e) $C_{1-3}$ alkyl, or
f) $NO_2$;

X is

a) H,
b) -CN,
c) $OR_{27}$,
d) halo,
e) $NO_2$,
f) tetrazoyl,
g) -SH,
h) $-S(=O)_iR_4$,
i) $-S(=O)_2-N=S(O)_jR_5R_6$,
j) $-SC(=O)R_7$,
k) $-C(=O)R_{25}$,
l) $-C(=O)NR_{27}R_{28}$,
m) $-C(=NR_{29})R_{25}$,
n) $-C(R_{25})(R_{28})-OR_{13}$,
o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,
p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,
q) $-NR_{27}R_{28}$,
r) $-N(R_{27})C(=O)R_7$,
s) $-N(R_{27})-S(=O)_iR_7$,
t) $-C(OR_{14})(OR_{15})R_{28}$,
u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or
v) $C_{1-8}$ alkyl substituted with one or more halos, OH, =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, $C_{2-5}$ alkenyl, $C_{2-5}$ alkynyl, or $C_{3-8}$ cycloalkyl;

$R_4$, $R_5$, $R_6$, $R_7$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, and $R_{17}$ are the same as defined above;

$R_{25}$ is

a) H,
b) $C_{1-8}$ alkyl optionally substituted with one or more halos, $C_{3-8}$

cycloalkyl, $C_{1-4}$ alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) $C_{2-5}$ alkenyl optionally substituted with CHO, or $CO_2R_{13}$;

$R_{26}$ is

a) $R_{28}$, or

b) $NR_{27}N_{28}$;

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

a) H,

b) $C_{1-8}$ alkyl,

c) $C_{3-8}$ cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) $R_{27}$ and $R_{28}$ taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

$R_{29}$ is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein $R_{30}$ is

a) H,

b) $C_{1-8}$ alkyl optionally substituted with one or more halos, or

c) $C_{1-8}$ alkyl optionally substituted with one or more OH, or $C_{1-6}$ alkoxy;

wherein E is

a) $NR_{39}$,

b) $-S(=O)_i$, or

c) O;

$R_{38}$ is

a) H,

b) $C_{1-6}$ alkyl,

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

d) halo;

$R_{39}$ is

a) H,

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

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

d) $-CO_2R_{40}$,

e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

$R_{40}$ is

a) H,

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

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

d) $-(CH_2)_q-OR_{42}$;

$R_{41}$ is

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

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

c) $-(CH_2)_q-OR_{42}$;

$R_{42}$ is

a) H,

b) $C_{1-6}$ alkyl,

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

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, or $C_{1-6}$ alkylthio;

wherein $R_{43}$ is

a) H,

b) $C_{1-2}$ alkyl,

c) F, or

d) OH;

$R_{44}$ is

a) H,

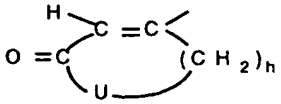
b) $CF_3$,

c) $C_{1-3}$ alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) $R_{44}$ and $R_{45}$ taken together are a 5-, 6-, or 7-membered ring of the

formula,

or 

f) $R_{44}$ and $R_{45}$ taken together are $-(CH_2)_k-$, when $R_{46}$ is an electron-withdrawing group;

$R_{45}$ and $R_{46}$ at each occurrence are the same or different and are

a) an electron-withdrawing group,

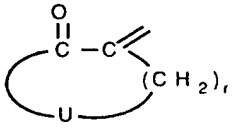
b) H,

c) $CF_3$,

d) $C_{1-3}$ alkyl optionally substituted with one halo,

e) phenyl, provided at least one of $R_{45}$ or $R_{46}$ is an electron-withdrawing group, or

f) $R_{45}$ and $R_{46}$ taken together are a 5-, 6-, 7-membered ring of the formula


;

U is

a) $CH_2$,

b) O,

c) S, or

d) $NR_{47}$;

$R_{47}$ is

a) H, or

b) $C_{1-5}$ alkyl;

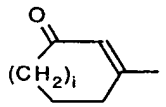
wherein $R_{48}$ is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,
f) $CF_3$,
g) $-NO_2$,
h) $C_{1-6}$ alkoxy,
i) $C_{1-6}$ alkoxycarbonyl,
j) $C_{1-6}$ alkythio,
k) $C_{1-6}$ acyl,
l) $-NR_{49}R_{50}$,
m) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, or $-NR_{49}R_{50}$,
n) $C_{2-8}$ alkenylphenyl optionally substituted with one or two $R_{51}$,
o) phenyl optionally substituted with one or two $R_{51}$,
p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two $R_{51}$, or
q)  ;

$R_{49}$ and $R_{50}$ at each occurrence are the same or different and are
a) H,
b) $C_{1-4}$ alkyl,
c) $C_{5-6}$ cycloalkyl, or
d) $R_{49}$ and $R_{50}$ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl;

$R_{51}$ is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) $CF_3$,
g) $-NO_2$,
h) $C_{1-6}$ alkoxy,

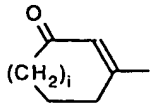
i) $C_{1-6}$ alkoxycarbonyl,
j) $C_{1-6}$ alkythio,
k) $C_{1-6}$ acyl,
l) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}\ R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

$R_{52}$ and $R_{53}$ at each occurrence are the same or different and are
a) H,
b) $C_{1-6}$ alkyl, or
c) phenyl;

$R_{54}$ is
a) $C_{1-4}$ alkyl, or
b) phenyl optionally substituted with $C_{1-4}$ alkyl;

wherein $R_{55}$ is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) $CF_3$,
g) $-NO_2$,
h) $C_{1-6}$ alkoxy,
i) $C_{1-6}$ alkoxycarbonyl,
j) $C_{1-6}$ alkythio
k) $C_{1-6}$ acyl,
l) $-NR_{56}\ R_{57}$,
m) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, or $-NR_{56}R_{57}$,
n) $C_{2-8}$ alkenylphenyl optionally substituted with one or two $R_{58}$,
o) phenyl optionally substituted with one or two $R_{58}$,
p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to

three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two $R_{58}$, or

q)  ;

$R_{56}$ and $R_{57}$ at each occurrence are the same or different and are

a) H,

b) formyl,

c) $C_{1-4}$ alkyl,

d) $C_{1-4}$ acyl,

e) phenyl,

f) $C_{3-6}$ cycloalkyl, or

g) $R_{56}$ and $R_{57}$ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl;

$R_{58}$ is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) $CF_3$,

g) $-NO_2$,

h) $C_{1-6}$ alkoxy,

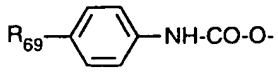
i) $C_{1-6}$ alkoxycarbonyl,

j) $C_{1-6}$ alkythio,

k) $C_{1-6}$ acyl,

l) phenyl,

m) $C_{1-6}$ alkyl optionally substituted with OH, azido, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, $-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or



n) $-C(=O)NR_{59}\ R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

$R_{54}$ is the same as defined above;

$R_{59}$ and $R_{60}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-6}$ alkyl,

c) phenyl, or

d) tolyl;

$R_{61}$ is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

$R_{62}$ and $R_{63}$ at each occurrence are the same or different and are

a) H, or

b) $C_{1-4}$ alkyl optionally substituted with phenyl or pyridyl;

$R_{64}$ is

a) H, or

b) a sodium ion;

$R_{65}$ and $R_{66}$ at each occurrence are the same or different and are

a) H,

b) formyl,

c) $C_{1-4}$ alkyl,

d) $C_{1-4}$ acyl,

e) phenyl,

f) $C_{3-6}$ cycloalkyl,

g) $R_{65}$ and $R_{66}$ taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of

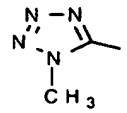
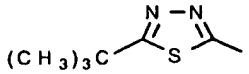
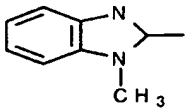
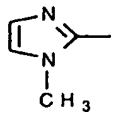
S, N, and O, optionally substituted with, including on the nitrogen

atom, phenyl, pyrimidyl, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

$R_{67}$ is

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

$R_{69}$ is

a) $C_{1-6}$ alkoxycarbonyl, or

b) carboxyl;

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

a) H, or

b) $C_{1-3}$ alkyl;

$R_{72}$ is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

$R_{73}$, $R_{74}$, $R_{75}$, $R_{76}$, and $R_{77}$ at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) $CF_3$,

h) $-NO_2$,

i) $C_{1-6}$ alkoxy,

j) $C_{1-6}$ alkoxycarbonyl,

k) $C_{1-6}$ alkythio,

l) $C_{1-6}$ acyl,

m) $-NR_{78}R_{79}$,

n) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, $-NR_{78}R_{79}$, -N(phenyl)($CH_2$-$CH_2$-OH), -O-CH($CH_3$)($OCH_2CH_3$), or -O-phenyl-[para-$NHC(=O)CH_3$],

o) $C_{2-8}$ alkenylphenyl optionally substituted with $R_{51}$,

p) phenyl optionally substituted with $R_{51}$, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with $R_{51}$;

$R_{51}$ is the same as defined above;

$R_{78}$ and $R_{79}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-4}$ alkyl,

c) phenyl, or

d) $R_{78}$ and $R_{79}$ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl;

wherein T is

a) O,

b) S, or

c) $SO_2$;

$R_{75}$, $R_{76}$, and $R_{77}$ are the same as defined above;

$R_{80}$ is

a) H,

b) formyl,

c) carboxyl,

d) $C_{1-6}$ alkoxycarbonyl,

e) $C_{1-8}$ alkyl,

f) $C_{2-8}$ alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with

OH, halo, $C_{1-6}$ alkoxy, $C_{1-6}$ acyl, $C_{1-6}$ alkylthio or $C_{1-6}$ alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, $CF_3$, $-NO_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ acyl, $C_{1-6}$ alkylthio, or $C_{1-6}$ alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

$R_{81}$ and $R_{82}$ at each occurrence are the same or different and are

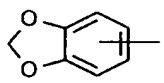
a) H,

b) $C_{3-6}$ cycloalkyl,

c) phenyl,

d) $C_{1-6}$ acyl,

e) $C_{1-8}$ alkyl optionally substituted with OH, $C_{1-6}$ alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, $CF_3$, halo, $-NO_2$, $C_{1-4}$ alkoxy, $-NR_{83}R_{84}$, or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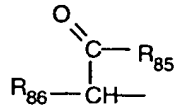
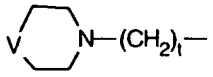
f) 
, or

g) 
;

V is

a) O,

b) $CH_2$, or

c) $NR_{87}$;

$R_{83}$ and $R_{84}$ at each occurrence are the same or different and are

a) H, or

b) $C_{1-4}$ alkyl;

$R_{85}$ is

a) OH,

b) $C_{1-4}$ alkoxy, or

c) $-NR_{88}R_{89}$;

$R_{86}$ is

a) H, or

b) $C_{1-7}$ alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

$R_{87}$ is

a) H,

b) phenyl, or

c) $C_{1-6}$ alkyl optionally substituted by OH;

$R_{88}$ and $R_{89}$ at each occurrence are the same or different and are

a) H,

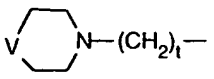
b) $C_{1-5}$ alkyl

c) $C_{3-6}$ cycloalky, or

d) phenyl;

$R_{90}$ is

a) $C_{1-8}$ alkyl optionally substituted with $C_{1-6}$ alkoxy or $C_{1-6}$ hydroxy, $C_{3-6}$ cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, $CF_3$, halo, -CN, OH, $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or $C_{1-5}$ acyl;

b) 

,

c) phenyl, or

d) pyridyl;

$R_{91}$ is

a) $C_{1-16}$ alkyl,

b) $C_{2-16}$ alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with $C_{1-6}$ alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, $CF_3$, $-NO_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ acyl, $C_{1-6}$ alkylthio, or $C_{1-6}$ alkoxycarbonyl;

$R_{92}$ and $R_{93}$ at each occurrence are the same or different and are

a) H,

b) phenyl,

c) $C_{1-6}$ alkyl, or

d) benzyl;

$R_{94}$ and $R_{95}$ at each occurrence are the same or different and are

a) H,

b) OH,

c) $C_{1-6}$ alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) $R_{94}$ and $R_{95}$ taken together are =O;

$R_{96}$ is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, $CF_3$, halo, -CN, OH, phenyl, $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or $C_{1-5}$ acyl,

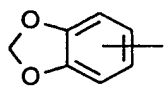
c) morpholinyl,

d) OH,

e) $C_{1-6}$ alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

h)  ;

$R_{97}$ is

a) morpholinyl,

b) OH, or

c) $C_{1-6}$ alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

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

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

The new compounds of the invention can be prepared using known compounds and intermediates of oxzolidinones, isoxazolines and butyolactones as intermediates and synthetic methods known in the art. Thioamides of the invention can typically be prepared by the reaction of the corresponding amide with Lawesson's reagent.

Compounds disclosed in the following publications are suitable intermediates for preparation of the compounds of this invention and are hereby incorporated by reference for their disclosure of suitable compounds that can be converted to the subject thiocarbonyl derivatives.

U.S. Patents 5,225,565; 5,182,403; 5,164,510; 5,247,090; 5,231,188; 5,565,571; 5,547,950; and 5,523,403.

PCT Application and publications PCT/US93/04850, WO94/01110; PCT/US94/08904, WO95/07271; PCT/US95/02972, WO95/25106; PCT/US95/10992, WO96/13502; PCT/US96/05202, WO96/35691; PCT/US96/12766; PCT/US96/13726;

PCT/US96/14135; PCT/US96/17120; PCT/US96/19149; PCT/US97/01970; PCT/US95/12751, WO96/15130; and PCT/US96/00718, WO96/23788.

Chemical conversion techniques for converting various intermediates having a $CH_2NH_2$ on the oxazolidinone ring to $CH_2NH$-C(S)-$CH_3$ is disclosed by Hartke, K., Barrmeyer, S., J. prakt. Chem. 1996, 338, 251-6. Similarly, conversion of $CH_2NHC(=0)CH_3$ to $CH_2NHC(S)NHCH_3$ is reported by Cava, M.P.; Levinson, M.I., Thionation Reactions of Lawesson's Reagents, Tetrahedron 1985, 41, 5061-87.

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix $C_{i-j}$ defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, $C_{1-4}$ alkyl refers to alkyl of 1-4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

The terms "$C_{1-2}$ alkyl", "$C_{1-3}$ alkyl", "$C_{1-4}$ alkyl", "$C_{1-5}$ alkyl", "$C_{1-6}$ alkyl", "$C_{1-8}$ alkyl", and "$C_{1-16}$ alkyl" refer to an alkyl group having one to two, one to three, one to four, one to five, one to six, one to eight, or one to sixteen carbon atoms respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof.

The terms "$C_{2-4}$ alkenyl", "$C_{2-5}$ alkenyl", "$C_{2-8}$ alkenyl", "$C_{2-14}$ alkenyl" and "$C_{2-16}$ alkenyl" refer to at least one double bond alkenyl group having two to four, two to five, two to eight, two to fourteen, or two to sixteen carbon atoms, respectively such as, for example, ethenyl, propenyl, butenyl, pentenyl, pentdienyl, hexenyl, hexdienyl, heptenyl, heptdienyl, octenyl, octdienyl, octatrienyl, nonenyl, nonedienyl, nonatrienyl, undecenyl, undecdienyl, dodecenyl, tridecenyl, tetradecenyl and their isomeric forms thereof.

The terms "$C_{2-5}$ alkynyl", "$C_{2-8}$ alkynyl", and "$C_{2-10}$ alkynyl" refer to at least one triple bond alkynyl group having two to five, two to eight, or two to ten carbon atoms respectively such as, for example, ethynyl, propynyl, butynyl, pentynyl, pentdiynyl, hexynyl, hexdiynyl, heptynyl, heptdiynyl, octynyl, octdiynyl, octatriynyl, nonynyl, nonediynyl, nonatriynyl and their isomeric forms thereof.

The terms "$C_{3-4}$ cycloalkyl", "$C_{3-6}$ cycloalkyl", "$C_{5-6}$ cycloalkyl", and "$C_{3-8}$ cycloalkyl" refer to a cycloalkyl having three to four, three to six, five to six, or three to eight carbon atoms respectively such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof.

The terms "$C_{1-4}$ alkoxy", "$C_{1-6}$ alkoxy", and "$C_{1-8}$ alkoxy" refer to an alkyl

group having one to four, one to six, or one to eight carbon atoms respectively attached to an oxygen atom such as, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

The terms "$C_{1-6}$ alkylamino", and "$C_{1-8}$ alkylamino" refer to an alkyl group having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, heptylamino, or octoylamino and their isomeric forms thereof.

The terms "$C_{1-6}$ dialkylamino", and "$C_{1-8}$ dialkylamino" refer to two alkyl groups having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, dimethylamino, methylethylamino, diethylamino, dipropylamino, methypropylamino, ethylpropylamino, dibutylamino, dipentylamino, dihexylamino, methylhecylamino, diheptylamino, or dioctoylamino and their isomeric forms thereof.

The terms "$C_{1-3}$ acyl", "$C_{1-4}$ acyl", "$C_{1-5}$ acyl", "$C_{1-6}$ acyl", "$C_{1-8}$ acyl", and "$C_{2-8}$ acyl" refer to a carbonyl group having an alkyl group of one to three, one to four, one to five, one to six, one to eight, or two to eight carbon atoms.

The terms "$C_{1-4}$ alkoxycarbonyl", "$C_{1-6}$ alkoxycarbonyl", and "$C_{1-8}$ alkoxycarbonyl" refer to an ester group having an alkyl group of one to four, one to six, or one to eight carbon atoms.

The term "$C_{1-8}$ alkyl phenyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "$C_{2-8}$ alkenyl phenyl" refers to a at least one double bond alkenyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "$C_{1-8}$ alkyl pyridyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one pyridyl radical.

The term "$C_{1-8}$ hydroxyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a hydroxy group.

The term "$C_{1-8}$ alkylsulfonyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a $SO_2$ moiety.

The term "$C_{1-6}$ alkylthio" refers to an alkyl group having one to six carbon atoms and isomeric forms thereof attached to a sulfur atom.

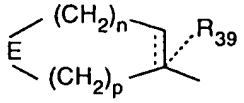
The term "Het" refers to 5 to 10 membered saturated, unsaturated or aromatic heterocyclic rings containing one or more oxygen, nitrogen, and sulfur forming such groups as, for example, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl,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

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

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

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

When Q is the structure of




the dotted line in the heterocyclic ring means that this bond can be either single or double. In the case where the dotted line is a double bond, the $R_{39}$ group will not be

present.

The compounds of Formula I of this invention contain a chiral center at C5 of the isoxazoline ring, and as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on substituents, additional chiral centers and other isomeric forms may be present in any of A or $R_1$ group, and this invention embraces all possible stereoisomers and geometric forms in these groups.

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

The pharmaceutical compositions of this invention may be prepared by combining the compounds of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound according to this invention.

The quantity of active component, that is the compound according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be

administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., 2-4 four times per day.

When the compounds according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound or a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound of this invention generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/mL to about 400 mg/mL of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds according to this invention are advantageously administered orally in solid and liquid dosage forms.

MIC Test Method

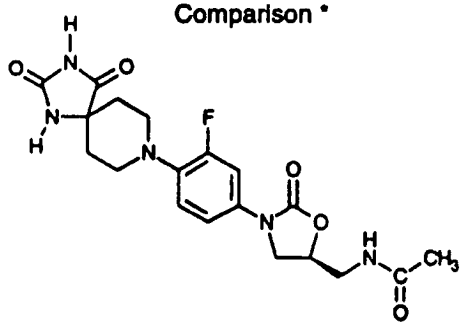
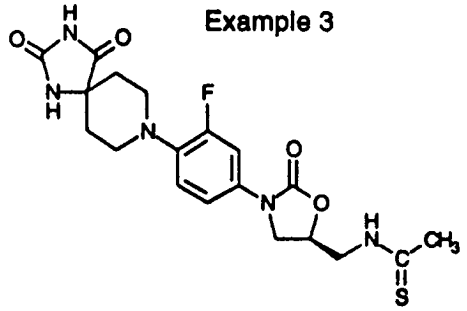
The in vitro MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog is prepared in the preferred solvent, usually DMSO:$H_2O$ (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug is added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar is mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to

inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension is made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately $10^4$ to $10^5$ cells per spot. The plates are incubated overnight at 35°C.

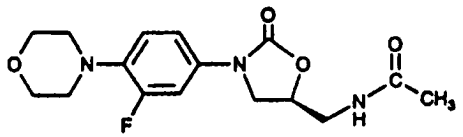
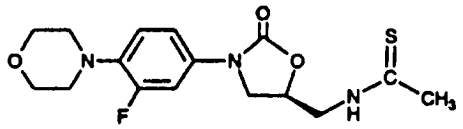
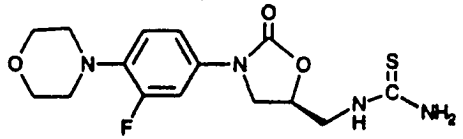
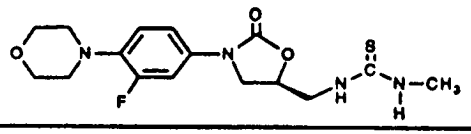
Following incubation the Minimum Inhibitory Concentration (MIC μg/ml), the lowest concentration of drug that inhibits visible growth of the organism, is read and recorded. The data is shown in Tables I and II.

**TABLE 1**

| Structure | Oxazolidinone MIC Values (Gram+) | | | | |
|---|---|---|---|---|---|
| | SAUR 9213 | SEPI 12084 | EFAE 9217 | SPNE 9912 | SPYO 152 |
| Comparison *  | 16 | 4 | 8 | .5 | 1 |
| Example 3  | 4 | 1 | 2 | .25 | .5 |

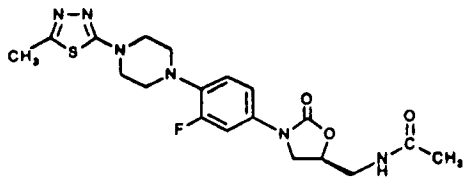
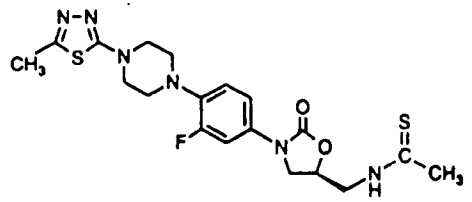
*not a compound of the subject invention

TABLE 1 (cont'd)

| Structure | Oxazolidinone MIC Values (Gram+) | | | | |
|---|---|---|---|---|---|
| | SAUR 9213 | SEPI 12084 | EFAE 9217 | SPNE 9912 | SPYO 152 |
| Comparison *  | 2 | 1 | 2 | .5 | 1 |
| Example 1  | 1 | .25 | .5 | .13 | .13 |
| Example 5  | 1 | .25 | .5 | <.125 | .25 |
| Example 6  | 2 | 1 | 2 | .5 | 1 |

*not a compound of the subject invention

TABLE 1 (cont'd)

| Structure | Oxazolidinone MIC Values (Gram+) | | | | |
|---|---|---|---|---|---|
| | SAUR 9213 | SEPI 12084 | EFAE 9217 | SPNE 9912 | SPYO 152 |
| Comparison *  | .5 | .25 | 1 | .13 | .25 |
| Example 2  | 8 | 2 | 4 | 2 | 4 |

SAUR: S. *aureus*
SEPI: S. *epidermidis*
EFAE: E. *faecalis*
SPNE: S. *pneumoniae*
SPYO: S. *pyogenes*

*not a compound of the subject invention

TABLE II

| Example No. | SAUR 9213 MIC | SEPI 30593 MIC | EFAE 12712 MIC | SPNE 9912 MIC | SPYO 152 MIC | HINF 30063 MIC | MCAT 30610 MIC | EFAE 9217 MIC |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 0.25 | 0.5 | <0.125 | <0.125 | 8 | 1 | 0.5 |
| 2 | 8 | 4 | 8 | 2 | 4 | >16 | >16 | 4 |
| 3 | 4 | 1 | 1 | 0.25 | 0.5 | 16 | 4 | 2 |
| 5 | 1 | 0.5 | 0.5 | <0.125 | 0.25 | 4 | 2 | 0.5 |
| 6 | 2 | 2 | 2 | 0.5 | 1 | 16 | 8 | 2 |
| 7 | 0.5 | 0.25 | 0.5 | <0.125 | 0.25 | 4 | 1 | 0.5 |
| 8 | 2 | 1 | 0.5 | <0.125 | 0.25 | 4 | 2 | 1 |
| 9 | 0.5 | 0.25 | 0.25 | <0.125 | <0.125 | 2 | 0.5 | 0.25 |
| 10 | 2 | 1 | 0.5 | <0.125 | 0.25 | 2 | 1 | 1 |
| 11 | 0.25 | 0.25 | 0.25 | <0.125 | 0.25 | 2 | 1 | 0.25 |
| 12 | 1 | 0.5 | 0.25 | <0.125 | <0.125 | 1 | 0.5 | 0.5 |
| 13 | 1 | 1 | 2 | 0.5 | 1 | >16 | 8 | 2 |
| 14 | 1 | 0.5 | 1 | 0.25 | 0.5 | 8 | 1 | 1 |
| 15 | 32 | 16 | 32 | 4 | 8 | >64 | 64 | 32 |
| 16 | 8 | 8 | 16 | 2 | 8 | >64 | 32 | 16 |
| 17 | 2 | 2 | 4 | 1 | 2 | 64 | 16 | 4 |
| 18 | 2 | 1 | 2 | <0.5 | 1 | 32 | 4 | 2 |
| 19 | 32 | 16 | 32 | 16 | 16 | 64 | 32 | 32 |
| 21 | 4 | 4 | 8 | 2 | 4 | 64 | 16 | 8 |
| 22, 23 | 0.5 | 0.5 | 1 | <0.125 | 0.25 | 4 | 2 | 1 |
| 24 | 1 | 0.25 | 0.5 | <0.125 | 0.25 | 4 | 2 | 0.5 |
| 25 | 0.5 | 0.25 | 0.5 | <0.125 | <0.125 | 2 | 2 | 0.5 |
| 26 | 1 | 0.5 | 1 | 0.25 | 0.5 | 16 | 2 | 1 |

TABLE II (cont'd)

| Example No. | SAUR 9213 MIC | SEPI 30593 MIC | EFAE 12712 MIC | SPNE 9912 MIC | SPYO 152 MIC | HINF 30063 MIC | MCAT 30610 MIC | EFAE 9217 MIC |
|---|---|---|---|---|---|---|---|---|
| 27 | 0.5 | 0.5 | 0.5 | <0.125 | 0.25 | 4 | 2 | 1 |
| 28 | 0.5 | 0.25 | 0.5 | 0.25 | 0.25 | 2 | 1 | 0.5 |
| 29 | 0.25 | 0.25 | 0.25 | <0.125 | <0.125 | 2 | 0.5 | 0.25 |
| 30 | 4 | 1 | 0.5 | <0.125 | 0.25 | 8 | 2 | 1 |
| 31 | 2 | 1 | 1 | <0.125 | 0.25 | 4 | 1 | 1 |
| 32 | 16 | 2 | 2 | 0.25 | 0.25 | 8 | 2 | 4 |
| 33 | 4 | 2 | 1 | 0.25 | 0.25 | 4 | 2 | 4 |
| 34 | 2 | 1 | 2 | 0.5 | 1 | >16 | 4 | 2 |
| 35 | 1 | 0.5 | 1 | 0.25 | 0.5 | 16 | 2 | 1 |

Key:

| | | |
|---|---|---|
| SAUR | 9213: | S. *aureus* |
| SEPI | 30593: | S. *epidermidis* |
| EFAE | 12712: | E. *Faecium* |
| SPNE | 9912: | S. *pneumoniae* |
| SPYO | 152: | S. *pyogenes* |
| HINF | 30063: | *Haemophilus influenzae* |
| MCAT | 30610: | *Moraxella catarrhalis* |
| EFAE | 9217: | *Enterococcus faecalis* |

As shown in Scheme 1, the intermediates **II** for the compounds of this invention are also intermediates disclosed in the oxazolidinone patents and published applications hereinabove incorporated by reference. The intermediates **IV** for this invention are final products (Examples) from the oxazolidinone patents and published applications hereinabove incorporated by reference.

As shown in Scheme 1, Step 1, and illustrated in Example 5, the isothiocyanates **III** can be conveniently prepared by allowing the amine intermediates (**II**) to react with 1,1'-thiocarbonyldi-2(1H)-pyridone in solvents such as methylene chloride at 0 to 25°C. The thioureas (**Ia**, R' = H, $alkyl_{1-4}$) can then be prepared as shown in Step 2 by the reaction of **III** with ammonia or the appropriate primary amines in solvents such as 1,4-dioxane or tetrahydrofuran at 0-50°C. Alternatively, as illustrated in Example 6 and shown in Step 3, the thioureas can be prepared by allowing **II** to react with an appropriate isothiocyanate (R' - N = C = S) in solvents such as tetrahydrofuran at 0-50°C. Thioamides (**Ib**, R" = H, $alkyl_{1-4}$) are prepared by allowing **II** to react with an appropriate dithioester (R'" S-C(=S)-R", Step 4 as illustrated in Example 4. This reaction is carried out in aqueous-alcoholic solvents at 0-50°C in the presence of an equivalent of an alkali metal hydroxide. This reaction, especially when R'" is methyl or ethyl, can be catalyzed by an alkali metal fluoride.

The reaction of II with R'"-S-C(S)-R'" (R'"=$CH_3$, $C_2H_5$) to give Ib (Step 4) can also be carried out in the presence of a tertiary amine base such as triethylamine in solvents such as THF, dioxane or methylene chloride at 10-50°C for 3-48 hr.

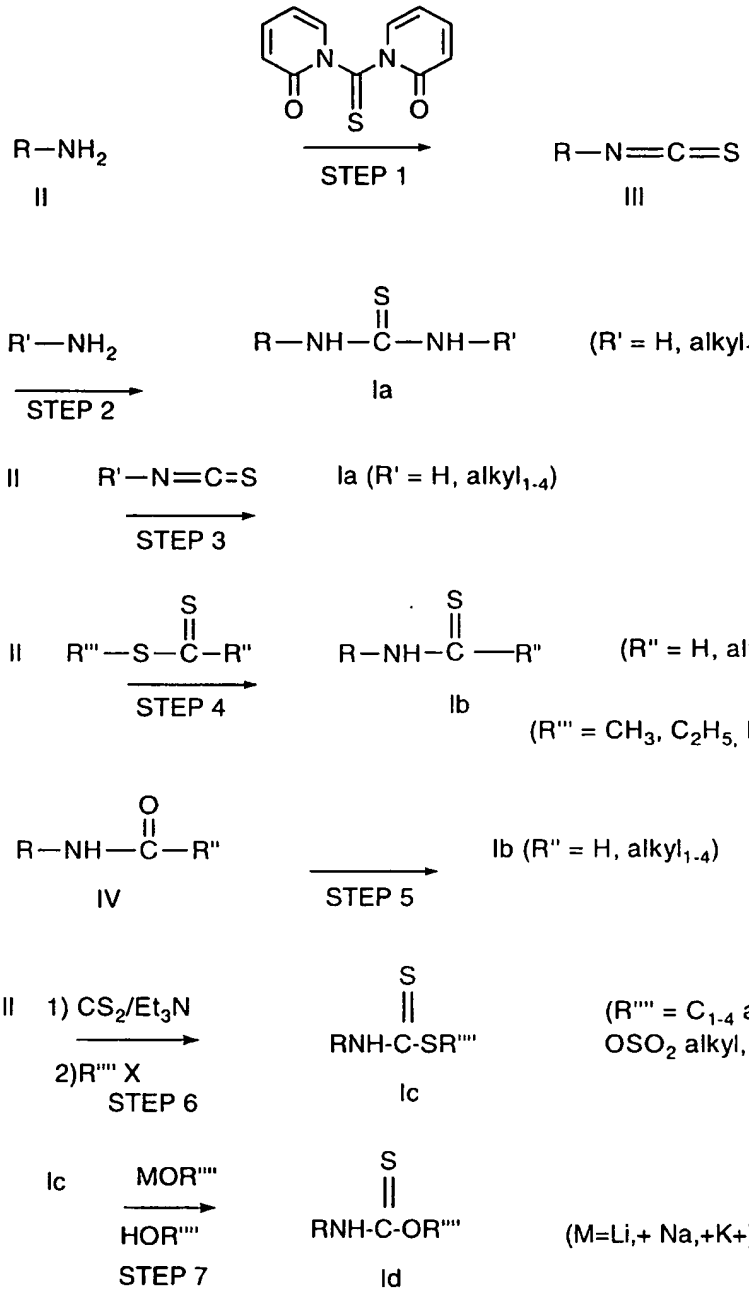
When the reaction conditions are tolerated by the substituents on R (see, for example, Examples 1-3) the thioamides (**Ib**, R" - H, $alkyl_{1-4}$) can also be conveniently prepared (Step 5) by allowing the appropriate amide intermediates (IV) to react with reagents such as 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (Lawesson's Reagent) in 1,4-dioxane, benzene, toluene or tetrahydrofuran at 60-110°C; phosphorus decasulfide and sodium carbonate in tetrahydrofuran at 20-50°C [Brillon, D., Synthetic Communications, 20, 3085 (1990)] or phosphorus decasulfide and sodium fluoride in 1,2-dimethoxyethane at 20-50°C [Hartke, K., Gerber, H.-D., J. Prakt. Chem., 338, 763 (1996)].

Compounds Ic are prepared (Step 6) by allowing II to react first with carbon disulfide and a tertiary amine base such as triethylamine in solvent mixtures containing water and methanol, ethanol or isopropanol at 10-50°C for 5-24 hours. The resulting intermediate is treated with an alkylating agent (R"" X where X represents bromo, iodo, alkylsulfonyloxy or arylsulfonyloxy) at 0-30°C to give

compounds Ic. In Step 7, compounds Ic are allowed to react with alkali metal alkoxide such as sodium methoxide or potassium ethoxide in the corresponding alkanol as solvent. This reaction is conveniently carried out at the reflux temperature of the alkanol for 1-24 hr.

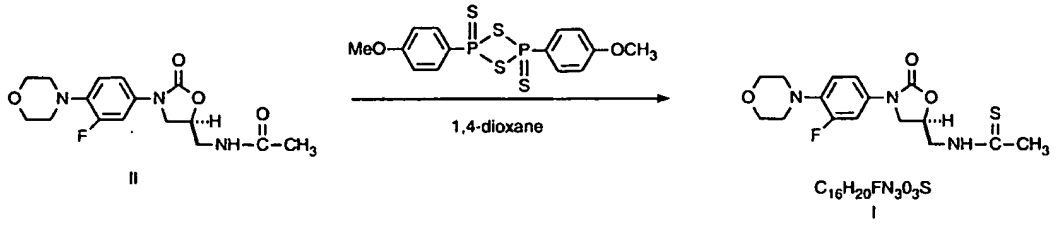
5

SCHEME 1




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

EXAMPLE 1: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (I)

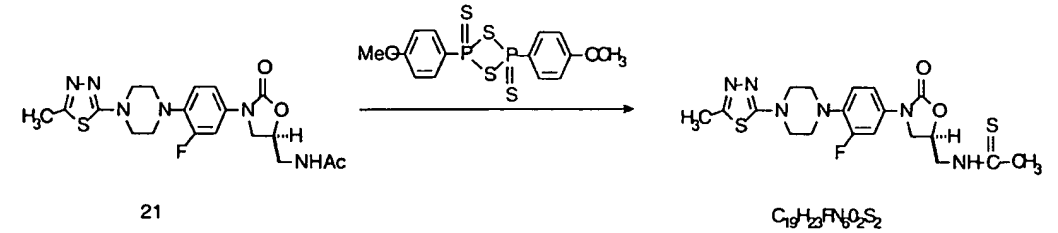



II

$C_{16}H_{20}FN_3O_3S$
I

A stirred mixture of II (PCT/US94/08904, 3.37 g, 10.0 mmol) in dry dioxane (100 mL), under nitrogen was treated with Lawesson's Reagent (4.04g, 10.0 mml), warmed to reflux during 1 h and refluxed for 1.5 h. The reaction was complete by TLC on silica gel with 10% MeOH-$CHCl_3$. It was kept at ambient temperature for 18 h and concentrated in vacuo. Chromatography of the residue on silica gel with mixtures of acetone-methylene chloride containing 10-15% acetone gave the product which was crystallized from acetone-hexane to give 1: mp 157.5-158.5 °C; HRMS theory for $C_{16}H_{20}FN_3O_3S$ ($M^+$): 353.1209; found: 353.1212. Anal. calcd for $C_{16}H_{20}FN_3O_3S$: C, 54.38; H, 5.38; N, 11.89; S, 9.07. Found: C, 54.21; H, 5.58; N, 11.78; S, 8.93.

EXAMPLE 2: (*S*)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (2)



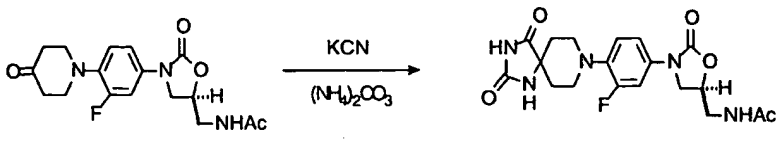

21

$C_{19}H_{23}FN_6O_2S_2$
2

According to Example 1, for the preparation of 1, 21 (PCT/US97/01970) was allowed to react with Lawesson's Reagent in refluxing dioxane to give 2: mp 222-223 °C; HRMS theory for $C_{19}H_{24}FN_6O_2S_2$ ($M+H^+$): 451.1386; found 451.1381.

EXAMPLE 3: (*S*)-N-[[3-[3-Fluoro-4-[2',5'-dioxospiro[piperidine-4,4'-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).

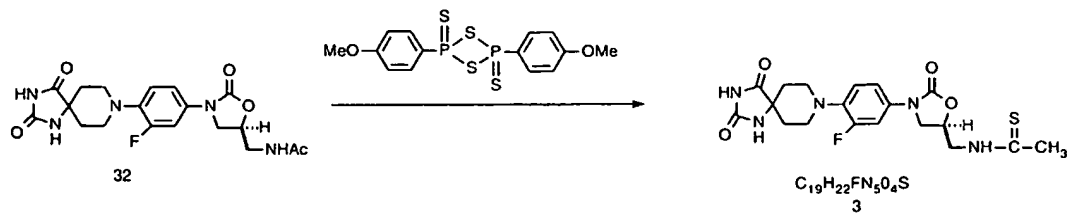
STEP A: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (32).




31 $C_{19}H_{22}FN_5O_5$ 32

A stirred suspension of 31 (Case 4780.P CP, 0.349 g, 1.00 mmol) in 1:1 EtOH:$H_2O$ (5 mL), under nitrogen, was treated with potassium cyanide (0.130 g, 2.00 mmol) and ammonium carbonate (0.701 g, 7.30 mmol), warmed at 55-60 °C for 5 h 15 min and kept at ambient temperature for 17 h 15 min. It was then chromatographed on silica gel with mixtures of MeOH-$NH_4OH$-$CHCl_3$ containing 5-20% MeOH and 0.5% $NH_4OH$ to give 0.280 g of 32: HRMS calcd for $C_{19}H_{22}FN_5O_5$: 419.1605 ($M^+$); found 419.1613; Anal. calcd for $C_{19}H_{22}FN_5O_5 \cdot 1\ H_2O$: C, 52.17; H, 5.53; N, 16.01. Found: C, 52.44; H, 5.30; N, 16.11.

STEP B: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).




32 $C_{19}H_{22}FN_5O_4S$ 3

A stirred suspension of 32 (0.210 g, 0.500 mmol) in dioxane (5.0 mL), under nitrogen was treated with Lawesson's Reagent (0.202 g, 0.500 mmol), refluxed for 4 h and concentrated in vacuo. The residue was chromatographed on silica gel with mixtures of MeOH-$NH_4OH$-$CHCl_3$ containing 1-10% MeOH and 0.1-0.5% $NH_4OH$ and the resulting product was crystallized from MeOH-$CHCl_3$-EtOAc to give 0.0491 g of 3: mp 218.5 °C; HR FAB MS theory for $C_{19}H_{22}FN_5O_4S$ ($M^+$): 435.1376; found 435.1370. Anal. calcd for $C_{19}H_{22}FN_5O_4S \cdot 0.5\ H_2O$: C, 51.34; H, 5.21; N, 15.76. Found: C, 51.69; H, 5.00; N, 15.25.

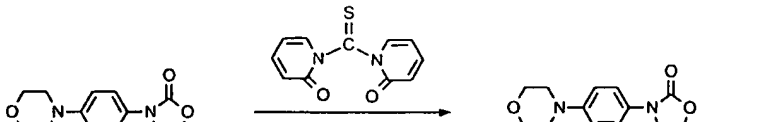
EXAMPLE 4: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (4).


41 $C_{16}H_{20}FN_3O_3S$ 4

A solution of 41 (148 mg, 0.500 mmol) and 0.97 M KOH (0.515 mL) in absolute EtOH (5 mL) was added to a solution of ethyl dithioacetate (57 µL, 0.50 mmol) and sodium fluoride (20 mg, 0.47 mmol) in absolute EtOH (5 mL) and the mixture was kept at ambient temperature for 3 h 40 min. Additional ethyl dithioacetate (5 µL) was added after 1 h 55 min and additional 0.97 M KOH (40 mL) and sodium fluoride (6 mg) were added to the mixture after 3h 5 min. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$ and 30% acetone-$CH_2Cl_2$. The major product had an $R_f$ on TLC that was the same as that of 4.

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

STEP A:

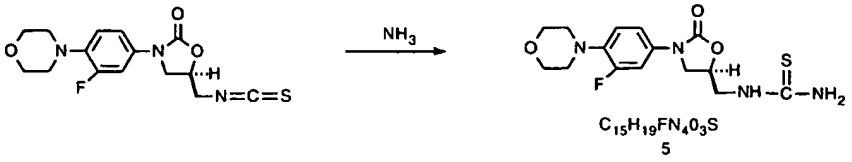



51 $C_{15}H_{16}FN_3O_3S$

A solution of 51 (PCT/US94/08904, 2.07 g, 7.00 mmol) in $CH_2Cl_2$ was added, dropwise during 30 min, under nitrogen to an ice cold, stirred solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (1.95 g, 8.40 mmol) in $CH_2Cl_2$ (70 mL). The mixture was warmed slowly to ambient temperature and kept for 18 h. It was then diluted with $CH_2Cl_2$, washed with water and aqueous NaCl, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 10% acetonitrile-$CH_2Cl_2$ gave 1.60 g of the isothiocyanate: HRMS theory for $C_{15}H_{16}FN_3O_3S$ ($M^+$): 337.0896; found

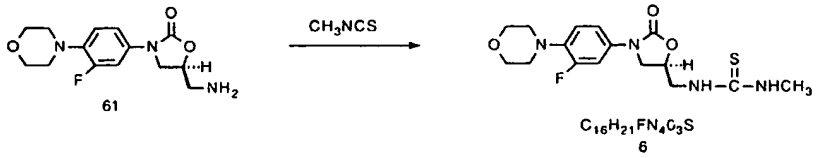
337.0888.

STEP B:



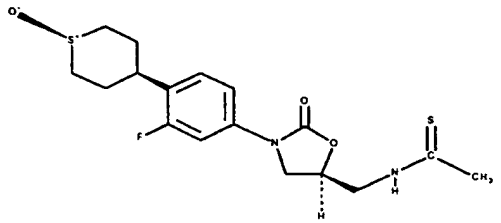

Anhydrous ammonia was bubbled for 7 min through a stirred solution of the product from Step I (1.00 g, 2.96 mmol) in THF (10 mL) and the mixture was kept at ambient temperature for 3 h 25 min and concentrated in vacuo. Crystallization of the residue from acetone-hexane gave 0.861 g of 5: mp 199-199.5 °C; MS *m/z* 354 ($M^+$). Anal. calcd for $C_{15}H_{19}FN_4O_3S$: C, 50.84; H, 5.40; N, 15.81. Found: C, 50.87; H, 5.39; N, 15.72.

EXAMPLE 6: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea (6).




A stirred solution of methyl isothiocyanate (93 mg, 1.27 mmol) in THF, was treated with 61 (295 mg, 1.00 mmol), kept at ambient temperature for 18 h and concentrated in vacuo. The residue was recrystallized from EtOAc-hexane to give 246 mg of 6: mp 158-160 °C; MS *m/z* 368 ($M^+$). Anal. calcd for $C_{16}H_{21}FN_4O_3S$: C, 52.16; H, 5.74; N, 15.21. Found: C, 52.20; H, 5.85; N, 15.17.

EXAMPLE 7 (S)-cis-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



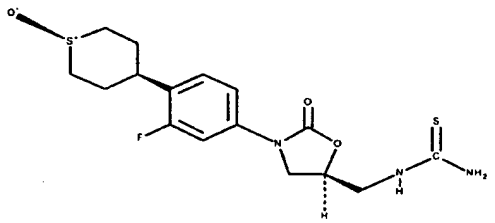
Step 1: A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide (4.50 g, can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) and platinum oxide (697 mg) in methanol (164 mL) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 18 hours. The catalyst is then removed by filtration through Celite, and the filtrate is concentrated under reduced pressure and the residue chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3/97 - 7/93). Pooling and concentration of those fractions with an $R_f$ = 0.44 by TLC (methanol/chloroform, 10/90) gives (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, mp 203 - 204°C.

Step 2: A mixture of the compound prepared in Step 1 (2.50 g) and hydroxylamine hydrochloride (2.36 g) in pyridine (30.6 mL) and ethanol (3.4 mL) is stirred in a screw-cap vial at 100°C for 22 hrs and at ambient temperature for 16 hrs, during which additional hydroxylamine hydrochloride (944 mg) and pyridine (4 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (100 mL) and saline (50 mL), adjusted to pH 11 with solid sodium carbonate and extracted with methanol/methylene chloride (10/90, 5 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (6/94 - 10/90). Pooling and concentration of those fractions with an $R_f$ = 0.14 by TLC (methanol/chloroform, 10/90) gives (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 159 - 161°C.

Step 3: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-

yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 2,(300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 4 hours and was then diluted with methylene chloride (150 mL) and washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and the crude product was triturated with methylene chloride/diethyl ether and filtered to give the title compound, mp 176 - 177°C (dec.).

EXAMPLE 8 (S)-cis-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea

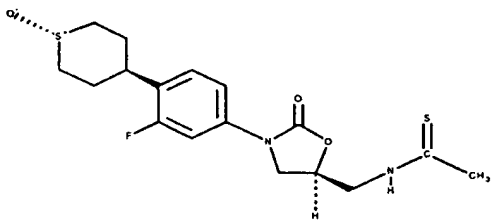


Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (235 mg, 1.01 mmol) in anhydrous methylene chloride (10 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 7, Step 2, (275 mg, 0.843 mmol) in anhydrous methylene chloride (34 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1 hour and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (70 - 230 mesh, 20 g), eluting with acetonitrile/methylene chloride (40/60), and those fractions with an $R_f$ = 0.07 by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-cis-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 187 - 190°C (dec.).

Step 2: A solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 290 mg, 0.787 mmol) in anhydrous tetrahydrofuran (39 mL) at 0°C under a nitrogen atmosphere was treated

(bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 206 - 208°C (dec.).

EXAMPLE 9 (S)-trans-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide

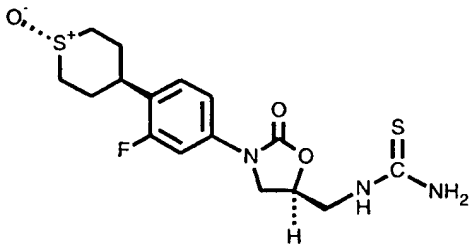


Step 1: (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-ox azolidinyl]methyl]acetamide S-oxide (disclosed in International Publication No. WO 97/09328) may be reduced to the corresponding cis- and trans-sulfoxides by catalytic hydrogenation in the presence of a catalyst and solvent. Alternatively, the sulfide by product of this reduction reaction can be oxidized with an oxidizing agent such $NaIO_4$ or meta-chloroperoxybenzoic acid in solvent to provide the cis- and trans-sulfoxides. The isomeric mixture can then be separated by chromatography to isolate the trans-sulfoxide, mp 211 - 212°C (dec.). A mixture of the trans-sulfoxide, (S)-trans-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (0.90 g) and hydroxylamine hydrochloride (0.85 g) in pyridine (11.0 mL) and ethanol (1.2 mL) is stirred in a screw-cap vial at 100°C for 23 hrs and at ambient temperature for 19 hrs, during which additional hydroxylamine hydrochloride (340 mg) and pyridine (1 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium carbonate (50 mL) and saline (50 mL) and extracted with methanol/methylene chloride (10/90, 6 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of methanol/methylene chloride (7.5/92.5 - 10/90). Pooling and concentration of those fractions with an $R_f$ =

0.14 by TLC (methanol/chloroform, 10/90) gives (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 138 - 140°C.

Step 2: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepare in Step 1, (300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 17 hours and was then diluted with methylene chloride (150 mL), washed with water (2 x 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 35 g), eluting with methanol/methylene chloride (3/97), and those fractions with an $R_f$ = 0.56 by TLC (methanol/chloroform, 10/90) were pooled and concentrated and the residue recrystallized from methylene chloride/diethyl ether to give the title compound, mp 193 - 194°C (dec.).

EXAMPLE 10 (S)-trans-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea

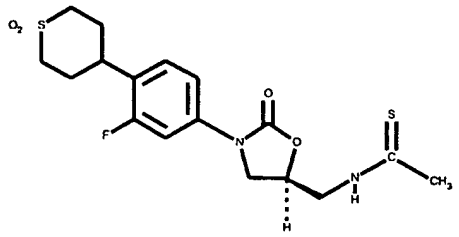


Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (192 mg, 0.827 mmol) in anhydrous methylene chloride (8.3 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 9, Step 1, (225 mg, 0.689 mmol) in anhydrous methylene chloride (28 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 40 minutes and was then diluted with methylene chloride (20 mL), washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (32 - 63 mm, 40 g), eluting with a gradient of acetonitrile/methylene chloride (30/70 -

60/40) under 15 psi $N_2$, and those fractions with an $R_f = 0.12$ by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-trans-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4- yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 165 - 167°C.

Step 2: A solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 230 mg, 0.624 mmol) in anhydrous tetrahydrofuran (31.2 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Trituration with methanol/methylene chloride/diethyl ether gave the title compound, mp 209 - 210°C (dec.).

EXAMPLE 11 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide

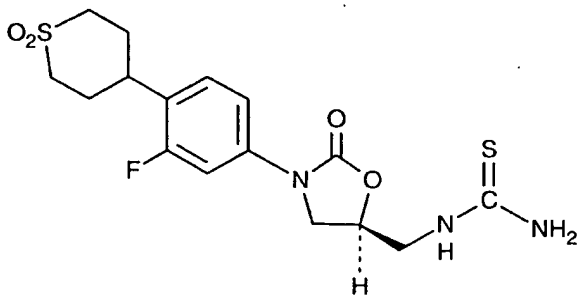


Step 1: Starting with (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as prepared in Example 7, Step 1, and following the general procedure of Step 2, and making non-critical variations by substituting (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (disclosed in International Publication No. WO 97/09328) for (S)-cis-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the product (S)-(-)-3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone is obtained, mp 194°C (dec.).

Step 2: A solution of ethyl dithioacetate (100 mL, 0.876 mmol) and sodium fluoride (37 mg, 0.876 mmol) in ethanol (8.8 mL) under a nitrogen atmosphere was

treated with a mixture of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 1, (300 mg, 0.876 mmol) and aqueous potassium hydroxide (1M, 0.88 mL) in ethanol (43.8 mL). The resulting mixture was stirred at ambient temperature for 26 hours, during which additional ethyl dithioacetate (50 mL, 0.438 mmol), sodium fluoride (19 mg, 0.438 mmol), aqueous potassium hydroxide (1M, 0.44 mL) and ethanol (3.0 mL) was added, and was then diluted with methylene chloride (150 mL), washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was recrystallized from methylene chloride/diethyl ether to give the title compound, mp 186 - 187°C (dec.).

EXAMPLE 12 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea

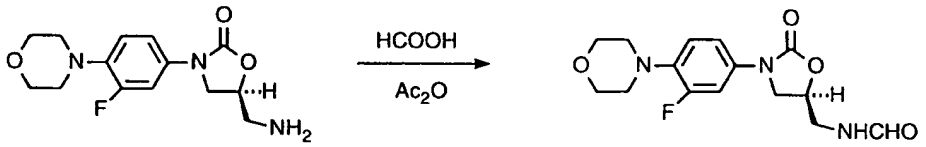



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (304 mg, 1.31 mmol) in anhydrous methylene chloride (13 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 11, Step 1, (375 mg, 1.09 mmol) in anhydrous methylene chloride (88 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 30 minutes and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with acetonitrile/methylene chloride (7.5/92.5), and those fractions with an $R_f$ = 0.64 by TLC (acetonitrile/methylene chloride, 20/80) were pooled and concentrated to give (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 158 - 162°C (dec.).

Step 2: A solution of (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 380 mg, 0.988 mmol) in anhydrous tetrahydrofuran (49 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 196 - 198°C (dec.).

EXAMPLE 13: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide (7).**

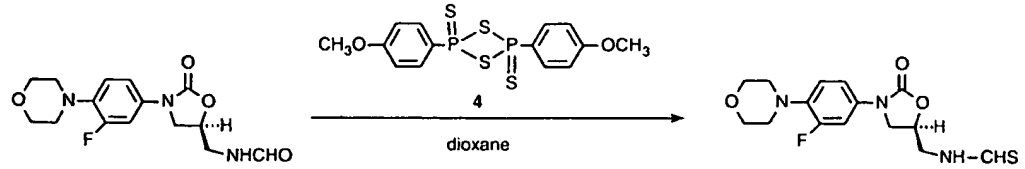
1.




39 6

A stirred mixture of acetic anhydride (0.23 mL, 0.0024 mol) and 95-97% formic acid (0.10 mL, 0.0027 mL) was warmed, under nitrogen at 50-55 °C for 2 h, cooled to ambient temperature and treated, portionwise during 2 min, with **39**[8] (0.45 g, 0.0015 mol). The suspension was kept at ambient temperature for 4 h and the resulting solution was treated with $Et_2O$ (1 mL) and kept at ambient temperature for 18 h. The mixture was diluted with additional $Et_2O$ (10 mL) and the solid was collected by filtration, washed with $Et_2O$ and dried to give 0.38 g of **6**[9]: MS (ES) *m/z* 324 ($M+H^+$), 346 ($M+Na^+$); $^1H$ NMR (300 mHz, $CDCl_3$) d 3.08 (m, 4H), 3.72 (m, 2H), 3.77 (d,d, 1H), 3.89 (m, 4H), 4.04 (t, 1H), 4.80 (m, 1H), 6.33 (s, 1H), 7.05 (m, 2H), 7.45 (d,d, 1H), 8.27 (s, 1H).

2.

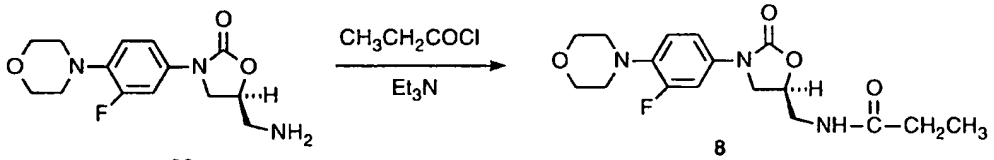



6 7

A stirred mixture of **6** (0.38 g, 0.00118 mol) in dioxane (20 mL), under nitrogen was treated with 4 (0.51 g, 0.00126 mol), warmed to reflux during 30 min and kept at this temperature for 90 min. It was then evaporated under a stream of nitrogen. The residue was chromatographed on silica gel with 1.25% MeOH-$CH_2Cl_2$ and the slightly impure product was rechromatographed on silica gel with 25% EtOAc-$CH_2Cl_2$. The resulting product was crystallized from EtOAc-methyl *tert*-butyl ether to give 0.114 g of **7**: mp 150-155 °C (dec); IR (DRIFT) 3322, 1752 $cm^{-1}$; MS(ES) *m/z* 340 ($M+H^+$), 362 ($M+Na^+$); $^1$HNMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.72 (m, 4H), 3.77 (d,d, 1H), 3.94 (t, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.33 (d, 1H), 10.59 (s, 1H). Anal. calcd for $C_{15}H_{18}FN_3O_3S$: C, 53.08; H, 5.35; N, 12.38. Found: C, 53.02; H, 5.44; N, 12.36.

EXAMPLE 14: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiopropion-amide (9).**

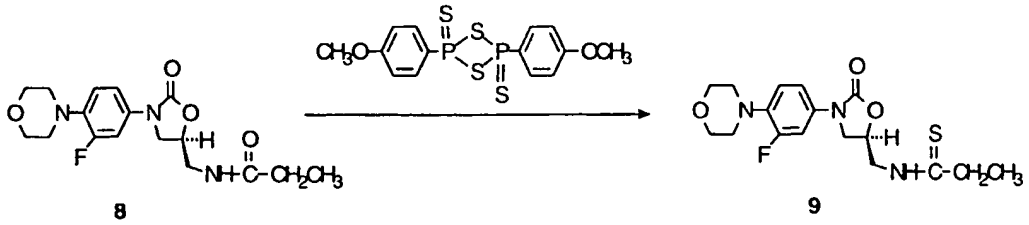
1.




39 8

An ice cold, stirred solution of **39**[8] (0.395 g, 0.00134 mol) and triethyl amine (0.186 mL, 0.0027 mol) in $CH_2Cl_2$ (20 mL), under nitrogen was treated, dropwise during 2 min, with a solution of propionyl chloride (0.128 mL, 0.00147 mol) in $CH_2Cl_2$ (3 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 1 h. It was then diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue (**8**)[9] was used without further purification in the next reaction.

2.



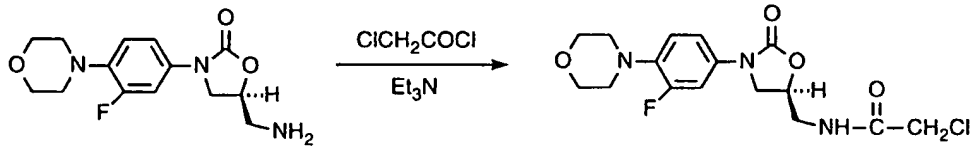

8 9

A stirred mixture of the product (**8**) from the previous reaction and dioxane (20 mL), under nitrogen, was treated, portionwise during 1 min, with Lawesson's reagent

(0.58 g, 0.0014 mol) and refluxed for 2 h; it was then concentrated. The residue was chromatographed on silica gel with 2% MeOH-$CHCl_3$ and the product was crystallized from methyl *tert*-butyl ether to give 0.259 g of **9**: mp 138-139 °C; MS(ES) *m/z* 368 ($M+H^+$), 390 ($M+Na^+$); IR (DRIFT) 3284, 3266, 1748, 1744 $cm^{-1}$; $[\alpha]^{24}_D$ +20° (MeOH); 1H NMR[300 MHz, $(CD_3)_2SO$] d 1.12 (t, 3H), 2.56 (q, 2H), 2.94 (m, 4H), 3.72 (m, 4H), 3.78 (d,d, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 10.30 (broad s, 1H). Anal. calcd for $C_{17}H_{22}FN_3O_3S$: C, 55.57; H, 6.03; N, 11.44. Found: C, 55.68; H, 6.21; N, 11.37.

EXAMPLE 15: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2-chlorothioacetamide (11).**

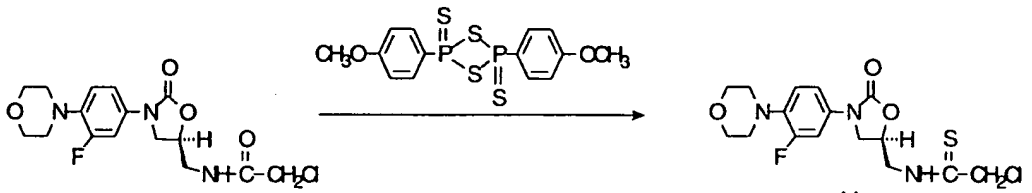
1.




39 10

A stirred solution of **39** (1.54 g, 5.2 mmol) and triethylamine (750 mg, 7.5 mmol) in $CH_2Cl_2$ (50 mL), under nitrogen, was treated, dropwise, during 15 min with a solution of chloroacetyl chloride (465 mL, 5.8 mmol) in $CH_2Cl_2$ (30 mL) and kept at ambient temperature for 18 h. It was then washed with saturated $NaHCO_3$ and dilute NaCl, dried ($Na_2SO_4$) and concentrated. The residue was flash chromatographed on silica gel with 20-30% acetone-$CH_2Cl_2$ to give 1.49 g of **10**[9] which was used in the next reaction without further purification.

2.



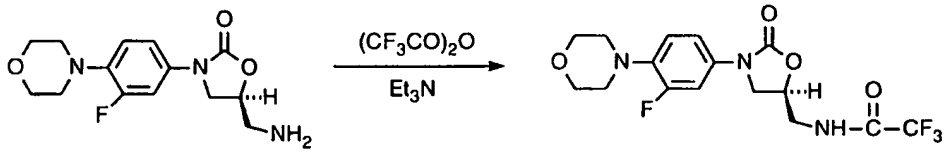
10 11

A stirred mixture of **10** (0.371 g, 1.0 mmol) and Lawesson's reagent (0.420 mg, 1.04 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h and concentrated under reduced pressure. The residue was chromatographed on silica gel with 3-10% acetone-$CH_2Cl_2$ to give 0.143 g of **11**: MS (CI) *m/z* 388 ($M+H^+$); $^1H$ NMR (300 MHz, $CDCl_3$) d 3.07 (m, 4H), 3.77 (d,d, 1H), 3.88 (m, 4H), 4.04 (m, 1H), 4.12 (t, 1H),

4.35 (m, 1H), 4.61 (s, 2H), 4.98 (m, 1H), 6.96 (t, 1H), 7.08 (d,d, 1H), 7.44 (d,d, 1H), 8.69 (s, 1H). Anal. calcd for $C_{16}H_{19}ClFN_3O_3S$: C, 49.55; H, 4.94; N, 10.83. Found: C, 49.38; H, 5.20; N, 10.27.

EXAMPLE 16: **(*S*)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide (13).**

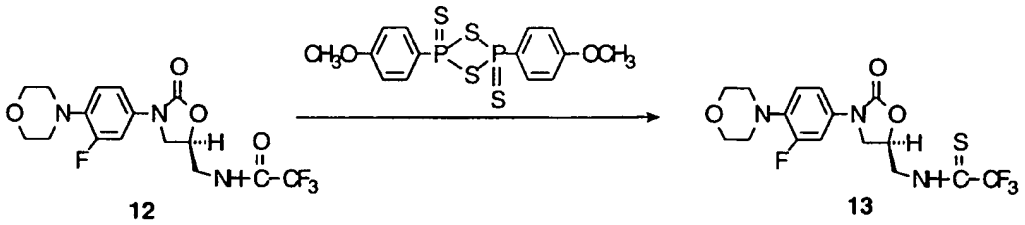
1.




39 12

An ice cold stirred solution of **39** (0.590 g, 2.0 mmol) and triethylamine (640 mL, 4.6 mmol) in $CH_2Cl_2$ (10 mL) was treated with trifluoroacetic anhydride (325 mL, 2.3 mmol) and kept in the ice bath for 10 min and then at ambient temperature. The reaction was followed by TLC on silica gel with 30% acetone-$CH_2Cl_2$. Additional trifluoroacetic anhydride and triethylamine were added after 3 d (64 mL / 125 mL), 4 d (100 mL / 220 mL) and 6 d (325 mL / 1.0 mL). The reaction was complete 1 h after the last addition; it was mixed with $CH_2Cl_2$, washed with water and dilute NaCl, dried ($Na_2SO_4$) and concentrated. The solid residue was recrystallized from acetone-heptane to give 0.566 g of **12**: mp 161-164 °C (dec); MS(EI) *m/z* 391 ($M^+$). Anal. calcd for $C_{16}H_{17}F_4N_3O_4$: C, 49.11; H, 4.38; N, 10.74. Found: C, 48.99; H, 4.56; N, 10.73.

2.



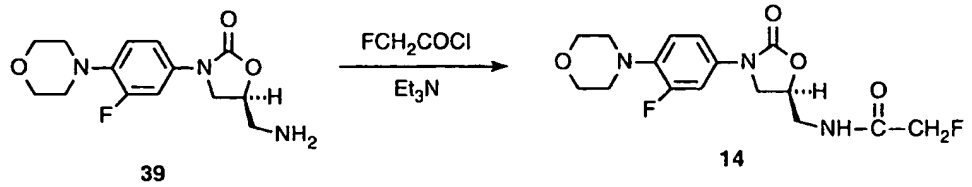

12 13

A stirred mixture of **12** (0.391 g, 1.0 mmol) and Lawesson's reagent (0.422 g, 1.1 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h, cooled slowly to ambient temperature and concentrated in vacuo. The residue was flash chromatographed on silica gel with 5-15% acetone-$CH_2Cl_2$ and the product was crystallized from acetone-heptane to give 0.249 g of **13**: mp 151-152 °C; MS(EI) *m/z* 407 ($M^+$), 363, 209, 151, 95; $^1H$ NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (d,d,

1H), 3.87 (m, 4H), 3.95 (m, 1H), 4.14 (t, 1H), 4.32 (m, 1H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.38 (d,d, 1H), 9.03 (s, 1H). Anal. calcd for $C_{16}H_{17}F_4N_3O_3S$: C, 47.17; H, 4.21; N, 10.31. Found: C, 47.09; H, 4.35; N, 10.27.

EXAMPLE 17: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide (15).**

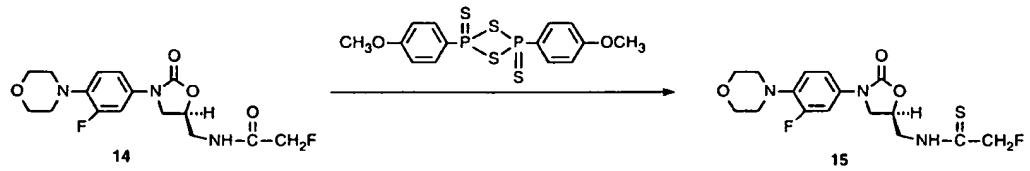
1.




39 14

A stirred, ice cold solution of **39** (0.590 g, 2.0 mmol) and triethylamine (611 mL, 4.4 mmol) in $CH_2Cl_2$ (10 mL), under nitrogen, was treated, dropwise, with a solution of fluoroacetyl chloride (220 mL, 2.2 mmol) in $CH_2Cl_2$ (5 mL), kept in the ice bath for 10 min and at ambient temperature for 2 h. It was then diluted with $CH_2Cl_2$, washed with water and dilute NaCl, dried ($Na_2SO_4$) and concentrated. The residue was chromatographed on silica gel with 10-30% acetone-$CH_2Cl_2$ to give 0.180 g of **14**: MS(ES) *m/z* 356 ($M+H^+$), 378 ($M+Na^+$).

2.

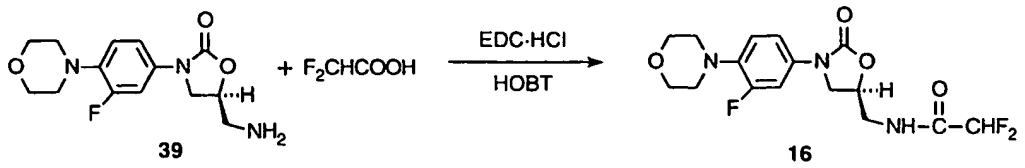



14 15

A solution of **14** (0.180 g, 0.507 mmol) in dioxane, under nitrogen, was treated with Lawesson's reagent (0.206 g, 0.51 mmol), warmed at 90-100 °C for 1 h and concentrated in vacuo. The residue was chromatographed on silica gel with 15% acetone-$CH_2Cl_2$ to give 0.161 g of **15**: MS(EI) *m/z* 371 ($M^+$); $^1H$ NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.78 (d,d, 1H), 3.87 (m, 4H), 4.03 (m, 1H), 4.11 (t, 1H), 4.38 (m, 1H), 4.98 (m, 1H), 5.07 (s, 1H), 5.23 (s, 1H), 6.93 (t, 1H), 7.08 (dd, 1H), 7.42 (d,d, 1H), 8.42 (s, 1H). Anal. calcd for $C_{16}H_{19}F_2N_3O_3S$: C, 51.74; H, 5.16; N, 11.31. Found: C, 51.79; H, 5.31; N, 11.02.

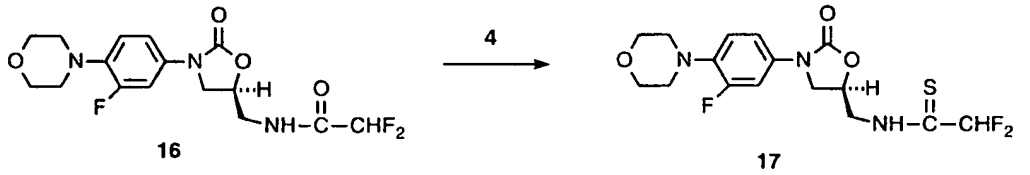
EXAMPLE 18: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide (17).**

1.




A stirred, ice cold mixture of **39** (0.590 g, 2.0 mmol), difluroacetic acid (190 mL, 2.0 mmol), and 1-hydroxybenzotriazole (0.297 g, 2.2 mmol) in DMF (5 mL) under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.843 g, 4.4 mmol) and kept at ambient temperature for 18 h. It was diluted with $CH_2Cl_2$, washed with water and dilute NaCl, dried ($Na_2SO_4$) and concentrated. The solid residue was crystallized form EtOAc-heptane to give 0.617 g of **16**: mp 149-150 °C; 1H NMR (300 MHz, CDCl3) d 3.05 (m, 4H), 3.66 (m, 2H), 3.85 (m, 5H), 4.08 (t, 1H), 4.80 (m, 1H), 5.93 (t, $J$ = 53.9 Hz, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.39 (d,d, 1H); MS(EI) $m/z$ 373 ($M^+$). Anal. calcd for $C_{16}H_{18}F_3N_3O_4$: C, 51.48; H, 4.86; N, 11.26. Found: C, 51.59; H, 4.91; N, 11.29.

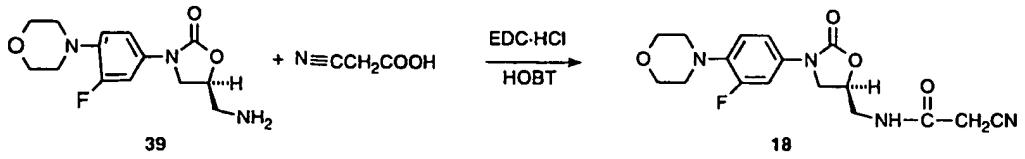
2.




A stirred solution of **16** (0.373 g, 1.00 mmol) in dioxane (10 mL), under nitrogen was treated with Lawesson's reagent (0.404 g, 1.00 mmol), warmed at about 95 °C for 1 h and concentrated in vacuo. Chromatography of the residue on silica gel with 10% acetone-$CH_2Cl_2$ and cyrstallization of the product from EtOAc-heptane gave 0.276 g of **17**: mp 125-127 °C; MS(EI) $m/z$ 389 ($M^+$), 345, 305, 247, 209, 195, 151, 138, 123, 109, 95; $^1$H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.76 (d,d, 1H), 3.86 (m, 4H), 4.01 (m, 1H), 4.12 (t, 1H), 4.30 (m, 1H), 4.99 (m, 1H), 6.20 (t, $J$ = 55.9 Hz, 1H), 6.92 (t, 1H), 7.06 (d,d, 1H), 7.38 (d,d, 1H), 8.78 (broad s, 1H). Anal. calcd for $C_{16}H_{18}F_3N_3O_3S$: C, 49.35; H, 4.66; N, 10.79. Found: C, 49.37; H, 4.71; N, 10.83.

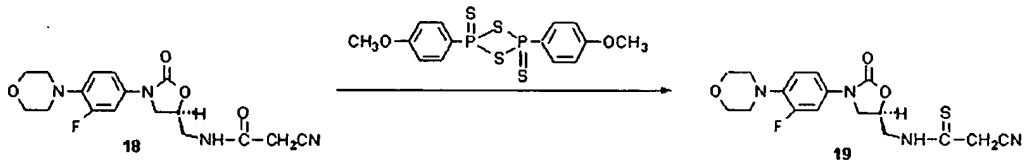
EXAMPLE 19: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide (19).**

1.




An ice cold, stirred mixture of **39** (0.646 g, 2.19 mmol), cyanoacetic acid (0.179 g, 2.1 mmol) and 1-hydroxybenzotriazole (0.351 g, 2.6 mmol) in DMF (5 mL), under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.997 g, 5.2 mmol) and kept at ambient temperature for 24 h. It was diluted with $CH_2Cl_2$, washed with water and dilute NaCl, dried ($Na_2SO_4$) and concentrated. The solid residue was crystallized from EtOAc-heptane to give 0.546 g of **18**: mp 172-174 °C: IR (DRIFT) 3316, 2256, 1754, 1684 $cm^{-1}$; MS(EI) *m/z* 362 ($M^+$). Anal. calcd for $C_{17}H_{19}FN_4O_4$: C, 56.35; H, 5.28; N, 15.46. Found: C, 56.33; H, 5.30; N, 15.36.

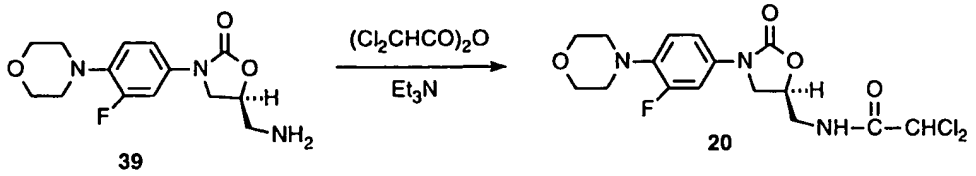
2.




A stirred solution of **18** (0.453 mg, 1.25 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.505 g, 1.25 mmol) and warmed at about 100 °C. When the reaction was over (TLC with 30% acetone-$CH_2Cl_2$) the mixture was cooled and concentrated in vacuo. Chromatography of the residue on silica gel with 10-20% acetone-$CH_2Cl_2$ and crystallization of the product from EtOAc-heptane gave 0.110 g of **19**: mp 186-187 °C (dec); MS(ES) *m/z* 379 ($M+H^+$), 401 ($M+Na^+$); $^1H$ NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.89 (s, 2H), 4.09 (t, 1H), 4.14 (m, 2H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.34 (d,d, 1H), 9.15 (s, 1H); IR (DRIFT) 3244, 2260, 1754 $cm^{-1}$. Anal. calcd for $C_{17}H_{19}FN_4O_3S$: C, 53.96; H, 5.06; N, 14.81. Found: C, 53.88; H, 5.39; N, 14.61.

EXAMPLE 20: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide (21).**

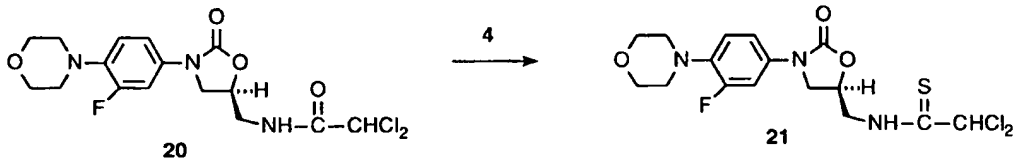
1.




39 20

A stirred, ice cold solution of **39** (0.885 g, 3.00 mmol) and triethylamine (975 mL, 7 mmol) in $CH_2Cl_2$ (15 mL), under nitrogen was treated, dropwise with a solution of dichloroacetic anhydride (555 mL, 3.5 mmol) in $CH_2Cl_2$ (5 mL) and kept in the ice bath for 15 min and at ambient temperature for 18 h. It was diluted with $CH_2Cl_2$, washed with water, saturated $NaHCO_3$ and dilute NaCl, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 10% acetone-$CH_2Cl_2$ and crystallization of the product from acetone-heptane gave 0.463 g of **20**: mp 197-198 °C (dec); MS(ES) *m/z* 406 ($M+H^+$), 428 ($M+Na^+$); $^1H$ NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (m, 3H), 3.86 (m, 4H), 4.07 (t, 1H), 4.83 (m, 1H), 5.94 (s, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.41 (d,d, 1H).

2.

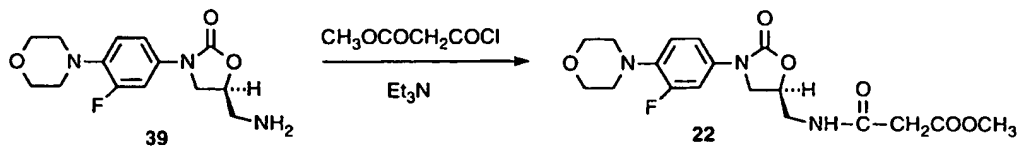



20 21

A stirred solution of **20** (0.305g, 0.75 mmol) in dioxane (5 ml), under nitrogen, was treated with Lawesson's reagent (0.202g, 0.5 mmol), warmed at about 90°C for 1 hour, cooled and concentrated in vacuo. Chromatography of the residue on silica gel first with 30% acetone-heptane and then with 10% acetone-methylene chloride and crystallization of rh product form methylene chloride - heptane gave 0.203g with **21**: mp 143-144°cd.; HR17S (EI) calculated for $C_{16}H_{18}cl_2$ F $N_3$ $O_3$ S(M) 421.0431. Anal. calcd for $C_{16}H_{18}cl_2$ F $N_3$ $O_3$ S, C, 45.51; H, 4.30; N, 9.95. Found: C, 45.47; H, 4.24; H, 9.88.

EXAMPLE 21: **(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide (23).**

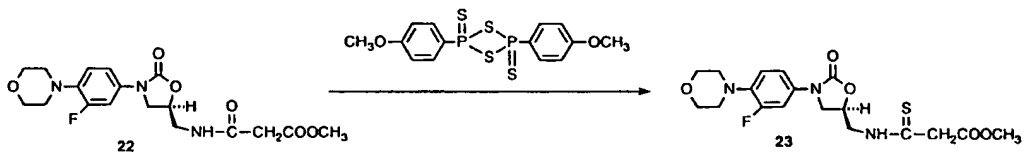
1.




39 22

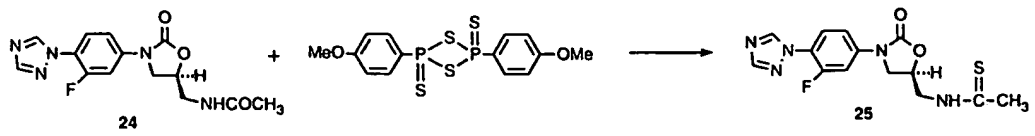
A stirred solution of **39** (0.955 g, 3.2 mmol) and triethylamine (650 mL, 4.5 mmol) in $CH_2Cl_2$ (50 mL), under nitrogen, was treated, dropwise during 15-20 min with a solution of methyl malonyl chloride (475 mL, 4.3 mmol) in $CH_2Cl_2$ (10 mL) and kept at ambient temperature for 3 days. It was then washed with water and dilute NaCl, dried and concentrated. The residue was flash chromatographed on silica gel with 15-30% acetone-$CH_2Cl_2$ and the product was crystallized form acetone-hexane to give 0.873 g of **22**: mp 150-151 °C; $^1$H NMR (300 MHz, $CDCl_3$) d 3.03 (m, 4H), 3.34 (s, 2H), 3.67 (s, 3H), 3.69 (m, 2H), 3.76 (d,d, 1H), 3.85 (m, 4H), 4.00 (t, 1H), 4.78 (m, 1H), 6.90 (t, 1H), 7.06 (d,d, 1H), 7.41 (d,d, 1H), 7.57 (t, 1H); MS(ES) *m/z* 396 ($M+H^+$), 418 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}FN_3O_6$ ($M+H^+$) 396.1571, found 396.1579. Anal. calcd for $C_{18}H_{22}FN_3O_6$: C, 54.68; H, 5.61; N, 10.63. Found: C, 54.69; H, 5.68; N, 10.58.

2.




A stirred solution of **22** (0.395 g, 1.0 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.202 g, 0.5 mmol) and kept at ambient temperature for 4 h 10 min and at 80-90 °C for 1.5 h. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$. At this time a new, less polar product had begun to form. It was kept at ambient temperature for 18 h and at 80 °C for 2 h; additional Laewsson's reagent (40 mg, 0.099 mmol) was added and warming at 80 °C was continued for 2 h; some starting material still remained. The mixture was concentrated and the residue was chromatographed on silica gel with 15% acetone-$CH_2Cl_2$ to give 0.348 g of **23**: $^1$H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.71 (s, 3H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.88 (s, 2H), 4.07 (t, 1H), 4.19 (m, 2H), 4.99 (m, 1H), 6.91 (t, 1H), 7.07 (d,d, 1H), 7.42 (d,d, 1H), 9.52 (s, 1H); IR (DRIFT) 3269, 1743 $cm^{-1}$; MS(EI) *m/z* 411 ($M^+$). Anal. calcd for $C_{18}H_{22}FN_3O_5S$: C, 52.54; H, 5.39; N, 10.21. Found: C, 52.58; H, 5.43; N, 10.14.

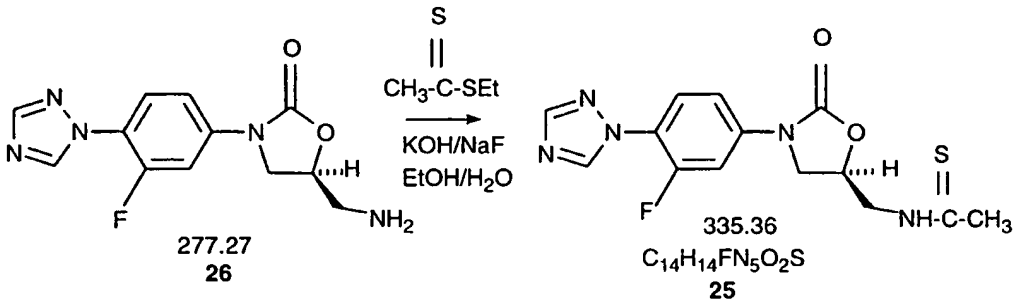
EXAMPLE 22: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**



24 25

A stirred mixture of **24**[10,11] (0.150 g, 0.470 mmol) and dioxane (12.5 mL), under nitrogen, was treated with Lawesson's reagent (0.20 g, 0.50 mmol), refluxed for 1.5 h, kept at ambient temperature for 18 h and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave the product which was crystallized from MeOH to give 0.100 g (63.4%) of **25**: mp 161-163 °C; $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.43 (s, 3H), 3.87 (m, 3H), 4.22 (t, 1H), 4.99 (m, 1H), 7.51 (d, 1H), 7.77 (m, 2H), 8.26 (s, 1H), 8.97 (d, 1H), 10.35 (broad s, 1H); IR (mull) 3259, 3226, 3044, 1752 $cm^{-1}$; MS(ES) *m/z* 336 ($M+H^+$), 358 ($M+Na^+$). Anal. calcd for $C_{14}H_{14}FN_5O_2S$: C, 50.14; H, 4.21; N, 20.88. Found: C, 50.18; H, 4.26; N, 20.94.

EXAMPLE 23: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**



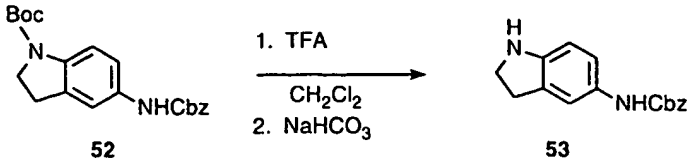
277.27
**26**

335.36
$C_{14}H_{14}FN_5O_2S$
**25**

A stirred mixture of **26**[10,12] (0.26 g, 0.938 mmol), ethyl dithioacetate (0.12 g, 0.998 mmol), sodium fluoride (0.040 g, 0.953 mmol) and absolute EtOH (10 mL), under nitrogen, was treated during 5 min with a solution of 0.97 M KOH (1.03 mL) in EtOH and kept at ambient temperature for 2 h. It was then diluted with $CH_2CL_2$ (75mL), washed with water, 1M $KHSO_4$, water and brine and evaporated. The residue was flash chromatographed on silica gel with 5% MeOH-$CHCl_3$ and the product was crystallized from MeOH to give 0.118 g, mp 164-165°C (dec) and 0.026 g, mp 162-163°C (dec) of **25**.

EXAMPLE 24: **(*S*)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (28).**

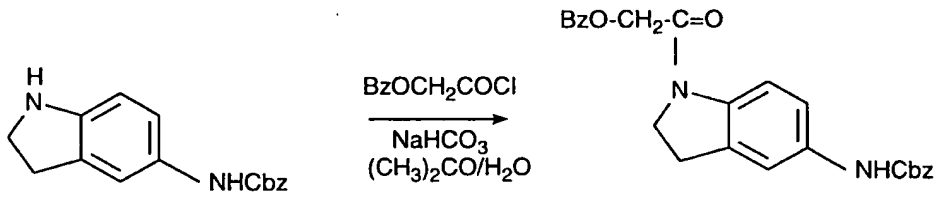
1.




52 53

A stirred, ice cold solution of **52**[13,14] (8.80 g, 0.0240 mol) in $CH_2Cl_2$ (25 mL) was treated during 20 min with a solution of trifluoroacetic acid (25 mL) in $CH_2Cl_2$ (10 mL). The mixture was kept in the ice bath for 2 h 15 min and concentrated under reduced pressure. A solution of the residue in $CH_2Cl_2$ was washed with saturated $NaHCO_3$ and dilute NaCl, dried ($Na_2SO_4$) and concentrated. The residue was used in the next reaction without further purification. A sample of this material (**53**) had: $^1H$ NMR (300 MHz, $CDCl_3$) d 3.00 (t, 2H), 3.54 (t, 2H), 3.85 (broad s, 1H), 5.17 (s, 2H), 6.59 (d, 1H), 6.66 (broad s, 1H), 6.91 (d, 1H), 7.23 (s, 1H), 7.36 (m, 5H); MS *m/z* 269 ($M+H^+$).

2.



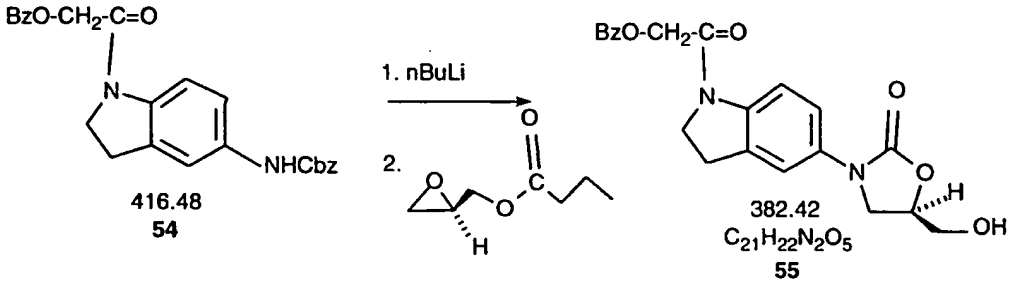

268.22
$C_{16}H_{16}N_2O_2$
**53**

416.48
$C_{25}H_{24}N_2O_4$
**54**

An ice cold, stirred mixture of **53** (crude product from the previous reaction), acetone (200 mL), saturated $NaHCO_3$ (200 mL) and water (30 mL) was treated, dropwise during 20 min, with a solution of benzyloxyacetyl chloride (4.70 mL, 0.030 mol) in acetone (55 mL), warmed slowly to ambient temperature and kept for 18 h. Additional benzyloxytacetyl chloride (1.0 mL) in acetone 35 mL) was added dropwise and the mixture was kept at ambient temperature for an additional 3 h and diluted with EtOAc and water. A solid was collected by filtration and dried to give 4.00 g of crude product. The EtOAc solution was dried ($Na_2SO_4$) and concentrated to give 5.36 g of additional crude product. Crystallization of the product from EtOAc gave a total of 6.35 g of **54**[14], mp 157-159.5°C. The analytical sample had: mp 158-159.5°C; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3,16 (t,2H), 4.01(t,2H), 4.21 (s, 2H), 4.69 (s,

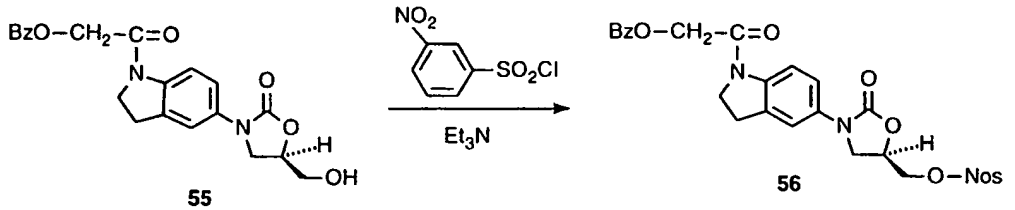
2H), 5.19 (s, 2H), 6.67 (s, 1H), 6.97 (d, 1H), 7.36 (m, 10H), 7.50 (braod s, 1H), 8.15 (d, 1H); MS(EI) *m/z* (relative intensity) 416 ($M^+$, 9), 310 (8), 202 (10), 133 (8), 92 (8), 91 (99), 79 (7), 77 (9), 65 (12), 51 (6); IR (mull) 2381, 1722, 1659, 1608, 1558 $cm^{-1}$. Anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.05; H, 5.86; N, 6.68.

3.




A stirred suspension of **54** (1.16 g, 2.78 mmol) in THF (42 mL) was cooled, under nitrogen, to -78°C and treated, dropwise, during 5 min with 1.6 M n-BuLi in hexane (1.83 mL). It was kept at -78°C for 50 min, treated, dropwise, during 5 min with a solution of (R)-(-)-glycidyl butyrate (0.500 g, 3.47 mmol) in THF (2 mL), allowed to warm to ambient temperature during 3 h and kpet for 18 h. It was then diluted with EtOAc, washed with saturated $NH_4Cl$, water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 3% MeOH-0.2% $NH_4OH$-$CHCl_3$ gave 0.60 g (56%) of **55**[14]: $^1H$ NMR [300 MHz, $(CD_3)_2SO$] δ 3.14 (t, 2H), 3.59 (m, 2H), 3.79 (d,d, 1H), 4.03 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.65 (m, 1H), 5.20 (t, 1H), 7.31 (m, 6H), 7.55 (s, 1H), 8.03 (d, 1H); MS(ES) *m/z* 383 ($M+H^+$), 405 ($M+Na^+$).

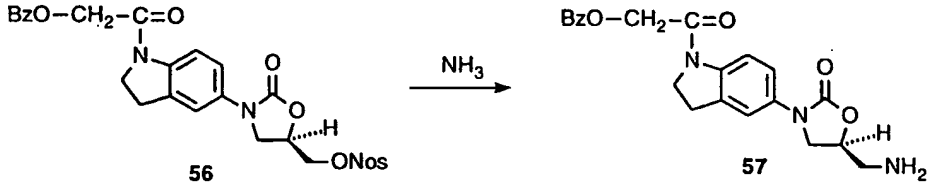
4.




An ice cold, stirred mixture of **55** (0.60 g, 1.57 mmol), triethylamine (2.2 mL), and $CH_2Cl_2$ (12 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (0.44 g, 1.99 mmol) and kept in the ice bath for 30 min and at ambient temperature for 60 min. It was then diluted with $CH_2Cl_2$, washed with water and brine, dried

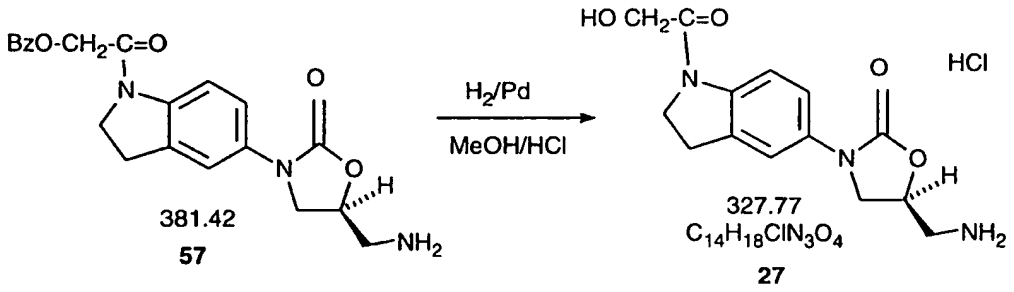
($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 15% $CH_3CN$-$CH_2Cl_2$ gave 0.70 g of **56**: $^1H$ NMR (300 MHz, $CDCl_3$) d 3.19 (t, $J$ = 8.3 Hz, 2H), 3.88 (d,d, 1H), 4.04 (t, $J$ = 8.4 Hz, 2H), 4.14 (t, 1H), 4.23 (s, 2H), 4.42 (m, 2H), 4.70 (s, 2H), 4.84 (m, 1H), 6.97 (m, 1H), 7.34 (m, 5H), 7.58 (s, 1H), 7.81 (t, 1H), 8.22 (m, 2H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) $m/z$ 568 ($M+H^+$), 590 ($M+Na^+$).

5.




A stirred mixture of **56** (crude product from 0.00314 mol of **55**), acetonitride (70 mL), isopropanol (70 mL) and 29% ammonium hydroxide (70 mL) was warmed at 40-44 °C for 7h and kept at ambient temperature for 18 h. It was concentrated in vacuo to an aqueous residue with was extracted with $CH_2Cl_2$. The extract was washed with water and brine, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 8% MeOH-0.5% $NH_4OH$-$CHCl_3$ gave 1.05 g of **57**: $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.78 (m, 2H), 3.13 (t, 2H), 3.82 (d,d, 1H), 4.01 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.58 (m, 1H), 7.31 (m, 6H), 7.54 (broad s, 1H), 8.03 (d, 1H); MS(ES) $m/z$ 382 ($M+H^+$), 404 ($M+Na^+$).

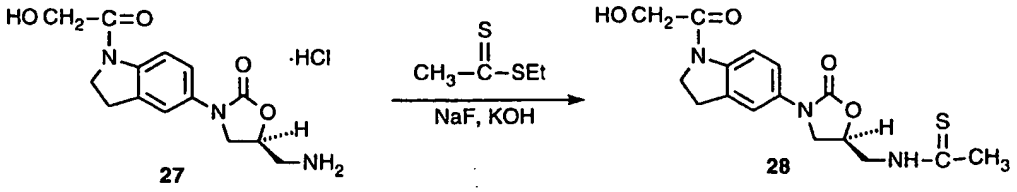
6.




A mixture of **57** (0.46 g, 1.21 mmol), MeOH (150 mL), 1 M HCl (1.2 mL) and 5% palladium-on-carbon catalyst (250 mg) was hydrogenated at an initial pressure of 49 psi for 5 h. Additional 1M HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 18 h. The catalyst was removed by filtration and

the filtrate was concentrated to give 0.34 g of **27**: $^1$H NMR [300 MHz, $(CD_3)_2SO$] δ 3.15 (t, 2H), 3.22 (broad s, 2H), 3.84 (d,d, 1H), 4.00 (t, 2H), 4.15 (s, 2H), 4.15 (m, 1H), 4.92 (m, 1H), 7.24 (q, 1H), 7.50 (d, 1H), 8.03 (d, 1H), 8.37 (broad s, 3H); MS(ES) *m/z* 2.92 ($M+H^+$).

7.

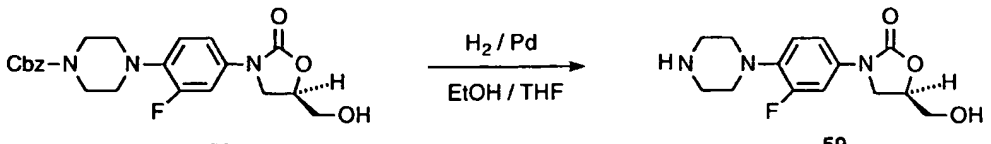



27 28

A suspension of **27** (0.10 g, 0.34 mmol) in a mixture of EtOH (15 mL) and 0.97 M KOH (0.7 mL) was added, under nitrogen to a stirred mixture of ethyl dithioacetate (0.0412 g, 0.343 mmol) and sodium fluoride (0.0137 g, 0.326 mmol) in EtOH (5 mL) and the mixture was kept at ambient temperature for 2h 15 min. Additional 0.97 M KOH (0.2 mL), sodium iodide (6 mg) and ethyl dithioacetate (20 mg) were added and the mixture was stirred for 2 h, mixed with $CH_2Cl_2$ (150 mL), washed with water, 1M $KHSO_4$ and brine, dried ($Na_2SO_4$) and concentrated. The residue was crystallized from acetone to give 0.0404 g of **28**: mp 175-176 °C (dec); MS (FAB) *m/z* 350 ($M+H^+$), 349 ($M^+$), 331, 316, 205, 73; HR MS (FAB) calcd for $C_{16}H_{20}N_3O_4S$ ($M+H^+$) 350.1174, found 350.1183; $^1$H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.14 (t, 2H), 3.79 (d,d, 1H), 3.89 (t, 2H), 4.00 (t, 2H), 4.12 (m, 3H), 4.83 (t, 1H), 4.90 (m, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 8.03 (d, 1H), 10.35 (s, 1H); IR (DRIFT) 3255, 3223, 3068, 1747, 1639, 1614 $cm^{-1}$.

EXAMPLE 25: **(*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (30).**

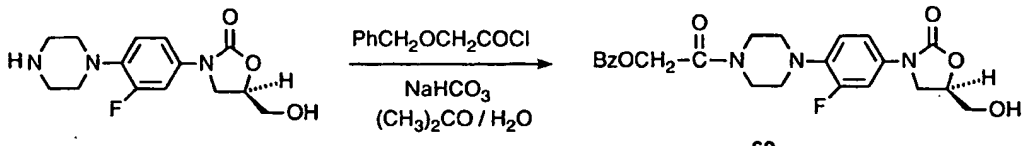
1.




58 59

A mixture of **58**[15] (3.00 g, 7.00 mmol), THF (60 mL), absolute EtOH (100 mL) and 10% palladium-on-carbon catalyst (415 mg) was hydrogenated at an initial pressure of 58 psi for 2 h 50 min. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 2.67 g of **59** which was used without further purification in the next reaction: $^1$H NMR (300 MHz, $CDCl_3$) d 2.16 (broad s), 3.02 (m, 8H), 3.73 (d,d, $J$ = 3.9, 12.6 Hz, 1H), 3.96 (m, 3H), 4.72 (m, 1H), 6.92 (t, $J$ = 9.2 Hz, 1H), 7.11 (m, 1H), 7.43 (d,d, $J$ = 2.6, 14.3 Hz, 1H); MS(ES) $m/z$ 296 ($M+H^+$).

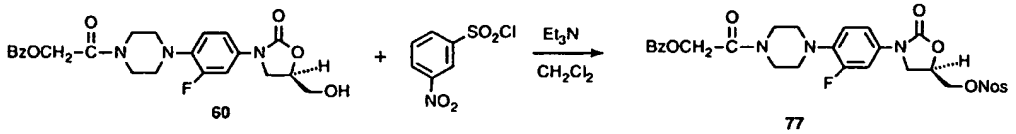
2.




**59** **60**

A stirred, ice cold mixture of **59** (2.67 g from the previous reaction), acetone (190 mL) and saturated $NaHCO_3$ (70 mL) was treated, dropwise during 2-3 min with a solution of benzyloxyacetyl chloride (1.34 mL, 8.61 mmol) in acetone (25 mL), kept in the ice bath for 1 h and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic solution was washed with dilute NaCl, dried and concentrated. Chromatography of the residue on silica gel with 30% acetone-$CH_2Cl_2$ gave 2.64 g of **60**: $^1$H NMR (300 MHz, $CDCl_3$) d 2.28 (broad s, 1H), 3.00 (m, 4H), 3.66 (m, 2H), 3.77 (m, 3H), 3.96 (m, 3H), 4.22 (s, 2H), 4.61 (s, 2H), 4.74 (m, 1H), 6.88 (t, $J$ = 9.2 Hz, 1H), 7.12 (m, 1H), 7.35 (s, 5H), 7.46 (d,d, $J$ = 2.6, 14.2 Hz, 1H); IR (mull) 3406, 1748, 1647 $cm^{-1}$; HRMS(EI) calcd for $C_{23}H_{26}FN_3O_5$ ($M^+$) 443.1856, found 443.1842.

3.

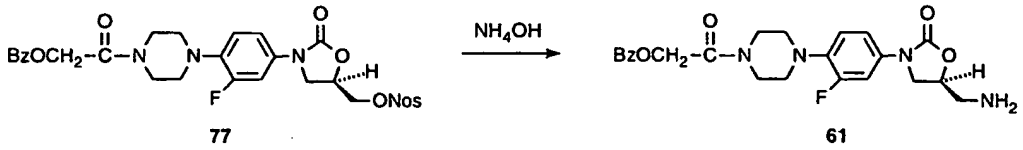



**60** **77**

A stirred, ice cold mixture of **60** (2.64 g, 6.00 mmol) and triethylamine (1.14 mL, 8.16 mmol) in $CH_2Cl_2$ (200 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (1.78 g, 8.04 mmol), warmed to ambient temperature and kept for 5 h 20 min. Additional 3-nitrobenzenesulfonyl chlroide (180 mg) and triethylamine (0.20 mL) were added and the mixture was kept at ambient

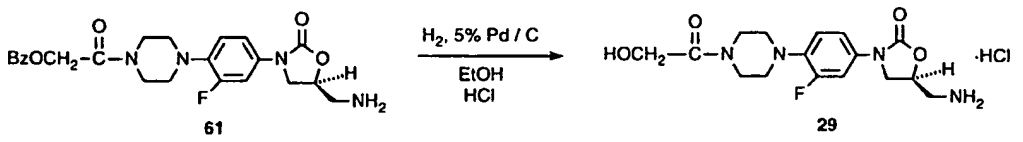
temperature for 18 h, diluted with $CH_2Cl_2$ and washed with water and dilute NaCl, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 40-60% acetone-hexane gave 3.36 g of **77**: $^1$H NMR (300 MHz, $CDCl_3$) d 3.02 (broad s, 4H), 3.66 (broad s, 2H), 3.78 (broad s, 2H), 3.87 (d,d, $J$ = 5.9, 9.1 Hz, 1H), 4.09 (t, $J$ = 9.2 Hz, 1H), 4.22 (s, 2H), 4.41 (m, 2H), 4.61 (s, 2H), 4.84 (m, 1H), 6.88 (t, $J$ = 9.1 Hz, 1H), 7.02 (m, 1H), 7.35 (m, 6H), 7.82 (t, $J$ = 8.0 Hz, 1H), 8.23 (m, 1H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) $m/z$ 629 ($M+H^+$).

4.




A solution of **77** (3.36 g, 5.34 mmol) in a mixture of acetonitrile (90 mL), isopropanol (90 mL) and concentrated ammonium hydroxide (90 mL) was warmed at 40-45 °C for 18 h, treated with additional ammonium hydroxide (30 mL), warmed at 40-45 °C for 8 h, treated with additional ammonium hydroxide (25 mL) and warmed at 45 °C for 18 h. It was then mixed with water and extracted with $CH_2Cl_2$. The extract was washed with dilute NaCl, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% $NH_4OH$-$CHCl_3$ gave 2.44 g of **61**: $^1$H NMR (300 MHz, $CDCl_3$) d 1.50 (broad s), 3.04 (m, 6H), 3.65 (broad s, 2H), 3.81 (m, 3H), 3.99 (t, 1H), 4.21 (s, 2H), 4.61 (s, 2H), 4.66 (m, 1H), 6.88 (t, 1H), 7.12 (m, 1H), 7.33 (m, 5H), 7.47 (d,d, 1H); MS(ES) $m/z$ 443 ($M+H^+$).

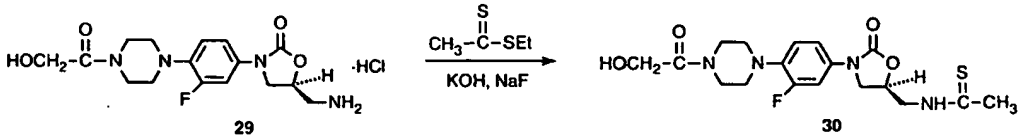
5.




A solution of **61** (1.45 g, 3.3 mmol) and 1.0 N HCl (3.65 mL) in 95% EtOH (150 mL) was treated with 5% palladium-on-carbon catalyst (500 mg) and hydrogenated at an initial pressure of 54 psi for 20 h 15 min. Additional 1.0 N HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 20 h 30 min at an initial pressure of 60 psi. The reaction was compete by TLC; it was neutralized with concentrated $NH_4OH$, filtered and concentrated in vacuo to give 1.18 g of **29**: $^1$H NMR [300 MHz, $(CD_3)_2SO$] d 2.94 (broad s, 4H), 3.19 (m, 2H), 3.48 (broad s, 2H),

3.60 (broad s, 2H), 3.84 (m, 1H), 4.14 (m, 3H), 4.66 (broad s, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.16 (d,d, 1H), 7.48 (d,d, 1H), 8.04 (broad s); IR (mull) 3420, 3099, 3040, 3008, 1755, 1641 $cm^{-1}$; MS(ES) *m/z* 353 ($M+H^+$). Anal. calcd for $C_{16}H_{22}ClFN_4O_4$: C, 49.42; H, 5.70; Cl, 9.12; N, 14.41. Found: C, 48.16; H, 5.82; Cl, 10.00; N, 14.28.

6.




29 30

A stirred mixture of ethyl dithioacetate (180 mL, 1.56 mmol), sodium fluoride (72 mg, 1.7 mmol), **29** (500 mg, 1.29 mmol) and EtOH (70 mL) under nitrogen, was treated with 0.97M KOH (1.46 mL, 1.42 mmol) and the resulting solution was kept at ambient temperature for 3 h 35 min, diluted with $CHCl_3$, washed with water and dilute NaCl, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% $NH_4OH$-$CHCl_3$ and crystallization of the resulting product from absolute EtOH gave 0.238 mg (44.9%) **30**: mp 163-165 °C; $^1H$ NMR (300 MHz, $CDCl_3$) d 2.60 (s, 3H), 3.06 (m, 4H), 3.45 (m, 2H), 3.61 (m, 1H), 3.82 (m, 3H), 4.07 (m, 2H), 4.25 (m, 3H), 4.97 (m, 1H), 6.91 (t, 1H), 7.07 (m, 1H), 7.45 (d,d, 1H), 7.91 (broad s, 1H); MS(FAB) *m/z* (relative intensity) 411 ($M+H^+$, 100), 410 ($M^+$, 66.5), 266 (3.1); IR 3292, 1733, 1653 $cm^{-1}$. Anal. calcd for $C_{18}H_{23}FN_4O_4S$: C, 52.67; H, 5.65; N, 13.65. Found: C, 52.76; H, 5.58; N, 13.64.

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

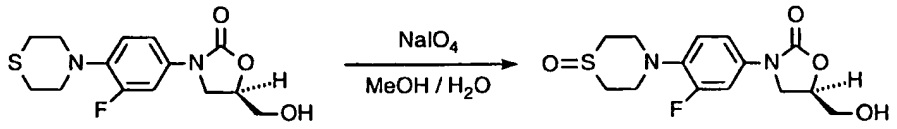

31 32

An ice cold, stirred mixture of **31** (0.38 g, 0.0012 mol) and triethylamine (0.38 mL, 0.0027 mol) in THF (12 mL), under nitrogen, was treated with ethyl dithioacetate (0.16 mL, 0.0014 mol) and then kept at ambient temperature for 24.5 h and concentrated in vacuo. A solution of the residue in $CH_2Cl_2$ was washed with

saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from EtOAc-hexane gave 0.355 g of **32**: mp 155-156 °C; MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$); IR (DRIFT) 3206, 3042, 1759, 1738 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) d 2.60 (s, 3H), 2.95 (s, 4H), 3.43 (m, 4H), 3.82 (d, d, 1H), 4.08 (m, 2H), 4.27 (m, 1H), 4.98 (m, 1H), 7.06 (m, 1H), 7.33 (broad s, 1H), 7.51 (d, 1H), 8.03 (broad s, 1H). Anal. calcd for $C_{16}H_{20}FN_3O_2S_2$: C, 52.01; H, 5.46; N, 11.37. Found: C, 51.86; H, 5.43; N, 11.20.

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

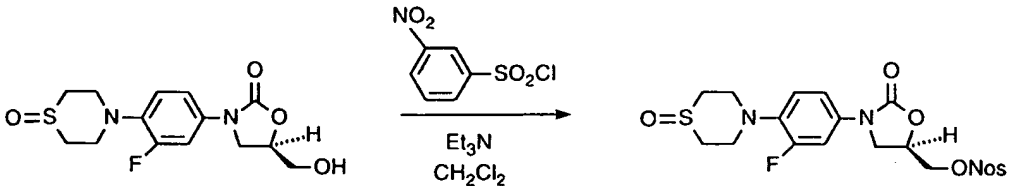
1.




**62** **63**

An ice cold, stirred mixture of sodium metaperiodate (1.08 g, 5.05 mmol) and water (12 mL), under nitrogen, was treated with **62**[16] (1.5 g, 4.8 mmol) and MeOH (17 mL) and kept at 6 °C for 18 h and at 4 °C for 3 h. It was then treated with additional sodium metaperiodate (0.1 g), kept at 4°C for 3 h and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concntrated to give 1.4 g of **63**: $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.84 (m, 2H), 3.01 (m, 2H), 3.16 (m, 2H), 3.50 (m, 3H), 3.65 (m, 1H), 3.77 (d,d, 1H), 4.03 (t, 1H), 4.66 (m, 1H), 5.18 (t, 1H), 7.16 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 329 ($M+H^+$), 351 ($M+Na^+$).

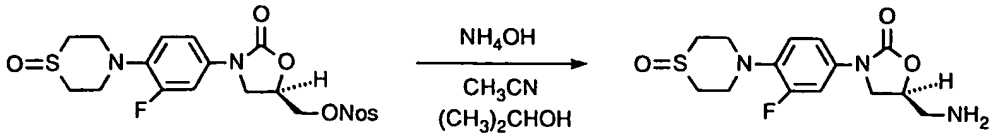
2.




**63** **78**

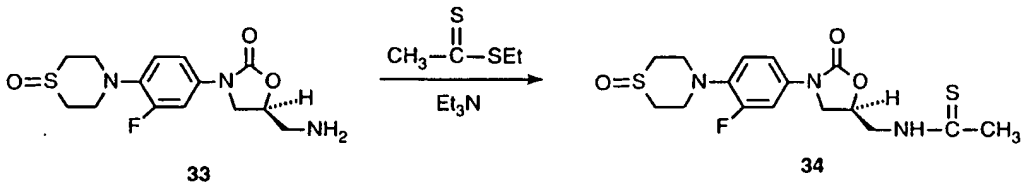
An ice cold, stirred mixture of **63** (1.27 g, 3.87 mmol) and triethylamine (0.732 mL, 5.25 mmol) in $CH_2Cl_2$ (130 mL), under nitrogen, was treated with *m*-nitrobenzenesulfonyl chloride (1.15 g, 5.19 mmol) and kept at ambient temperature for about 24 h. It was diluted with $CH_2Cl_2$, washed with water and brine, dried ($Na_2SO_4$) and concentrated to give **78** which was used in the next reaction without

purification.

3. 


78 33

A stirred mixture of the product (**78**) from the previous reaction, acetonitrile (70 mL) and isopropanol (70 mL) was treated with concentrated ammonium hydroxide (70 mL, 29.9% $NH_3$) and kept at 40 °C for 2 h, at ambient temperature for 18 h and at 40-45 °C for 4 h; it was concentrated to about 50 mL, diluted with water and extracted with $CH_2Cl_2$. The extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave 0.58 g of **33**: MS(ES) *m/z* 328 ($M+H^+$), 350 ($M+Na^+$); $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.81 (m, 4H), 3.01 (m, 2H), 3.16 (m, 2H), 3.30 (broad s), 3.49 (m, 2H), 3.80 (d,d, 1H), 4.01 (t, 1H), 4.58 (m, 1H), 7.19 (m, 2H), 7.51 (m, 1H).

4. 

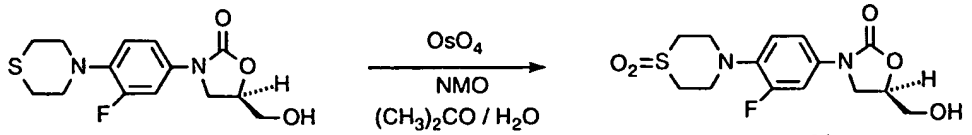

33 34

A stirred suspension of **33** (3.7 g, 0.011 mol) and triethylamine (3.5 mL, 0.025 mol) in THF (120 mL) was cooled, in an ice bath, under nitrogen, treated, dropwise during 2 min, with a solution of ethyl dithioacetate (1.47 mL, 0.0128 mol) in THF (2 mL) and kept at ambient temperature for 22 h. The resulting solution was concentrated and the residue crystallized from acetonitrile to give 3.61 g of **34**: mp 176-177 °C ; $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 2.85 (m, 2H), 3.01 (m, 2H), 3.18 (m, 3H), 3.50 (m, 2H), 3.78 (d,d, 1H), 3.89 (broad s, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.49 (m, 1H), 10.33 (s, 1H); IR (DRIFT) 3186, 3102, 1741 $cm^{-1}$; MS(ES) *m/z* 386 ($M+H^+$), 408 ($M+Na^+$). Anal. calcd for $C_{16}H_{20}FN_3O_3S_2 \cdot 0.5 H_2O$: C, 48.71; H, 5.37; N, 10.65; S, 16.26; $H_2O$, 2.38. Found: C, 48.75; H, 5.17; N, 10.72; S, 16.07; $H_2O$, 1.72.

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

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

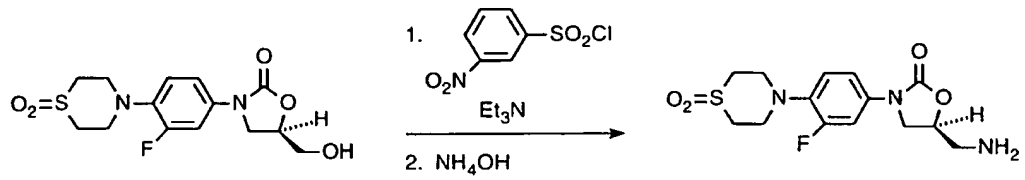
1.




62 64

A stirred mixture of **62**[16] (0.399 g, 0.00128 mol) in 25% water/acetone (12 mL), under nitrogen was treated with N-methylmorpholine, N-oxide (0.45 g, 0.00384 mol) and 0.1 mL of a 2.5 wt% solution of osmium tetroxide in *tert*-butanol. It was kept at ambient temperature for 18 h, mixed with saturated $NaHSO_3$ (50 mL) and extracted with $CH_2Cl_2$. The extract was washed with saturated $NaHSO_3$ and brine, dried ($Na_2SO_4$) and concentrated. The residue was mixed with 3.5% MeOH-$CH_2Cl_2$ and filtered; the solid was dissolved in 15% MeOH-$CH_2Cl_2$ and concentrated to give 0.29 g of **64**. The filtrate was chromatographed on silica gel with 3.5% MeOH-$CH_2Cl_2$ to give 0.1 of additional **64**: MS(ES) *m/z* 345 ($M+H^+$), 367 ($M+Na^+$); $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 3.26 (m, 4H), 3.44 (m, 4H), 3.60 (m, 2H), 3.80 (d,d, 1H), 4.05 (t, 1H), 4.69 (m, 1H), 7.22 (m, 2H), 7.54 (d, 1H).

2.

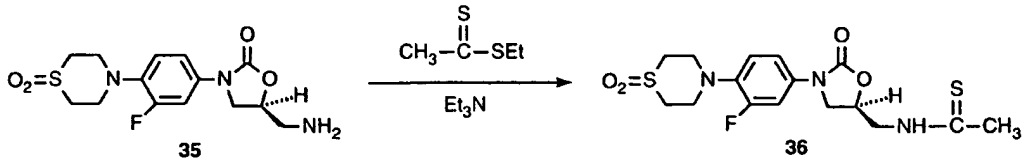



64 35

A stirred mixture of **64** (0.39 g, 0.00113 mol) and triethylamine (0.214 mL, 0.00154 mol) in $CH_2Cl_2$ (37 mL) was cooled, under nitrogen, in an ice bath and treated, portionwise during 5 min, with 3-nitrobenzenesulfonyl chloride (0.335 g, 0.00151 mol). The mixture was kept in the ice bath for 20 min and at ambient temperature for 18 h and concentrated in vacuo. A stirred solution of the residue in 2-propanol (25 mL) and acetonitrile (25 mL), under nitrogen, was treated with 30% $NH_4OH$ (25 mL), warmed at 50-55 °C for 6 h and kept at ambient temperature for 48 h. It was concentrated to remove the organic solvents, diluted with water and extracted with $CH_2Cl_2$. The extract was washed with water and brine, dried ($MgSO_4$) and

concentrated. Flash chromatography of the residue on silica gel with 6% MeOH-0.4% $NH_4OH$-$CHCl_3$ gave 0.29 g of **35**: $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 1.59 (broad s, 2H), 2.78 (m, 2H), 3.24 (m, 4H), 3.43 (m, 4H), 3.81 (d,d, 1H), 4.01 (t, 1H), 4.57 (m, 1H), 7.18 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 344 ($M+H^+$), 366 ($M+Na^+$).

3.

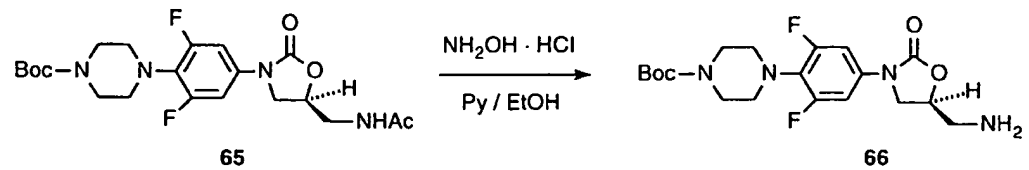



**35** **36**

A stirred, ice cold suspension of **35** (0.28 g, 0.85 mmol) in a mixture of $Et_3N$ (0.26 mL, 1.9 mmmol) and THF (10 mL) was treated with ethyl dithioacetate (0.11 mL, about 6 drops) and kept in the ice bath for 20 min and then at ambient temperature; the reaction was followed by TLC. After 20 h there was still a suspension and only partial reaction; additional THF (10 mL) and ethyl dithioacetate (3 drops) were added. After an additional 48 h the reaction was still incomplete; the suspension was treated with $CH_2Cl_2$ (10 mL) and kept for 72 h. At this time almost complete solution and an almost complete conversion to product had been obtained. An additional drop of ethyl dithioacetate was added and the mixture was kept at ambient temperature for 5 d and concentrated in vacuo. The residue was mixed with EtOAc, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH-EtOAc gave 0.209 g of **36**: mp 197-198 °C; $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.24 (m, 4H), 3.43 (m, 4H), 3.78 (d,d, 1H), 3.88 (m, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.50 (m, 1H), 10.37 (broad s, 1H); IR (mull) 3300, 3267, 1743 $cm^{-1}$; MS(ES) *m/z* 424 ($M+Na^+$). Anal. calcd for $C_{16}H_{20}FN_3O_4S_2$: C, 47.87; H, 5.02; N, 10.47. Found: C, 47.84; H, 5.23; N, 10.28.

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

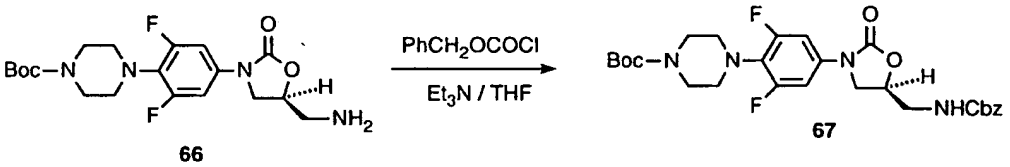
1.




**65** **66**

A stirred mixture of **65**[17,18] (1.8 g, 0.00396 mol), pyridine (30 mL) and absolute EtOH (3 mL), under nitrogen, was treated with hydroxylamine hydrochloride (1.44 g, 0.0207 mol), warmed to the reflux temperature during 2 h, refluxed for 3.5 h, kept at ambient temperature for 18 h and at reflux for 4 h. It was concentrated in vacuo and the residue was mixed with water, adjusted to pH 11 with saturated $NaHCO_3$ and extracted with $Et_2O$. The extracts were washed with brine, dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.35% $NH_4OH$-$CHCl_3$ gave 0.75 g of recovered **65** and 0.72 g of **66**: $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 1.40 (s, 9H), 1.72 (broad s, 2H), 2.78 (m, 2H), 2.97 (m, 4H), 3.40 (m, 4H), 3.80 (d,d, 1H), 4.00 (t, 1H), 4.59 (m, 1H), 7.27 (d, 2H); MS(ES) *m/z* 413 ($M+H^+$), 435 ($M+Na^+$).

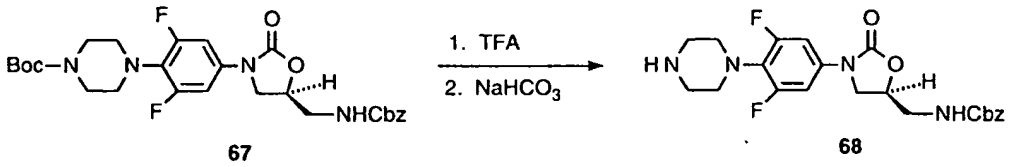
2.




**66** **67**

An ice cold, stirred mixture of **66** (0.75 g, 0.0018 mol) and triethylamine (0.315 mL, 0.00225 mol) in THF (12 mL), under nitrogen, was treated, dropwise with benzyl chloroformate (0.29 mL, 0.0020 mol), kept in the ice bath for 15 min and at ambient temperature for 2 h and concentrated in vacuo. The residue was mixed with $CH_2Cl_2$ and washed with saturated $NaHCO_3$, water and brine, dried ($Na_2SO_4$) and concentrated. This residue was mixed with $Et_2O$ and filtered to give 0.939 g of **67**: mp 116-118 °C; $^1H$ NMR (300 MHz, $CDCl_3$) d 1.48 (s, 9H), 3.08 (m, 4H), 3.53 (m, 4H), 3.60 (m, 2H), 3.73 (m, 1H), 3.96 (t, 1H), 4.76 (m, 1H), 5.10 (s, 2H), 5.21 (m, 1H),7.07 (d, 2H), 7.31 (s, 5H); MS(ES) *m/z* 547 ($M+H^+$), 569 ($M+Na^+$).

3.

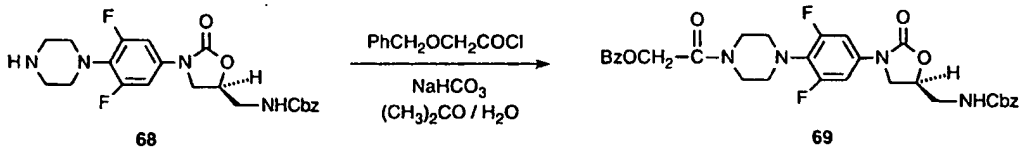



**67** **68**

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

The residue was mixed with ice and saturated $NaHCO_3$ and extracted with $CH_2Cl_2$; the extract was washed with water and brine, dried ($Na_2SO_4$) and concentrated to give 0.63 g of product. The combined aqueous layer was reextracted with EtOAc; the extracts were washed with water and brine, dried ($Na_2SO_4$) and concntrated to give additional product. The combined product amounted to 0.68 g of **68** which was used in the next reaction without further purification.

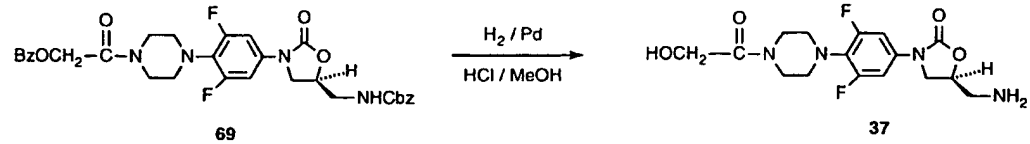
4.




68 69

An ice cold, stirred mixture of **68** (0.68 g, 0.00152 mol), saturated $NaHCO_3$ (15.2 mL) and acetone (40 mL), under nitrogen was treated, dropwise during 15 min, with a solution of benzyloxyacetyl chloride (0.29 mL, 0.0019 mol) in acetone (5 mL), kept at ambient temperature for 6 h, diluted with EtOAc and washed with water and brine. The extract was dried ($MgSO_4$) and concentrated in vacuo to give 0.72 g of **69**: MS(ES) *m/z* 395 ($M+H^+$), 617 ($M+Na^+$); $^1H$ NMR (300 MHz, $CDCl_3$) d 3.12 (m, 4H), 3.59 (m, 4H), 3.74 (m, 3H), 3.96 (t, 1H), 4.22 (s, 2H), 4.62 (s, 2H), 4.75 (broad s, 1H), 5.10 (s, 2H), 5.22 (m, 1H), 7.08 (d, 2H), 7.33 (m, 10H).

5.

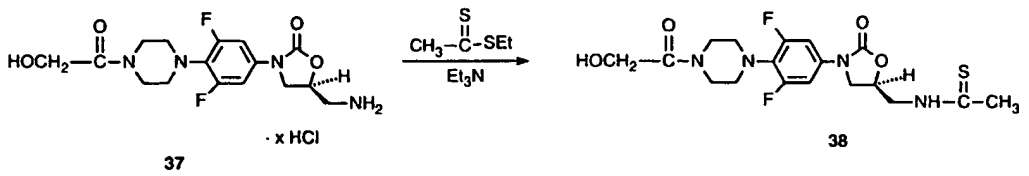



69 37

A mixture of **69** (0.72 g, 0.0012 mol), MeOH and 5% palladium-on-carbon catalyst (0.4 g) was hydrogenated at an initial pressure of 45 psi for 4 h. By TLC (8% MeOH-0.5% $NH_4OH$-$CHCl_3$) the starting material had been reduced and two products formed. 1M Hydrochloric acid (1.34 mL) was added and hydrogenation was continued at an initial pressure of 40 psi for 21 h. By TLC only the more polar product remained. The catalyst was removed by filtration and the filtrate was concentrated to give 0.40 g of **37**: MS(ES) *m/z* 371 ($M+H^+$), 393 ($M+Na^+$); $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 3.02 (s, 4H), 3.20 (m, 2H), 3.43 (s, 2H), 3.56 (s, 2H), 3.84 (m,

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

6.

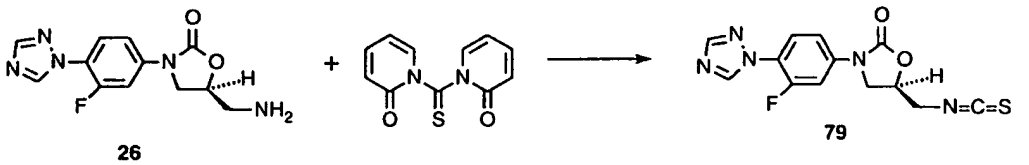



37 38

A stirred suspension of **37** (0.38 g) in a solution of $Et_3N$ (0.31 mL) and THF (10 mL), under nitrogen, was treated with ethyl dithioacetate (0.13 mL, about 7 drops) and kept at ambient temperature for 7 d; the reaction was followed by TLC (8% MeOH-0.5% $NH_4OH$-$CHCl_3$). Additional ethyl dithioacetate (2 drops) was added after 24 h; after 30 h $CH_2Cl_2$ (10 mL) and ethyl dithioacetate (3 drops) were added; after 48 h additional triethylamine (0.3 mL) was added. The mixture was concentrated in vacuo and the residue was mixed with ice and saturated $NaHCO_3$ an extracted with $CH_2Cl_2$. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 2.5% MeOH-$CH_2Cl_2$ and the product was crystallized from MeOH to give 0.182 g of **38**: mp 110-111 °C (dec); MS(ES) *m/z* 429 ($M+H^+$), 451 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}F_2N_4O_4S$ ($M+H^+$) 429.1408, found 429.1415; IR (DRIFT) 1760, 1652, 1639 $cm^{-1}$; $[\alpha^{24}_D$ 8° (MeOH).

EXAMPLE 30: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (44).**

1.

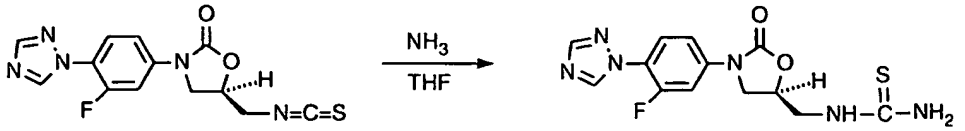



26 79

A solution of **26** (0.190 g, 0.685 mmol) in $CH_2Cl_2$ (20 mL) was added, dropwise during 20 min, under nitrogen, to an ice cold, stirred solution of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.193 g, 0.831 mmol) in $CH_2Cl_2$ (7 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, diluted with $CH_2Cl_2$,

washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 10-15% $CH_3CN$-$CH_2Cl_2$ gave 0.11 g of **79** which was used in the next reaction without further purification: MS(ES) *m/z* 320 ($M+H^+$), 342 ($M+Na^+$).

2.

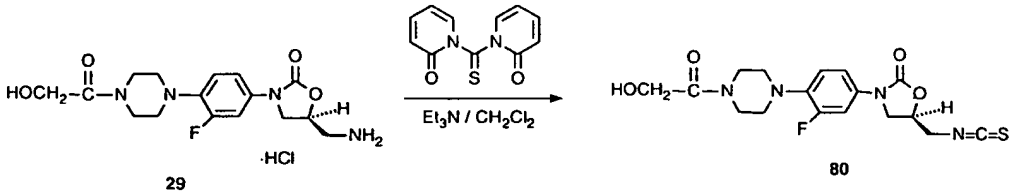



**79** **44**

A stirred, ice cold solution of **79** (0.10 g, 0.31 mmol) in THF (15 mL) was treated with excess anhydrous ammonia and kept in the ice bath for 90 min. It was then evaporated under a stream of nitrogen to a volume of about 5 mL to give a solid which was collected by filtration and washed with cold THF to give 0.105 g of **44**: mp 214-215 °C; $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 3.82 (m, 3H), 4.18 (t, 1H), 4.89 (broad s, 1H), 7.20 (broad s, 2H), 7.50 (d, 1H), 7.79 (m, 2H), 7.93 (t, 1H), 8.26 (s, 1H), 8.97 (s, 1H); MS(ES) *m/z* 337 ($M+H^+$), 359 ($M+Na^+$). Anal. calcd for $C_{13}H_{13}FN_6O_2S$: C, 46.42; H, 3.90; N, 24.99. Found: C, 46.22; H, 3.98; N, 24.55.

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

1.

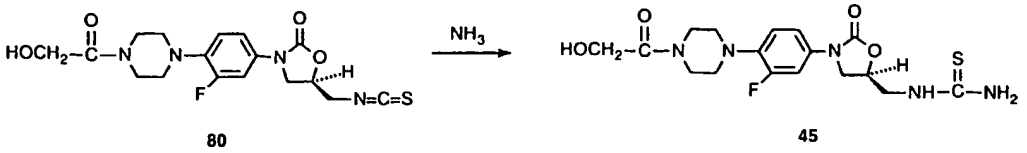



**29** **80**

An ice cold, stirred solution of 1,1¢-thiocarbonyl-2(1H)-dipyridone (0.123 g, 0.530 mmol) in $CH_2Cl_2$ (5 mL), under nitrogen, was treated with a suspension of **29** (0.17 g, 0.4 mmol) in $CH_2Cl_2$ (20 mL) and then during 10 min with a solution of triethylamine (0.111 mL, 0.8 mmol) in $CH_2Cl_2$ (10 mL). It was kept in the ice bath for 30 min, at ambient temperature for 2 h and at < 0 °C for 18 h. It was then diluted with $CH_2Cl_2$, washed with water and brine, dried ($MgSO_4$) and concentrated. The residue (**80**) was used without further purification in the next

reaction. A sample of **80** that was purified by flash chromatography on silica gel with 10-20% acetonitrile-$CH_2Cl_2$ had: $^1$H NMR (300 MHz, $CDCl_3$) d 1.60 (broad s), 3.07 (m, 4H), 3.45 (m, 2H), 3.85 (m, 4H), 3.97 (d,d, 1H), 4.16 (t, 1H), 4.21 (s, 2H), 4.82 (m, 1H), 6.95 (t, 1H), 7.13 (d,d, 1H), 7.47 (d,d, 1H); MS *m/z* 395 ($M+H^+$); 417 ($M+Na^+$).

2.

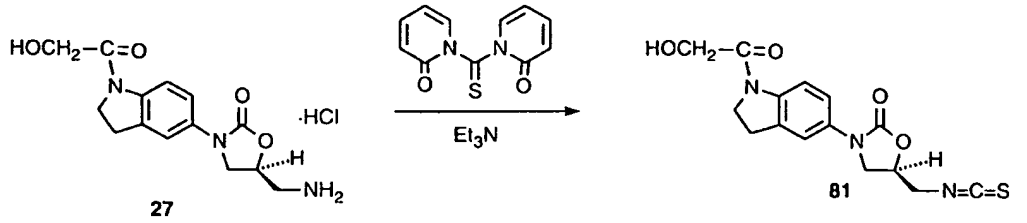



80 45

Excess anhydrous ammonia was bubbled into a stirred, ice cold solution of **80** (crude product from the previous reaction) in THF (25 mL) and the mixture was kept in the ice bath for 90 min and concentrated under a stream of nitrogen. The residue was chromatographed on silica gel with 5% MeOH-0.4% $NH_4OH$-$CHCl_3$ and the product was crystallized from acetonitrile to give 0.0544 g of **45**: mp 209-210 °C; $^1$H NMR [300 MHz, $(CD_3)_2SO$] d 294 (broad s, 4H), 3.47 (broad s, 2H), 3.60 (broad s, 2H), 3.78 (broad s, 3H), 4.07 (t, 1H), 4.10 (d, $J$ = 5.5 Hz, 2H), 4.63 (t, $J$ = 5.5 Hz, 1H), 4.81 (broad s, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.15 (broad s, 2H), 7.49 (d,d, 1H), 7.91 (t, 1H); IR (mull) 3443, 3403, 3321, 3202, 3081, 1753, 1655, 1648 $cm^{-1}$; HRMS (FAB) calcd for $C_{17}H_{23}FN_5O_4S$ ($M+H^+$) 412.1454, found 412.1447. Anal. calcd for $C_{17}H_{22}FN_5O_4S$: C, 49.63; H, 5.39; N, 17.02. Found: C, 49.63; H, 5.48; N, 16.99.

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

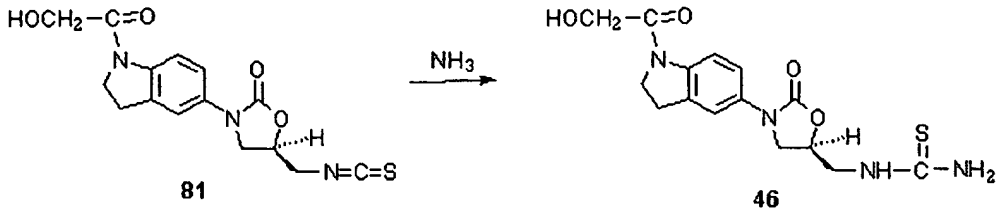
1.




27 81

An ice cold, stirred solution of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.096 g, 0.41 mmol) in $CH_2Cl_2$ (5 mL) was treated with a suspension of **27** (0.10 g, 0.34 mmol) in $CH_2Cl_2$ (15 mL) and then with 0.05 mL (0.36 mmol) of triethylamine. It was kept in the ice bath for 30 min and at ambient temperature for 2 h, diluted with $CH_2Cl_2$, washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography ofthe residue on silica gel with 20-40% $CH_3CN$-$CH_2Cl_2$ gave 0.04 g of **81**.

2.

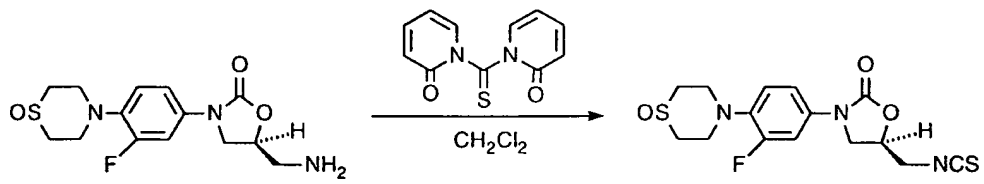



81 46

Excess anhydrous ammonia was bubbled into an ice cold solution of **81** (0.04 g) in THF (30 mL) and the mixture was kept in the ice bath for 80 min and concentrated under a stream of nitrogen. The residue was crystallized from $CH_3CN$ to give 0.0151 g of **46**: mp 214-215 °C (dec); MS (FAB) *m/z* 351 ($M+H^+$), 350 ($M^+$), 319, 304, 147; HRMS (FAB) calcd for $C_{15}H_{19}N_4O_4S$ ($M+H^+$) 351.1127, found 351.1130; IR (DRIFT) 3329, 3296, 3196, 1746, 1655, 1626 $cm^{-1}$.

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

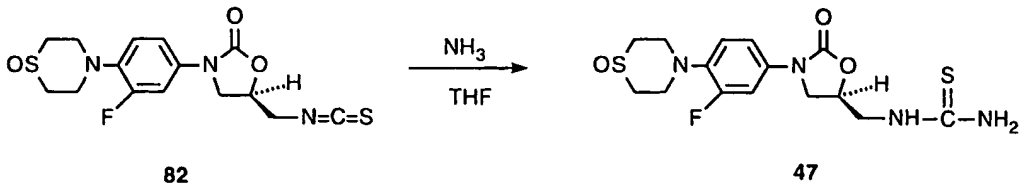
1.




33 82

A suspension of **33** (0.30 g, 0.92 mmol) in $CH_2Cl_2$ (7 mL) was added, during 20 min, to an ice cold, stirred mixture of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.258 g, 1.11 mmol) and $CH_2Cl_2$ (20 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, mixed with $CH_2Cl_2$ (50 mL), washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the product on silica gel with 20-50% $CH_3CN$-$CH_2Cl_2$ gave 0.27 g of **82** which was used in the next reaction: MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$).

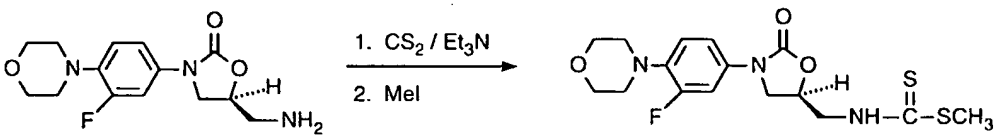
2.




82 47

A stirred, ice cold solution of **82** (0.27g , 0.73 mmol) in THF (15 mL), under nitrogen, was treated with excess anhydrous ammonia, kept in the ice bath for 1 h and concentrated; crystallization of the residue from MeOH gave 0.175 g of **47**; mp 212-213 °C; $^1$H NMR [300 MHz, $(CD_3)_2SO$] d 2.83 (m, 2H), 3.01 (m, 2H), 3.17 (m, 2H), 3.50 (t, 2H), 3.78 (broad s, 3H), 4.08 (t, 1H), 4.80 (broad s, 1H), 7.17 (m, 2H), 7.17 (broad s, 2H), 7.50 (d, 1H), 7.90 (t, 1H); MS(ES) *m/z* 409 ($M+Na^+$); IR (mull) 3335, 3284, 3211, 3175, 3097, 1750, 1630 $cm^{-1}$. Anal. calcd for $C_{15}H_{19}FN_4O_3S_2$: C, 46.62; H, 4.95; N, 14.50. Found: C, 46.50; H, 4.95; N, 14.40.

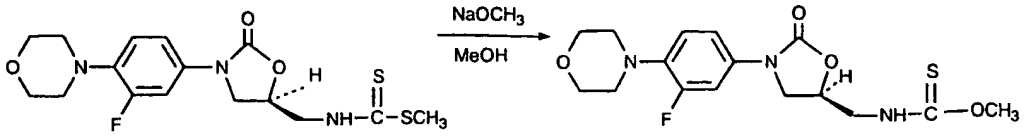
EXAMPLE 34: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-S-methyldithiocarbamate (48).**




39 48

An ice cold, stirred mixture of **39**[8] (0.59 g, 0.0020 mol), EtOH (1.5 mL), water (2 drops) and triethylamine (0.613 mL, 0.00440 mol), under nitrogen, was treated with carbon disulfide (0.066 mL, 0.0011 mol) and kept in the ice bath for 2 h and at ambient temperature for 18 h. (A solution was obtained after the addition of carbon disulfide; a white precipitate began to form soon after the mixture was warmed to ambient temperature.) The thick suspension was treated, dropwise during 2 min, with a solution of methyl iodide (0.137 mL, 0.00220 mol) in EtOH (2 mL) and the mixture was kept at ambient temperature for 1.5 h and concentrated in vacuo. A solution of the residue in EtOAc was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 1.8% MeOH-$CH_2Cl_2$ and the product was crystallized from EtOAc to give 0.197 g of **48**: mp 154-155 °C; IR (mull) 3354, 3346, 1726 $cm^{-1}$. Anal. calcd for $C_{16}H_{20}FN_3O_3S_2$: C, 49.85; H, 5.23; N, 10.90. Found: C, 49.73; H, 5.25; N, 10.82.

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

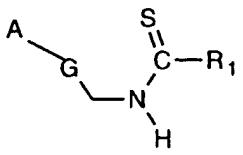



48 50

A stirred mixture of **48** (0.200 g, 0.518 mmol), sodium methoxide (0.003 g, 0.06 mmol) and MeOH (5 mL), under nitrogen, was refluxed for 4 h and kept at ambient temperature for 18 h. It was found that the starting material and product had similar mobilities on TLC. the reaction was therefore followed by MS(ES). Starting material was still present. The mixture was refluxed for 3 h, additional sodium methoxide (0.005 g) was added and reflux was continued for 2 h. It was kept at ambient temperature for 18 h, refluxed for 1 h, kept at ambient temperature 1.5 h and concentrated in vacuo. The residue was mixed with ice, the pH was adjusted to 9-10 with 1M $KHSO_4$ and saturated $NaHCO_3$ and the mixture was extracted with $CH_2Cl_2$. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 5% acetone-$CH_2Cl_2$ and the product was crystallized from EtOAc-hexane to give 0.107 g of **50**: mp 128-129 °C; MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$); IR (DRIFT) 3282, 3251, 1753, 1735 $cm^{-1}$; $^1H$ NMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.47, 374 (m,m, 7H), 3.86, 3.91 (s,s, 3H), 4.10 (m, 1H), 4.73, 4.86 (m,m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.41, 9.50 (s,s, 1H). Anal. calcd for $C_{16}H_{20}FN_3O_4S$: C, 52.02; H, 5.46; N, 11.38. Found: C, 51.97; H, 5.49; N, 11.35.

WHAT IS CLAIMED:

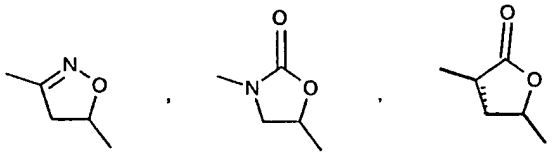
1. A compound of the formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



$R_1$ is

a) H,

b) $NH_2$,

c) NH-$C_{1-4}$ alkyl,

d) $C_{1-4}$ alkyl,

e) -O$C_{1-4}$ alkyl,

f) -S $C_{1-4}$ alkyl,

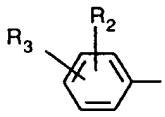
g) $C_{1-4}$ alkyl substituted with 1-3 F, 1-2 Cl, CNor -COO$C_{1-4}$ alkyl,

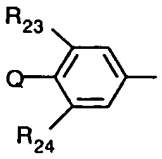
h) $C_{3-6}$ cycloalkyl,

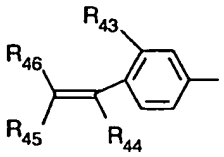
i) N($C_{1-4}$) alkyl)$_2$ or

j) N($CH_2$)$_{2-5}$;

A is

a)  ,

b)  ,

c)  ,

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

wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three $R_{48}$,

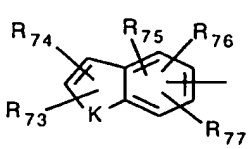
e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,

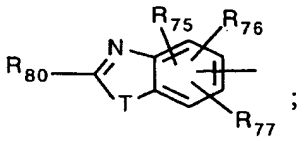
wherein the heteroaromatic moiety is bonded via a carbon atom,

wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three $R_{55}$,

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

g)  , or

h) 

;

wherein $R_2$ is

a) H,
b) F,
c) Cl,
d) Br,
e) $C_{1-3}$ alkyl,
f) $NO_2$, or
g) $R_2$ and $R_3$ taken together are -O-$(CH_2)_h$-O-;

$R_3$ is

a) -S(=O)$_i$ $R_4$,
b) -S(=O)$_2$-N=S(O)$_j$$R_5$$R_6$,
c) -SC(=O)$R_7$,
d) -C(=O)$R_8$,
e) -C(=O)$R_9$,
f) -C(=O)N$R_{10}$$R_{11}$,
g) -C(=N$R_{12}$)$R_8$,
h) -C($R_8$)($R_{11}$)-O$R_{13}$,
i) -C($R_9$)($R_{11}$)-O$R_{13}$,
j) -C($R_8$)($R_{11}$)-OC(=O)$R_{13}$,
k) -C($R_9$)($R_{11}$)-OC(=O)$R_{13}$,
l) -N$R_{10}$$R_{11}$,
m) -N($R_{10}$)-C(=O)$R_7$,
n) -N($R_{10}$)-S(=O)$_i$$R_7$,
o) -C(O$R_{14}$)(O$R_{15}$)$R_8$,
p) -C($R_8$)($R_{16}$)-N$R_{10}$$R_{11}$, or
q) $C_{1-8}$ alkyl substituted with one or more =O other than at alpha position, -S(=O)$_i$$R_{17}$, -N$R_{10}$$R_{11}$, $C_{2-5}$ alkenyl, or $C_{2-5}$ alkynyl;

$R_4$ is

a) $C_{1-4}$ alkyl optionally substituted with one or more halos, OH, CN, N$R_{10}$$R_{11}$, or -$CO_2$$R_{13}$,

b) $C_{2-4}$ alkenyl,

c) $-NR_{16}R_{18}$,

d) $-N_3$,

e) $-NHC(=O)R_7$,

f) $-NR_{20}C(=O)R_7$,

g) $-N(R_{19})_2$,

h) $-NR_{16}R_{19}$, or

i) $-NR_{19}R_{20}$,

$R_5$ and $R_6$ at each occurrence are the same or different and are

a) $C_{1-2}$ alkyl, or

b) $R_5$ and $R_6$ taken together are $-(CH_2)_k-$;

$R_7$ is $C_{1-4}$ alkyl optionally substituted with one or more halos;

$R_8$ is

a) H, or

b) $C_{1-8}$ alkyl optionally substituted with one or more halos, or $C_{3-8}$ cycloalkyl;

$R_9$ is $C_{1-4}$ alkyl substituted with one or more

a) $-S(=O)R_{17}$,

b) $-OR_{13}$,

c) $-OC(=O)R_{13}$,

d) $-NR_{10}R_{11}$, or

e) $C_{1-5}$ alkenyl optionally substituted with CHO;

$R_{10}$ and $R_{11}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-4}$ alkyl, or

c) $C_{3-8}$ cycloalkyl;

$R_{12}$ is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

$R_{13}$ is

a) H, or

b) $C_{1-4}$ alkyl;

$R_{14}$ and $R_{15}$ at each occurrence are the same or different and are

a) $C_{1-4}$ alkyl, or

b) $R_{14}$ and $R_{15}$ taken together are $-(CH)_l-$;

$R_{16}$ is

a) H,

b) $C_{1-4}$ alkyl, or

c) $C_{3-8}$ cycloalkyl;

$R_{17}$ is

a) $C_{1-4}$ alkyl, or

b) $C_{3-8}$ cycloalkyl;

$R_{18}$ is

a) H,

b) $C_{1-4}$ alkyl,

c) $C_{2-4}$ alkenyl,

d) $C_{3-4}$ cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

$R_{19}$ is

a) Cl,

b) Br, or

c) I;

$R_{20}$ is a physiologically acceptable cation;

$R_{21}$ and $R_{22}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-4}$ alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein $R_{23}$ and $R_{24}$ at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) $C_{1-2}$ alkyl,

e) CN

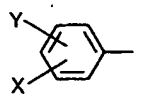
f) OH,

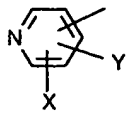
g) $C_{1-2}$ alkoxy,

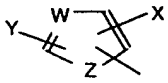
h) nitro, or

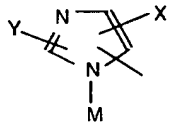
i) amino;

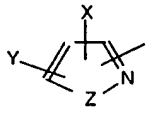
Q is

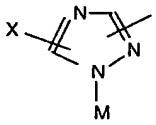
a)  ,

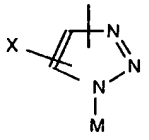
b)  ,

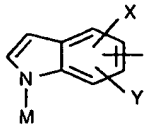
c)  ,

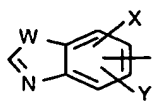
d)  ,

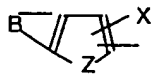
e)  ,

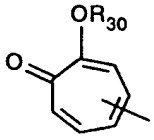
f)  ,

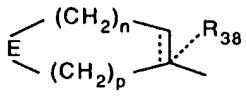
g)  ,

h)  ,

i)  ,

j) 

k)  ,

l)  ,

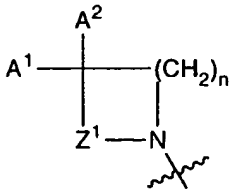
m) a diazinyl group optionally substituted with X and Y,

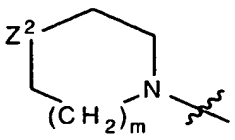
n) a triazinyl group optionally substituted with X and Y,

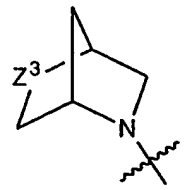
o) a quinolinyl group optionally substituted with X and Y,

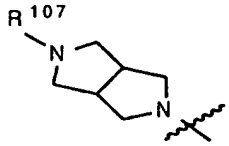
p) a quinoxalinyl group optionally substituted with X and Y,

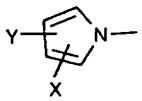
q) a naphthyridinyl group optionally substituted with X and Y,

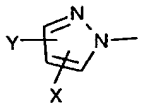
r)  ,

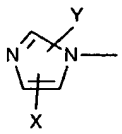
s)  ,

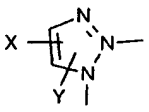
t)  ,

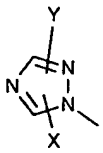
u)  ,

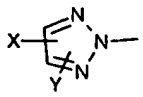
v)  ,

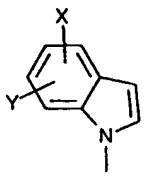
w)  ,

x)  ,

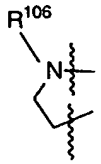
y)  ,

z)  ,

aa)  ,

bb)  or

Q and $R_{24}$ taken together are

 ,

wherein $Z^1$ is

a) $-CH_2-$,

b) $-CH(R^{104})-CH_2-$,

c) -C(O)-, or

d) $-CH_2CH_2CH_2-$;

wherein $Z^2$ is

a) $-O_2S-$,

b) -O-,

c) $-N(R^{107})-$,

d) -OS-, or

e) -S-;

wherein $Z^3$ is

a) $-O_2S-$,

b) -O-,

c) -OS-, or

d) -S-;

wherein $A^1$ is

a) H-, or

b) $CH_3$;

wherein $A^2$ is

a) H-,

b) HO-,

c) $CH_3$-,

d) $CH_3O$-,

e) $R^{102}O$-$CH_2$-C(O)-NH-

f) $R^{103}O$-C(O)-NH-,

g) ($C_1$-$C_2$)alkyl-O-C(O)-,

h) HO-$CH_2$-,

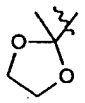
i) $CH_3O$-NH-,

j) ($C_1$-$C_3$)alkyl-$O_2C$-

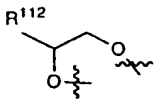
k) $CH_3$-C(O)-,

l) $CH_3$-C(O)-$CH_2$-,

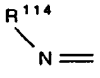
m)  , or

n)  ,

$A^1$ and $A^2$ taken together are:

a)  ,

b)  , or

c)  ;

wherein $R^{102}$ is

a) H-,

b) $CH_3$-,

c) phenyl-$CH_2$-, or

d) $CH_3C(O)$-;

wherein $R^{103}$ is

a) ($C_1$-$C_3$)alkyl-, or

b) phenyl-;

wherein $R^{104}$ is

a) H-, or

b) HO-;

wherein $R^{105}$ is

a) H-,

b) $(C_1-C_3)$alkyl-,

c) $CH_2 = CH-CH_2$-, or

d) $CH_3-O-(CH_2)_2$-;

wherein $R^{106}$ is

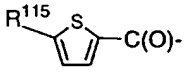
a) $CH_3-C(O)$-,

b) H-C(O)-,

c) $Cl_2CH-C(O)$-,

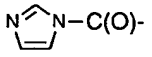
d) $HOCH_2-C(O)$-,

e) $CH_3SO_2$-,

f) 

,

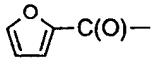
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C-C(O)-O-CH_2-C(O)$-,

j) $H-C(O)-O-CH_2-C(O)$-,

k) 

,

l) $HC\equiv C-CH_2O-CH_2-C(O)$-, or

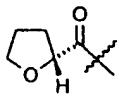
m) phenyl-$CH_2-O-CH_2-C(O)$-;

wherein $R^{107}$ is

a) $R^{102}O-C(R^{110})(R^{111})-C(O)$-,

b) $R^{103}O-C(O)$-,

c) $R^{108}-C(O)$-,

d) 

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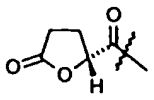
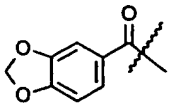
e)  ,

f) $H_3C$-C(O)-$(CH_2)_2$-C(O)-,

g) $R^{109}$-$SO_2$-,

h)  ,

i) HO-$CH_2$-C(O)-,

j) $R^{116}$-$(CH_2)_2$-,

k) $R^{113}$-C(O)-O-$CH_2$-C(O)-,

l) $(CH_3)_2$N-$CH_2$-C(O)-NH-,

m) NC-$CH_2$-, or

n) $F_2$-CH-$CH_2$-;

wherein $R^{108}$ is

a) H-,

b) $(C_1$-$C_4)$alkyl,

c) aryl -$(CH_2)_p$,

d) $ClH_2C$-,

e) $Cl_2HC$-,

f) $FH_2C$-,

g) $F_2HC$-, or

h) $(C_3$-$C_6)$cycloalkyl;

wherein $R^{109}$ is

a) -$CH_3$,

b) -$CH_2Cl$

c) -$CH_2CH$=$CH_2$,

d) aryl, or

e) -$CH_2CN$;

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

a) H-,

b) $CH_3$-; or

wherein $R^{112}$ is

a) H-,

b) $CH_3O$-$CH_2O$-$CH_2$-, or

c) $HOCH_2$-;

wherein $R^{113}$ is

a) $CH_3$-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-$CH_2$-;

wherein $R^{114}$ is

a) HO-,

b) $CH_3O$-,

c) $H_2N$-,

d) $CH_3O$-C(O)-O-,

e) $CH_3$-C(O)-O-$CH_2$-C(O)-O-,

f) phenyl-$CH_2$-O-$CH_2$-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) $CH_3O$-$CH_2$-O-$(CH_2)_2$-O-, or

i) $CH_3O$-$CH_2$-O-;wherein $R^{113}$ is

a) $CH_3$-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-$CH_2$-;

wherein $R^{115}$ is

a) H-, or

b) Cl-;

wherein $R^{116}$ is

a) HO-

b) $CH_3O$-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) $C_{1-8}$ alkyl,

c) $C_{3-8}$ cycloalkyl,

d) -$(CH_2)_m$$OR_{13}$, or

e) -$(CH_2)_h$-$NR_{21}R_{22}$;

Z is

a) O,

b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

Y is

a) H,

b) F,

c) Cl,

d) Br,

e) $C_{1-3}$ alkyl, or

f) $NO_2$;

X is

a) H,

b) -CN,

c) $OR_{27}$,

d) halo,

e) $NO_2$,

f) tetrazoyl,

g) -SH,

h) $-S(=O)_iR_4$,

i) $-S(=O)_2-N=S(O)_jR_5R_6$,

j) $-SC(=O)R_7$,

k) $-C(=O)R_{25}$,

l) $-C(=O)NR_{27}R_{28}$,

m) $-C(=NR_{29})R_{25}$,

n) $-C(R_{25})(R_{28})-OR_{13}$,

o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,

p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,

q) $-NR_{27}R_{28}$,

r) $-N(R_{27})C(=O)R_7$,

s) $-N(R_{27})-S(=O)_iR_7$,

t) $-C(OR_{14})(OR_{15})R_{28}$,

u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or

v) $C_{1-8}$ alkyl substituted with one or more halos, OH, =O other than at

alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, $C_{2-5}$ alkenyl, $C_{2-5}$ alkynyl, or $C_{3-8}$ cycloalkyl;

$R_4$, $R_5$, $R_6$, $R_7$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, and $R_{17}$ are the same as defined above;

$R_{25}$ is

a) H,

b) $C_{1-8}$ alkyl optionally substituted with one or more halos, $C_{3-8}$ cycloalkyl, $C_{1-4}$ alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) $C_{2-5}$ alkenyl optionally substituted with CHO, or $CO_2R_{13}$;

$R_{26}$ is

a) $R_{28}$, or

b) $NR_{27}N_{28}$;

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

a) H,

b) $C_{1-8}$ alkyl,

c) $C_{3-8}$ cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) $R_{27}$ and $R_{28}$ taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

$R_{29}$ is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein $R_{30}$ is

a) H,

b) $C_{1-8}$ alkyl optionally substituted with one or more halos, or

c) $C_{1-8}$ alkyl optionally substituted with one or more OH, or $C_{1-6}$ alkoxy;

wherein E is

a) $NR_{39}$,

b) $-S(=O)_i$, or

c) O;

$R_{38}$ is

a) H,

b) $C_{1-6}$ alkyl,

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

d) halo;

$R_{39}$ is

a) H,

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

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

d) $-CO_2R_{40}$,

e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

$R_{40}$ is

a) H,

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

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

d) $-(CH_2)_q-OR_{42}$;

$R_{41}$ is

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

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

c) $-(CH_2)_q-OR_{42}$;

$R_{42}$ is

a) H,

b) $C_{1-6}$ alkyl,

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

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, or $C_{1-6}$ alkylthio;

wherein $R_{43}$ is

a) H,

b) $C_{1-2}$ alkyl,

c) F, or

d) OH;

$R_{44}$ is

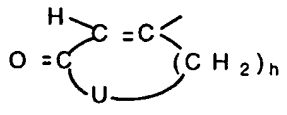
a) H,

b) $CF_3$,

c) $C_{1-3}$ alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) $R_{44}$ and $R_{45}$ taken together are a 5-, 6-, or 7-membered ring of the formula,

or 

f) $R_{44}$ and $R_{45}$ taken together are $-(CH_2)_k-$, when $R_{46}$ is an electron-withdrawing group;

$R_{45}$ and $R_{46}$ at each occurrence are the same or different and are

a) an electron-withdrawing group,

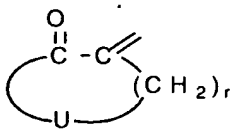
b) H,

c) $CF_3$,

d) $C_{1-3}$ alkyl optionally substituted with one halo,

e) phenyl, provided at least one of $R_{45}$ or $R_{46}$ is an electron-withdrawing group, or

f) $R_{45}$ and $R_{46}$ taken together are a 5-, 6-, 7-membered ring of the formula

 ;

U is

a) $CH_2$,

b) O,

c) S, or

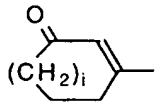
d) $NR_{47}$;

$R_{47}$ is

a) H, or

b) $C_{1-5}$ alkyl;

wherein $R_{48}$ is

a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) $CF_3$,
g) $-NO_2$,
h) $C_{1-6}$ alkoxy,
i) $C_{1-6}$ alkoxycarbonyl,
j) $C_{1-6}$ alkythio,
k) $C_{1-6}$ acyl,
l) $-NR_{49}R_{50}$,
m) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, or $-NR_{49}R_{50}$,
n) $C_{2-8}$ alkenylphenyl optionally substituted with one or two $R_{51}$,
o) phenyl optionally substituted with one or two $R_{51}$,
p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two $R_{51}$, or
q) 

;

$R_{49}$ and $R_{50}$ at each occurrence are the same or different and are
a) H,
b) $C_{1-4}$ alkyl,
c) $C_{5-6}$ cycloalkyl, or
d) $R_{49}$ and $R_{50}$ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl;

$R_{51}$ is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,

e) formyl,
f) $CF_3$,
g) $-NO_2$,
h) $C_{1-6}$ alkoxy,
i) $C_{1-6}$ alkoxycarbonyl,
j) $C_{1-6}$ alkythio,
k) $C_{1-6}$ acyl,
l) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}\ R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

$R_{52}$ and $R_{53}$ at each occurrence are the same or different and are
a) H,
b) $C_{1-6}$ alkyl, or
c) phenyl;

$R_{54}$ is
a) $C_{1-4}$ alkyl, or
b) phenyl optionally substituted with $C_{1-4}$ alkyl;

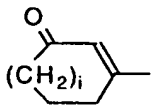
wherein $R_{55}$ is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) $CF_3$,
g) $-NO_2$,
h) $C_{1-6}$ alkoxy,
i) $C_{1-6}$ alkoxycarbonyl,
j) $C_{1-6}$ alkythio
k) $C_{1-6}$ acyl,
l) $-NR_{56}\ R_{57}$,
m) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, or

$-NR_{56}R_{57}$,

n) $C_{2-8}$ alkenylphenyl optionally substituted with one or two $R_{58}$,

o) phenyl optionally substituted with one or two $R_{58}$,

p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two $R_{58}$, or

q)  ;

$R_{56}$ and $R_{57}$ at each occurrence are the same or different and are

a) H,

b) formyl,

c) $C_{1-4}$ alkyl,

d) $C_{1-4}$ acyl,

e) phenyl,

f) $C_{3-6}$ cycloalkyl, or

g) $R_{56}$ and $R_{57}$ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl;

$R_{58}$ is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) $CF_3$,

g) $-NO_2$,

h) $C_{1-6}$ alkoxy,

i) $C_{1-6}$ alkoxycarbonyl,

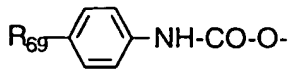
j) $C_{1-6}$ alkythio,

k) $C_{1-6}$ acyl,

l) phenyl,

m) $C_{1-6}$ alkyl optionally substituted with OH, azido, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl,

$-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or




,

n) $-C(=O)NR_{59}\ R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

$R_{54}$ is the same as defined above;

$R_{59}$ and $R_{60}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-6}$ alkyl,

c) phenyl, or

d) tolyl;

$R_{61}$ is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

$R_{62}$ and $R_{63}$ at each occurrence are the same or different and are

a) H, or

b) $C_{1-4}$ alkyl optionally substituted with phenyl or pyridyl;

$R_{64}$ is

a) H, or

b) a sodium ion;

$R_{65}$ and $R_{66}$ at each occurrence are the same or different and are

a) H,

b) formyl,

c) $C_{1-4}$ alkyl,

d) $C_{1-4}$ acyl,

e) phenyl,

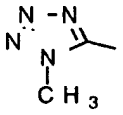
f) $C_{3-6}$ cycloalkyl,

g) $R_{65}$ and $R_{66}$ taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

$R_{67}$ is



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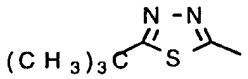

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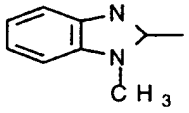

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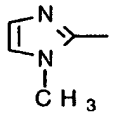


;

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

$R_{69}$ is

a) $C_{1-6}$ alkoxycarbonyl, or

b) carboxyl;

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

a) H, or

b) $C_{1-3}$ alkyl;

$R_{72}$ is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

$R_{73}$, $R_{74}$, $R_{75}$, $R_{76}$, and $R_{77}$ at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) $CF_3$,

h) $-NO_2$,

i) $C_{1-6}$ alkoxy,

j) $C_{1-6}$ alkoxycarbonyl,

k) $C_{1-6}$ alkythio,

l) $C_{1-6}$ acyl,

m) $-NR_{78}R_{79}$,

n) $C_{1-6}$ alkyl optionally substituted with OH, $C_{1-5}$ alkoxy, $C_{1-5}$ acyl, $-NR_{78}R_{79}$, -N(phenyl)($CH_2$-$CH_2$-OH), -O-CH($CH_3$)($OCH_2CH_3$), or -O-phenyl-[para-NHC(=O)$CH_3$],

o) $C_{2-8}$ alkenylphenyl optionally substituted with $R_{51}$,

p) phenyl optionally substituted with $R_{51}$, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with $R_{51}$;

$R_{51}$ is the same as defined above;

$R_{78}$ and $R_{79}$ at each occurrence are the same or different and are

a) H,

b) $C_{1-4}$ alkyl,

c) phenyl, or

d) $R_{78}$ and $R_{79}$ taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, $C_{1-3}$ alkyl, or $C_{1-3}$ acyl;

wherein T is

a) O,

b) S, or

c) $SO_2$;

$R_{75}$, $R_{76}$, and $R_{77}$ are the same as defined above;

$R_{80}$ is

a) H,

b) formyl,

c) carboxyl,

d) $C_{1-6}$ alkoxycarbonyl,

e) $C_{1-8}$ alkyl,

f) $C_{2-8}$ alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with OH, halo, $C_{1-6}$ alkoxy, $C_{1-6}$ acyl, $C_{1-6}$ alkylthio or $C_{1-6}$ alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, $CF_3$, $-NO_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ acyl, $C_{1-6}$ alkylthio, or $C_{1-6}$ alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

$R_{81}$ and $R_{82}$ at each occurrence are the same or different and are

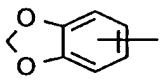
a) H,

b) $C_{3-6}$ cycloalkyl,

c) phenyl,

d) $C_{1-6}$ acyl,

e) $C_{1-8}$ alkyl optionally substituted with OH, $C_{1-6}$ alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, $CF_3$, halo, $-NO_2$, $C_{1-4}$ alkoxy, $-NR_{83}R_{84}$, or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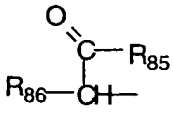
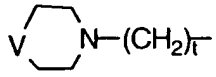
f) 
, or

g) 
;

V is

a) O,

b) $CH_2$, or

c) $NR_{87}$;

$R_{83}$ and $R_{84}$ at each occurrence are the same or different and are

a) H, or

b) $C_{1-4}$ alkyl;

$R_{85}$ is

a) OH,

b) $C_{1-4}$ alkoxy, or

c) $-NR_{88}R_{89}$;

$R_{86}$ is

a) H, or

b) $C_{1-7}$ alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

$R_{87}$ is

a) H,

b) phenyl, or

c) $C_{1-6}$ alkyl optionally substituted by OH;

$R_{88}$ and $R_{89}$ at each occurrence are the same or different and are

a) H,

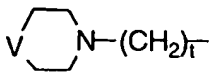
b) $C_{1-5}$ alkyl

c) $C_{3-6}$ cycloalky, or

d) phenyl;

$R_{90}$ is

a) $C_{1-8}$ alkyl optionally substituted with $C_{1-6}$ alkoxy or $C_{1-6}$ hydroxy, $C_{3-6}$ cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, $CF_3$, halo, -CN, OH, $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or $C_{1-5}$ acyl;

b)  ,

c) phenyl, or

d) pyridyl;

$R_{91}$ is

a) $C_{1-16}$ alkyl,

b) $C_{2-16}$ alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with $C_{1-6}$ alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, $CF_3$, $-NO_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ acyl, $C_{1-6}$ alkylthio, or $C_{1-6}$ alkoxycarbonyl;

$R_{92}$ and $R_{93}$ at each occurrence are the same or different and are

a) H,

b) phenyl,

c) $C_{1-6}$ alkyl, or

d) benzyl;

$R_{94}$ and $R_{95}$ at each occurrence are the same or different and are

a) H,

b) OH,

c) $C_{1-6}$ alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) $R_{94}$ and $R_{95}$ taken together are =O;

$R_{96}$ is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, $CF_3$, halo, -CN, OH, phenyl, $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or $C_{1-5}$ acyl,

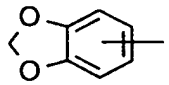
c) morpholinyl,

d) OH,

e) $C_{1-6}$ alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

h)  ;

$R_{97}$ is

a) morpholinyl,

b) OH, or

c) $C_{1-6}$ alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

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

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

2. A compound of Claim 1 which is :

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

b) (S)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

c) (S)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

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

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

f) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea;

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

h) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-

oxazolidinyl]methyl]thiopropion-amide;

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

j) (S)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide;

k) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide;

l) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide;

m) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide;

n) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide;

o) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide;

p) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

q) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

r)) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

s) (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

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

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

v) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S, S-dioxide;

w) (S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

x) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;

y) (*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea;

z) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-

oxazolidinyl]methyl]thiourea;

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

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

3. A method for treating microbial infections in patients comprising administering to a patient in need thereof an effective amount of a compound of Formula I.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/09889

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/20 C07D417/12 C07D413/10 C07D413/04 A61K31/42 C07D261/04 C07D307/32 C07D471/10 //(C07D471/10,235:00, 221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | EP 0 127 902 A (E.I.DU PONT DE NEMOURS AND COMPANY) 12 December 1984 see claims | 1-3 |
| Y | EP 0 184 170 A (E.I. DU PONT DE NEMOURS AND COMPANY) 11 June 1986 see claims | 1-3 |
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| Y | WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 see claims | 1-3 |
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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 August 1998 | 21/08/1998 |

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

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

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/09889

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/09889

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by the examples and the compounds of claim 2.
The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

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Information on patent family members

International Application No
PCT/US 98/09889

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Information on patent family members

.n .tional Application No
PCT/US 98/09889

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International Bureau

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(72) Inventors; and

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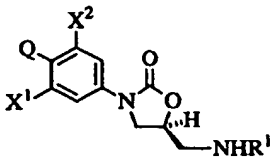
(74) Agent: YANG, Lucy, X.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, 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: THIADIAZOLYL AND OXADIAZOLYL PHENYL OXAZOLIDINONE ANTIBACTERIAL AGENTS




(I)

(57) Abstract

The present invention provides thiadiazolyl and oxadiazolyl phenyl oxazolidinone compounds of formula (I) wherein Q is thiadiazolyl or oxadiazolyl; wherein $X^1$ and $X^2$ are independently hydrogen, fluorine, or chlorine; and wherein $R^1$ is, for example, $-COCH_3$ or $-COCH_2CH_3$. These compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive and gram-negative aerobic bacteria.