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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ^{6} **:**
A61K 31/42, C07D 261/04

A1

(11) International Publication Number: **WO 97/23212**

(43) International Publication Date: 3 July 1997 (03.07.97)

(21) International Application Number: PCT/US96/20076

(22) International Filing Date: 17 December 1996 (17.12.96)

(30) Priority Data:

60/009,508	21 December 1995 (21.12.95)	US
08/646,903	8 May 1996 (08.05.96)	US
60/030,666	12 November 1996 (12.11.96)	US

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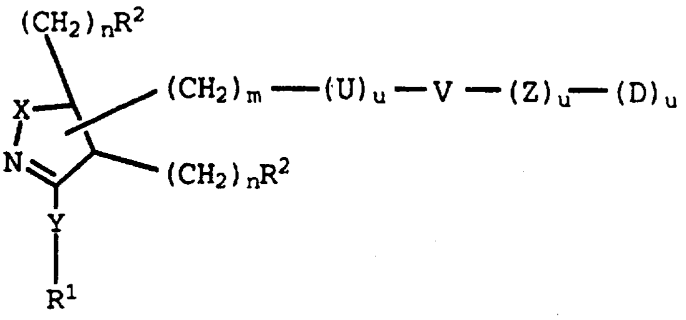
(81) Designated States: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ISOXAZOLINE, ISOTHIAZOLINE AND PYRAZOLINE FACTOR Xa INHIBITORS

(57) Abstract

Isoxazolines, isothiazolines and pyrazolines which are inhibitors of Factor Xa, pharmaceutical compositions containing these compounds, and methods of using these compounds as anticoagulant agents for treatment and prevention of thromboembolic disorders. The compounds can be represented by formula (I) where X is O, S or NR^{15}.



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TITLE

Isoxazoline, isothiazoline and pyrazoline
Factor Xa Inhibitors

FIELD OF THE INVENTION

This invention relates to isoxazolines, isothiazolines and pyrazolines which are inhibitors of Factor Xa, to pharmaceutical compositions containing these compounds, and to methods of using these compounds as anticoagulant agents for treatment and prevention of thromboembolic disorders.

BACKGROUND OF THE INVENTION

Stuerzebecher et al., Thrombosis Research, vol. 9, 637-646 (1976) describes comparative studies of a number of benzamidine derivatives as Factor Xa inhibitors. The most active inhibitors were 3-amidino-phenylaryl derivatives.

Tidwell et al., Thrombosis Research, vol. 19, 339-349 (1980) describes Factor Xa inhibitory activity of a series of heterocyclic aromatic mono- and di-amidines.

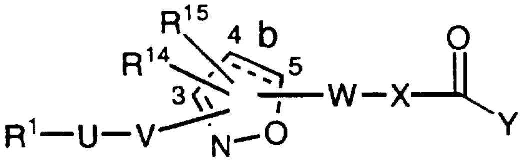
Stuerzebecher et al., Thrombosis Research, vol. 17, 545-548 (1980) describes Factor Xa inhibitory activity of a series of a,a'-bis-(4-amidinobenzyl)cycloalkanones, a,a'-bis-(4-aminobenzylidene)- and a,a'-bis-(3-aminobenzylidene) cycloalkanones with 5 to 8-membered rings, the corresponding non-cyclic derivatives, and derivatives containing only one amidino group.

Hauptmann et al., Blood Coagulation and Fibrinolysis, vol. 4, 577-582(1993) and Hauptmann et al., Thromb. Haemostasis, vol. 63(2), 220-223(1990) report testing of several synthetic compounds as Factor Xa inhibitors: Na-tosylglycyl-3-amidinophenylalanine methyl ester; 2,7-bis(4-amidinobenzylidene)-cycloheptanone-(1); Na-tosyl-4-amidinophenylalanine piperidide; Na-naphthylsulphonylglycyl-4-amidinophenylalanine piperidide; 4-methyl-1-N^2-(methyl-1,2,3,4-tethydro-8-quinolinesulphonyl-L-arginyl-2-piperidine carbonic acid; and D-phenylalanyl-L-propyl-L-arginine chloromethyl ketone.

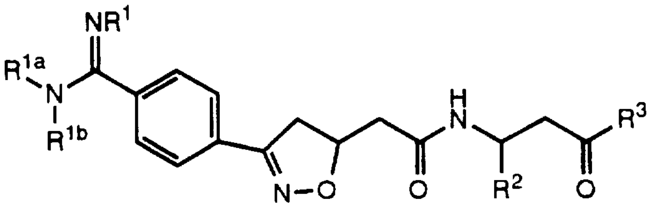
Nagahara et al., J. Med. Chem., vol. 37, 1200-1207(1994) describes several dibasic (amidinoaryl)propanoic acid derivatives as Factor Xa inhibitors.

Daiichi EPA 0 540 051 A1, published May 5, 1993, discloses aromatic amidine derivatives, including amidino naphthylenes, amidino-indoles, amidino-benzimidazoles, and amidino-benzothiophenes, which have Factor Xa inhibitory activity.

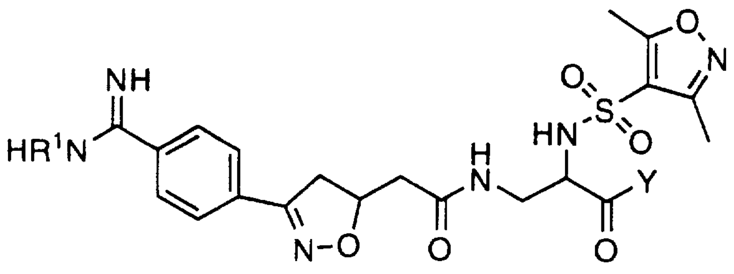
DuPont Merck WO 95/14683 and WO 95/14682, published June 1, 1995, disclose isoxazoles and isoxaolines as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor. The isoxazoles and isoxaolines of WO 95/14683 are represented by the formula:



The isoxazolines of WO 95/14682 are represented by the formula:



Copending, commonly assigned U.S. Patent Application Serial Number 08/449597, filed May 24, 1995, discloses isoxazoline antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor having the formula:



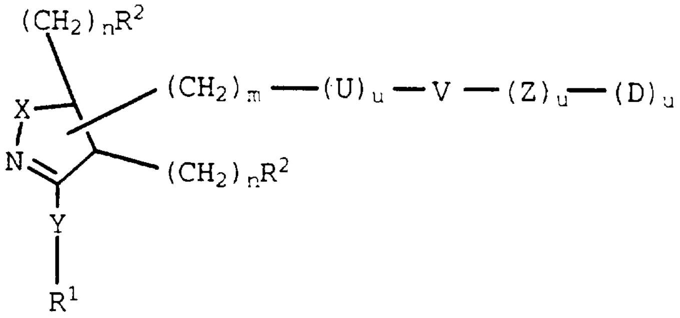
EP 53095 A and other references disclose various di-anilino-pyrazoline as components of photosensitive systems.

EP 438690 and other references disclose various 1-amido-pyrazolines as pesticides, e.g., insecticides, fungicides and acaricides.

To date there have been no isoxazoline, isothiazoline or pyrazoline derivatives described as Factor Xa inhibitors.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I:



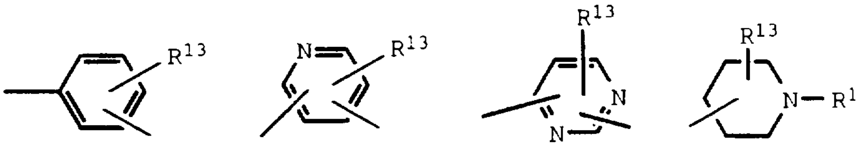
(I)

including pharmaceutically acceptable salts and prodrug forms thereof, and all stereoisomeric forms thereof and mixtures of such stereoisomeric forms, wherein:

U when present (i.e., when u=1) is selected from
$-CO-NH-(CH_2)_o-$
$-CO-(CH_2)_o-$
$-SO_2-NH-(CH_2)_o-$
$-SO_2-(CH_2)_o-$
$-NHSO_2-(CH_2)_o-$, provided $m \neq 0$
$-NHCO-(CH_2)_o-$, provided $m \neq 0$
$-NH-(CH_2)_o-$, provided $m \neq 0$
$-O-(CH_2)_o-$, provided $m \neq 0$
$-S-(CH_2)_o-$, provided $m \neq 0$
$-CH=CH-(CH_2)_o-$

X is O, S, NR^{15}

Y is selected from

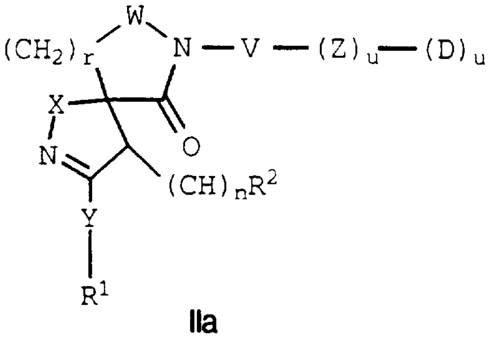


R^1 is selected from
$(CH_2)_pNR^5R^6$
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$
$NHC(NR^{14})H$
$CONR^5R^6$

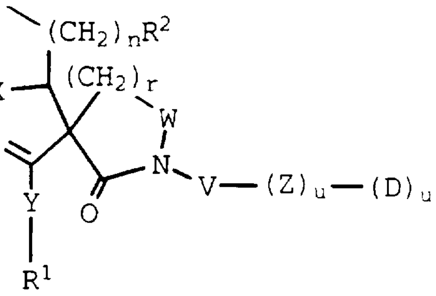
R^2 is selected from
H
C_1-C_6 alkyl

C_1-C_6 alkoxy
CO_2R^5
$CONHR^5$
$CONHCH_2CO_2R^5$
$CONH(CH_2)_q$-R^{10}
R^{10}
CO-R^5
$COCO_2R^5$
$COCONHR^5$
SO_nR^5
SO_2NHR^5
NHR^7
$CH=CHCO_2R^5$
$CH=CHCONHR^5$
O-$(CH_2)_n$-R^{10}
SO_n-$(CH_2)_n$-R^{10}
NH-$(CH_2)_n$-R^{10}

U and R^2 taken together provide a spiro compound of formula IIa and IIb, or a compound of formula IIIa or IIIb:

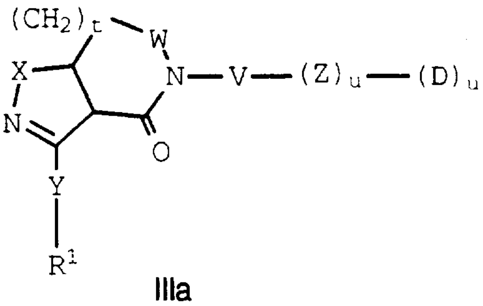


IIa

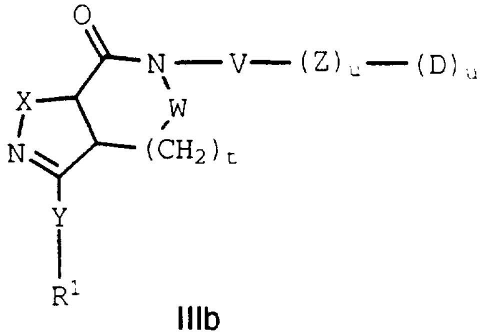


IIb

where W = CO, CH_2, $CHOR^5$ and r = 1-3



IIIa



IIIb

where W = CO, CH$_2$, CHOR^5 and t = 0-2

R^3 is selected from

$(CH_2)_sNR^5R^6$

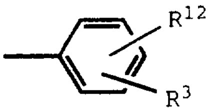
$C(NR^{14})NR^5R^6$

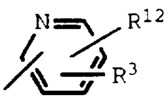
$NHC(NR^{14})NR^5R^6$

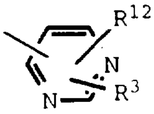
$NHC(NR^{14})H$

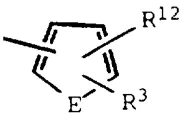
$CONR^5R^6$

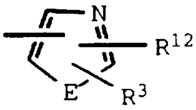
V is selected from the following when Z and D are both absent:

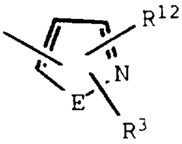


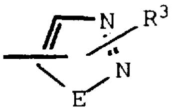


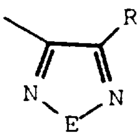


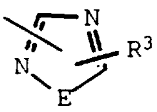


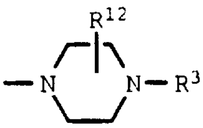


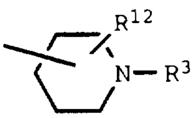


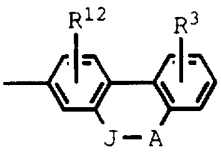


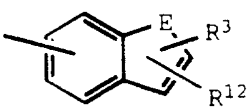


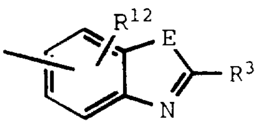


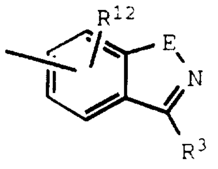


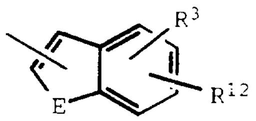


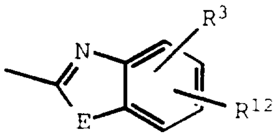


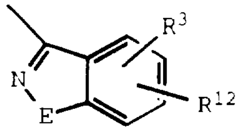


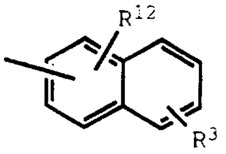












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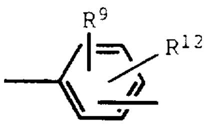
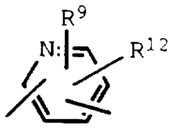
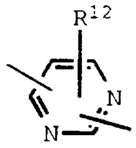
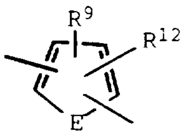
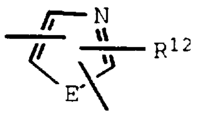
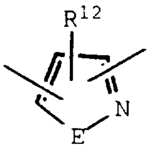


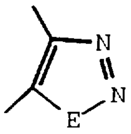


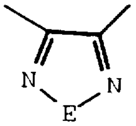


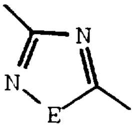


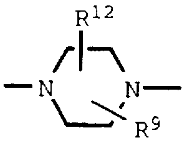


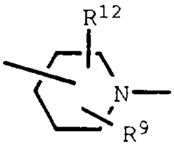


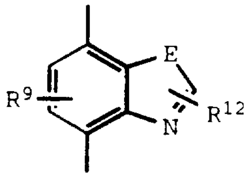


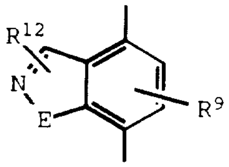


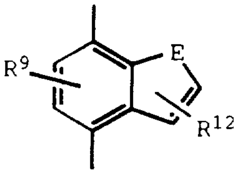


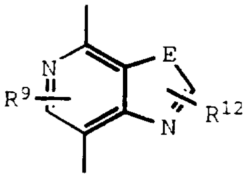


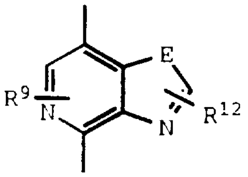


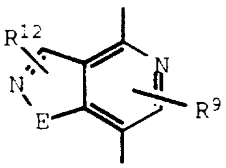


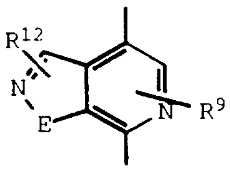
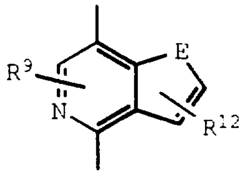
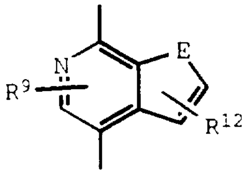
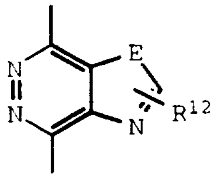
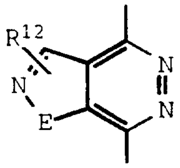
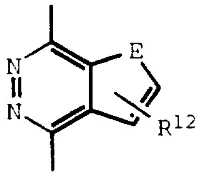






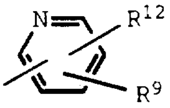
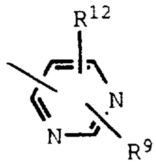
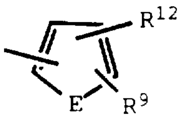
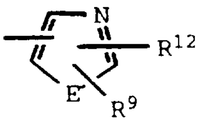
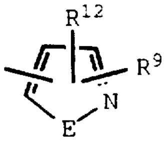
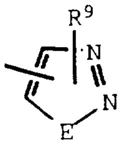
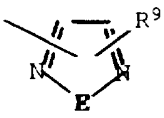
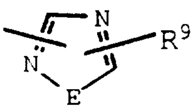
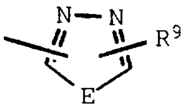
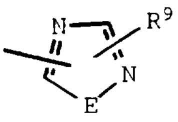


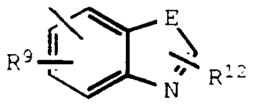


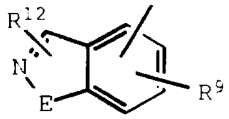







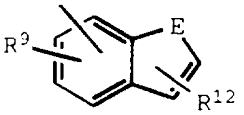
Z when present (i.e., when u = 1) is selected from
a single bond,
-CO-,
-$(CH_2)_t$-,
-SO_n-,
-SO_2NHR^4, provided D is absent
-NH-,
-NR^7-,
-O-

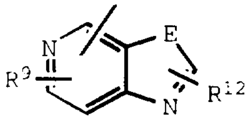
D when present (i.e., when u = 1) is selected from

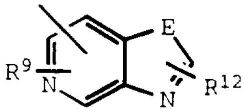












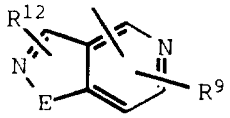


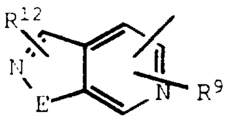


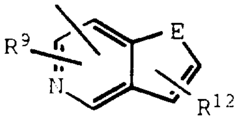


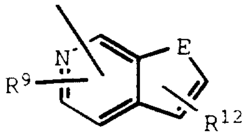


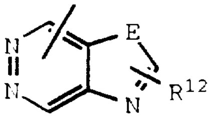


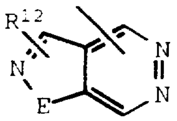


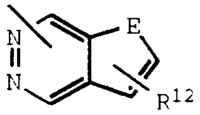












E is selected from N, NR^5, O, S;

J is selected from O, NR^7;

A is selected from CO, CH_2, SO, SO_2

R^4 is selected from
H
C_1-C_6 alkyl
$(CH_2)_n$-phenyl
$(CH_2)_n$-CONHR^5
$(CH_2)_n$-CONHR^5$CH_2CO_2R^5$

R^5 and R^6 at each appearance are independently
H
C_1-C_6 alkyl
$(CH_2)_n$-phenyl

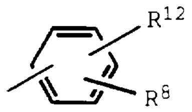
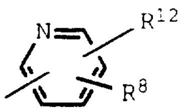
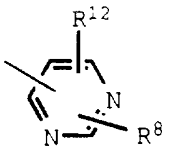
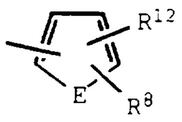
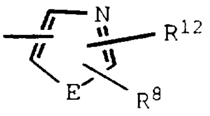
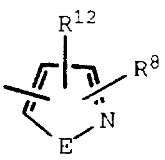
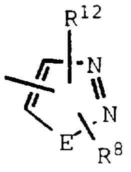
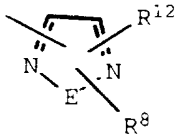
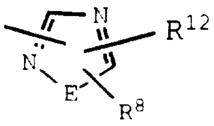
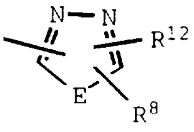
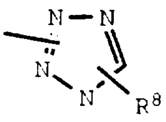
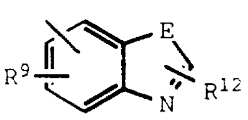
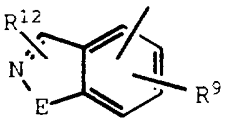
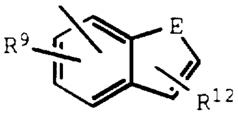
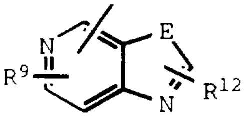
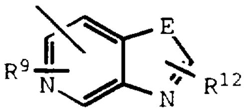
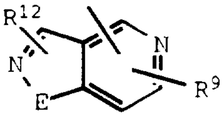
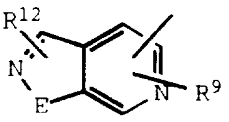
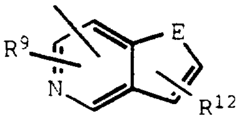
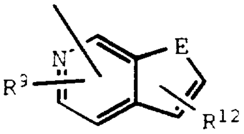
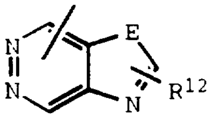
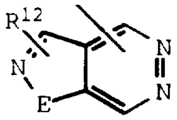
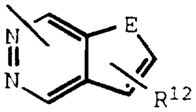
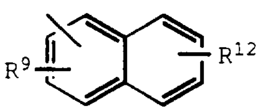
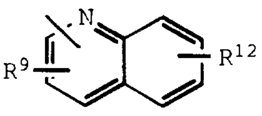
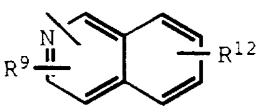
R^7 is selected from
H
C_1-C_6 alkyl

SO_2R^5
COR^5
$(CH_2)_r$-R^{10}
$(CH_2)_n$-phenyl

R^8 is selected from
H
C_1-C_6 alkyl
halogen
NO_2
CF_3
OR^5

R^9 is selected from
H
C_1-C_6 alkyl
halogen
NO_2
NHR^7
SO_2NHR^{11}
CF_3
OR^5
CO_2R^5
$CONR^5R^7$
CN
$(CH_2)_pNR^5R^6$
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$
$NHC(NR^{14})H$
SO_n-R^5
SO_n-CF_3
imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole and tetrazole, each optionally substituted with CF_3, halogen, NO_2, C_1-C_5 alkyl, or C_1-C_5 alkoxy;

R^{10} is selected from

R^{11} is selected from

H

C_1-C_6 alkyl

$(CH_2)_n$-phenyl
COR^5
CO_2R^5

R^{12} is selected from
H
C_1-C_6 alkyl
C_1-C_6 alkoxy
halogen
NO_2
NHR^7
CN
CF_3
$SONHR^{11}$

R^{13} is selected from
H
OH
C_1-C_{10} alkyl
C_1-C_{10} alkoxy
nitro
halo
CF_3

R^{14} is selected from
H
OH
C_1-C_{10} alkyl
C_1-C_{10} alkoxy
CO_2-C_1-C_{10} alkyl
CO-C_1-C_{10} alkyl
CONH-C_1-C_{10} alkyl
CONH-phenyl
$CO_2(CH_2)_n$-phenyl;

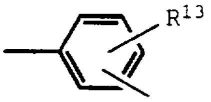
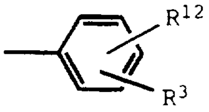
R^{15} is selected from

H
C_1-C_6 alkyl,
C_1-C_6 alkoxy
CO_2R^{14}
$CONHR^{14}$
$CONHCH_2CO_2R^5$
$CONH(CH_2)_q$-R^{10}
$(CH_2)_nR^{10}$
CO-R^5
$COCO_2R^5$
$COCONHR^5$
SO_2NHR^5

at each appearance each of the following are independently:

m = 0-2
n = 0-4, except that in $-SO_n-$, n = 0-2;
o = 0-2
p = 0-1
q = 0-4
r = 1-2
s = 0-2
t = 0-2
u = 0-1,

provided that, when X is NR^{15}, Z and D are both absent,

Y is  and V is  ,

then at least one of R^1 and R^3 must be
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$ or
$NHC(NR^{14})H$.

As used in this specification and the claims:

the terms "alkyl" and "alkoxy" mean straight or branched chain alkyl and straight or branched chain alkoxy, each optionally substituted with 1 to 3 substituents independently selected from halo, C_1-C_6 straight or branched alkoxy, $S(O)_n$-alkyl where alkyl is C_1-C_6 straight or branched alkyl and n is 0-2, morpholino, C_1-C_6 alkylacyloxy, NR^5R^7 where R^5 and R^7 are as defined in claim 1, CN, NO_2, and CF_3;

the term "phenyl" means phenyl optionally substituted with 1 to 3 substituents independently selected from halo, C_1-C_6 straight or branched alkoxy, $S(O)_n$-alkyl where alkyl is C_1-C_6 straight or branched alkyl and n is 0-2, morpholino, C_1-C_6 alkylacyloxy, NR^5R^7 where R^5 and R^7 are as defined in claim 1, CN, NO_2, and CF_3;

the terms "halo" and "halogen" mean chloro, fluoro, bromo and iodo.

Many compounds of this invention have one or more asymmetric centers or planes. All chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by asymmetric synthesis, or synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

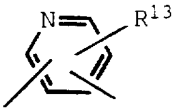
Preferred are those compounds of Formula I wherein, independently or concurrently:

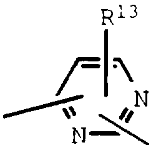
U is present and is selected from

$-CO-NH-(CH_2)_o-$
$-CO-(CH_2)_o-$
$-SO_2-NH-(CH_2)_o-$
$-SO_2-(CH_2)_o-$
$-NH-(CH_2)_o-$
$-O-(CH_2)_o-$

X is O

Y is selected from



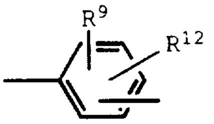


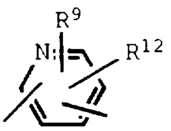
R^1 is selected from
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$

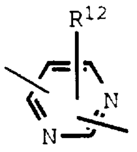
R^2 is selected from
H
C_1-C_6 alkyl
C_1-C_6 alkoxy
CO_2R^5
$CONHR^5$
$CONHCH_2CO_2R^5$
$CONH(CH_2)_q-R^{10}$
R^{10}
$CO-R^5$
$COCO_2R^5$
$COCONHR^5$
SO_nR^5
SO_2NHR^5
NHR^7
$CH=CHCO_2R^5$
$CH=CHCONHR^5$
$O-(CH)_n-R^{10}$

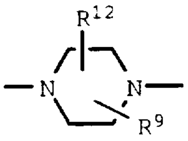
$SO_n-(CH)_n-R^{10}$
$NH-(CH)_n-R^{10}$

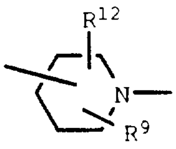
V is selected from the following when Z and/or D are present:

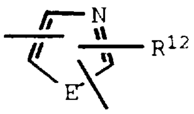




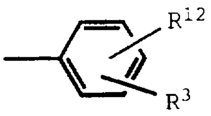


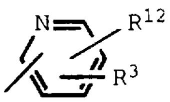


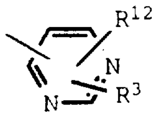


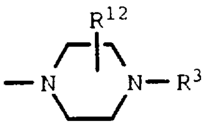


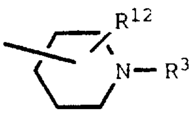
V is selected from the following when Z and D are both absent:

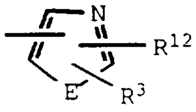




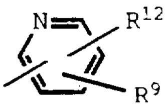


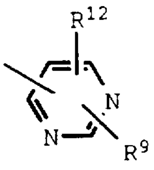




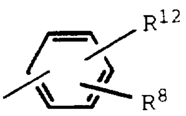


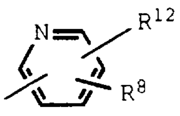
D when present (i.e., when u = 1) is selected from

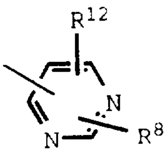


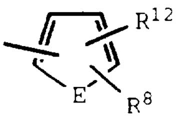


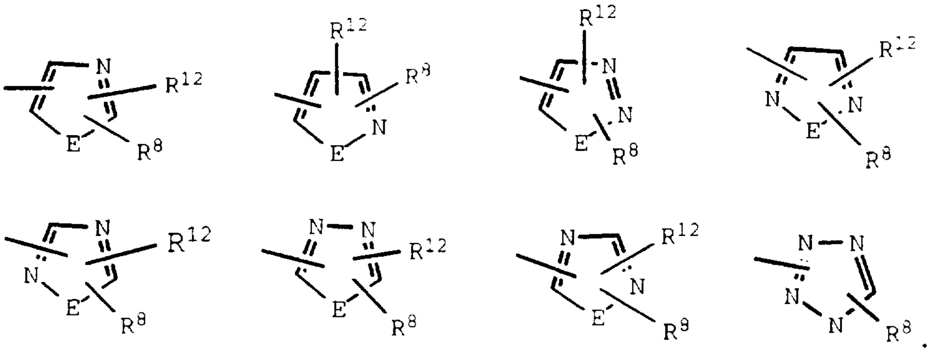
R^{10} is selected from







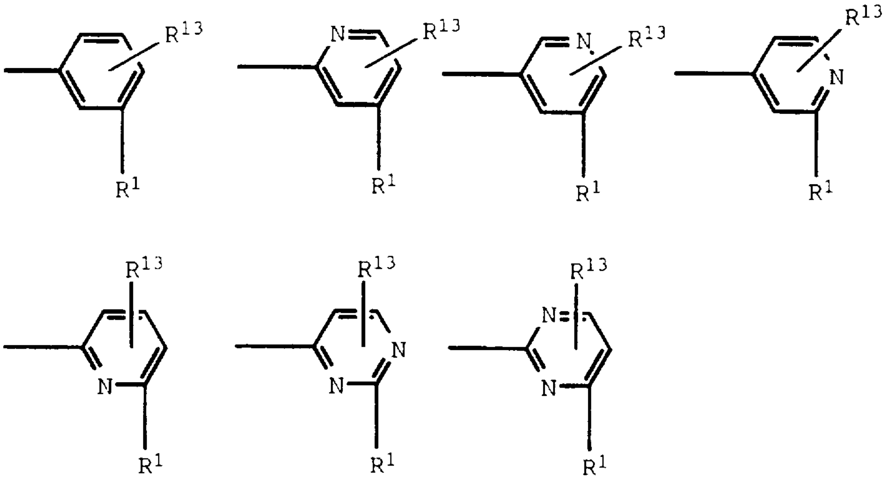




Of the preferred compounds, more preferred are those wherein, independently or concurrently:

U is $-CO-NH-(CH_2)_o-$

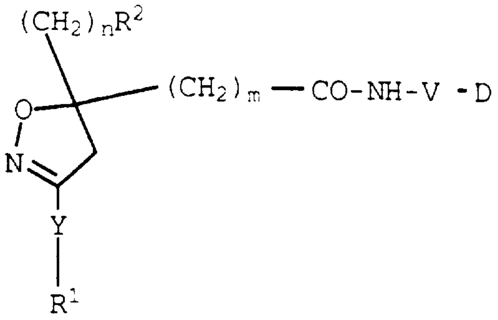
Y is selected from



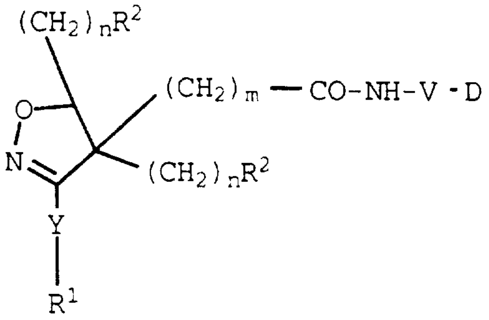
R^1 is $C(NR^{14})NR^5R^6$

Z is absent or is present and is selected from
$-O-$ and $-NR^7-$.

Of the more preferred compounds, especially preferred are those having the structures of V and VI:



(V)

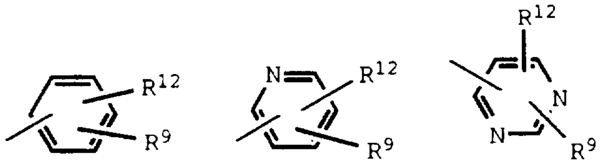


(VI)

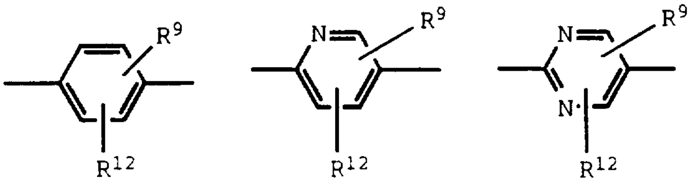
wherein

R^1 is $C(NR^{14})NR^5R^6$ and

D is selected from



V is selected from the following:



Specific preferred compounds of this invention include the following and pharmaceutically acceptable salt and prodrug forms thereof:

3-(3-Amidinophenyl)-5-[(2-naphthylsulfonyl)amino]methyl-isoxazoline

3-(3-amidinophenyl)-5-[[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)-methyl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)methyl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-7-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)methyl[1-oxa-2,7-diazaspiro[4,4]non-2-ene-6,8-diones

3-amidinophenyl 3-(4-amidinophenyl)-5-[(aminocarbonyl)isoxazolin-5-yl]acetamide

4-amidinophenyl 3-(3-amidinophenyl)-5-[(carbometoxy)isoxazolin-5-yl]acetamide

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]-5-[(carbomethoxymethyl)aminocarbonylmethyl]isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(4-amidinophenyl)-5-[(3-amidinophenyl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)methylaminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-benzenesulfonylpiperidin-1-yl)carbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[(4-pyrimidin-5-yl)piperidin-1-yl]carbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-benzenesulfonylphenyl-1-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(hydroxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3'-n-propyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4'-amino-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-trifluoromethyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl)]-5-(carbomethoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxyethylene)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl)-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethylaminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-[(imidazole-4-yl)ethylaminocarbonylmethyl]isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethylaminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-carbomethoxymethyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-carbomethoxymethyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylsulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylsulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-3-flouro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-3-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethyl-3-flouro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethyl-3-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-methoxymethyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylaminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-methylaminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylsulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylsulfonyl-fluoro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylsulfonyl-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethylsulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(imidazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethylsulfonyl-3-fluoro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethylsulfonyl-3-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(imidazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-4-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-methoxymethyl-isoxazoline

3-(3-amidinophenyl)-4-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-trifluoromethyl-isoxazoline

3-(3-amidinophenyl)-5-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-4-methoxymethyl-isoxazoline

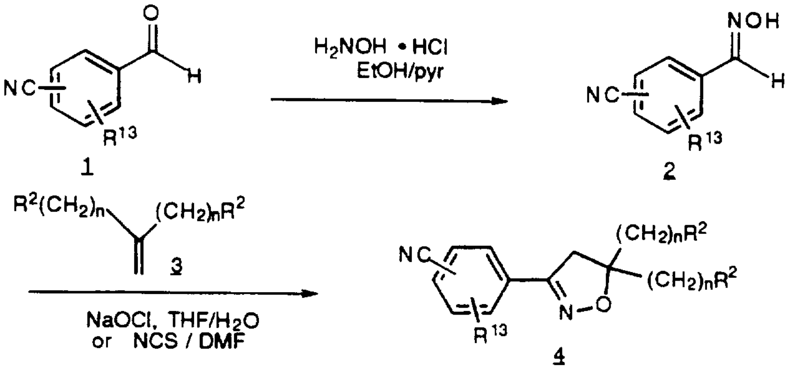
DETAILED DESCRIPTION OF THE INVENTION

Synthesis

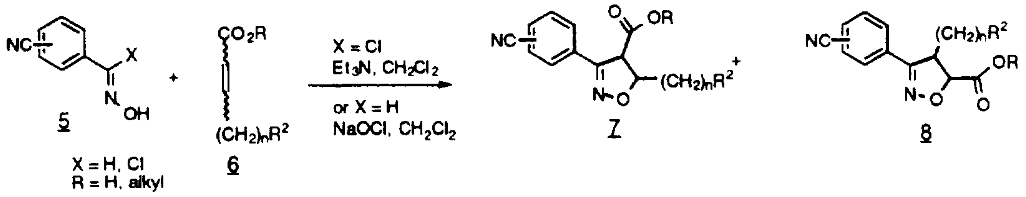
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

A convenient method for the synthesis of the isoxazoline compounds of this invention utilizes a dipolar cycloaddition of nitrile oxides with appropriate dipolarophiles to prepare the isoxazoline rings present in compounds of Formula I (for reviews of 1,3-dipolar cycloaddition chemistry, see 1,3-Dipolar Cycloaddition Chemistry (Padwa, ed.), Wiley, New York, 1984; Kanemasa and Tsuge, Heterocycles 1990, 30, 719). Scheme 1 shows a general synthesis of 3,5-substituted-isoxazolines. An appropriately substituted hydroxylamine is treated with NCS in DMF according to the method of Liu, et al. (J. Org. Chem. 1980, 45, 3916). The resulting hydroximinoyl chloride is then dehydrohalogenated in situ using TEA to give a nitrile oxide, which undergoes a 1,3-dipolar cycloaddition to a suitably substituted alkene to afford the isoxazoline. Alternatively, the oxime may be oxidatively chlorinated, dehydrochlorinated and the resulting nitrile oxide trapped by a suitable alkene under phase transfer conditions according to the method of Lee (Synthesis 1982, 508). The isoxazoline compounds of the general formula (I) wherein the 4 and 5 positions are substituted can be prepared following the 1,3-dipolar cycloaddition methodology using a suitable 1,2-disubstituted olefin as a dipolarophile. A mixture of regioisomers is formed and the regioisomers can be separated by column chromatography. An example is shown in Scheme 2. Optically active isoxazolines can be obtained by chiral HPLC separation of the two enantiomers, or enzymatic resolution on the regioisomeric esters. It can also be obtained by the use of an appropriate chiral auxilliary on the dipolarophile as described by Olsson (J. Org. Chem. 53, 2468, 1988). The synthetic methods described above may also be used for the synthesis of compounds of this invention where Y is pyridyl or pyrimidyl derivatives in formula (I).

Scheme 1

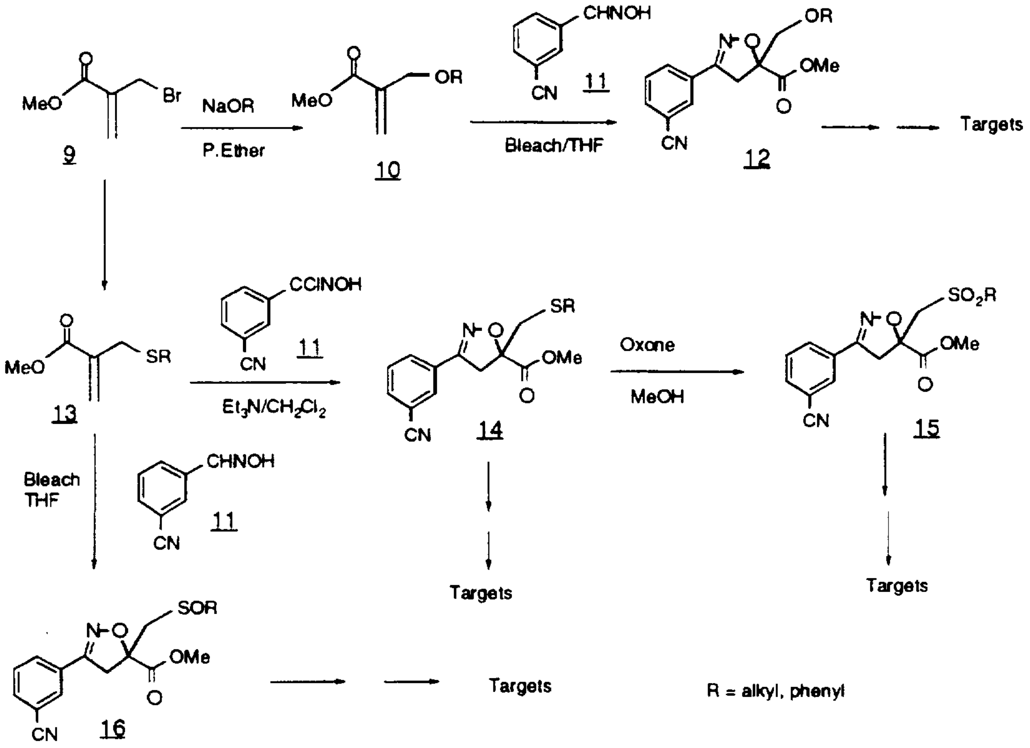


Scheme 2

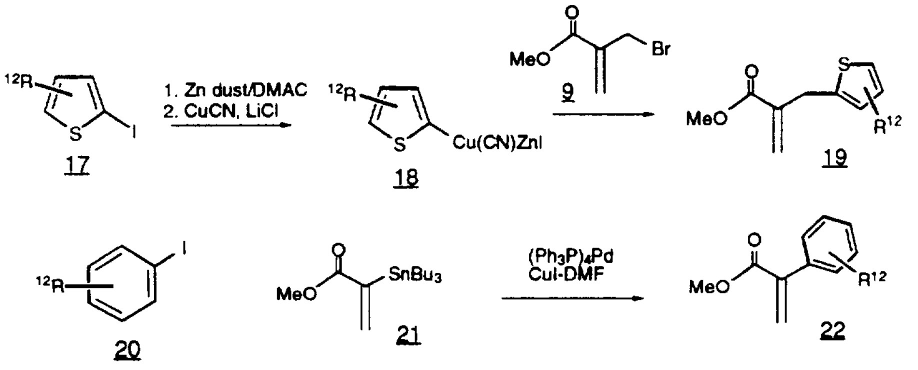


Many isoxazoline compounds of this invention can use commercially available substituted alkenes as starting materials. Compounds with R^2 is acid or amide can be prepared from the commercially available alkene-esters or alkene acids. The transformations of the functional groups can be done either at the alkene stage or after the isoxazoline ring is formed. Compounds with R^2 is $O(CH_2)_nR$, $NH(CH_2)_nR$, $S(CH_2)_nR$, where R is R^5 or R^{10}, can be prepared from substituted allyl bromide. An example is shown in Scheme 3. The sulfoxides and sulfones can be prepared from oxidation of the thio-compounds (Scheme 3). Compounds wh R^2 is aromatics and heteroaromatics (R^{10}) can be prepared from the reaction of the bromide or iodide of the aromatics and hetreoaromatics with allyl of vinyl bromide. The C-linked aromatic and hetreoaromatic compounds can be synthesized using Zinc and Copper organometallics shown by Knochel (Tet. Lett. 31, 4413-4416, 1990), or using palladium-catalyzed coupling of an a-stannyl acrylate to aryl iodides or triflates by Levin (Tet. Lett. 34, 6211-6214, 1993). These reactions are exemplified in Scheme 4. The N-linked heteroaromatic compounds can be prepared by alkylation of the hetroaromatics with allyl bromides. An example is shown in Scheme 5. Compounds with R^2 is $COCO_2R$ or COCONHR can be prepared by the method discribed by Iwanowicz (Bioorg. & Med. Chem. Lett., 2, 1607-1612, 1992).

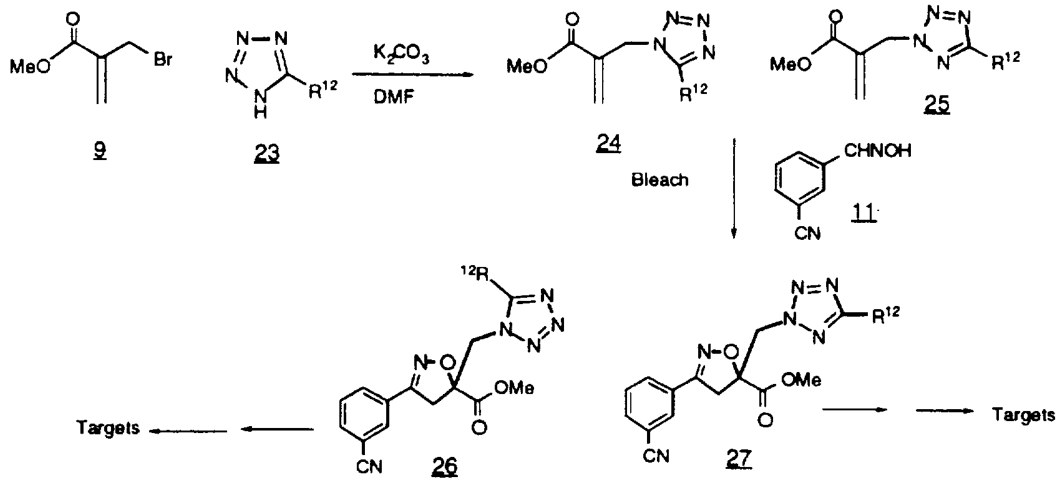
Scheme 3



Scheme 4

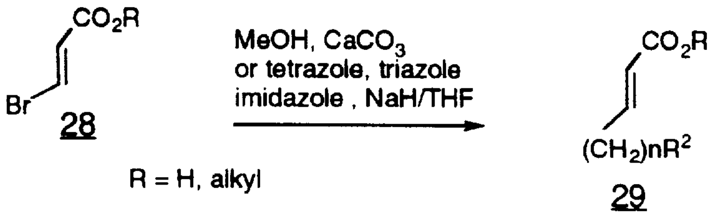


Scheme 5

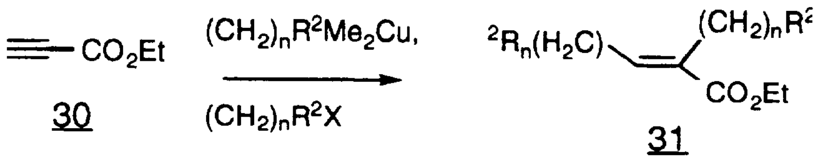


Appropriately substituted crotonate ester can be used as starting material for 4,5-disubstituted isoxazolines. The crotonate esters can be obtained from commertial sources or can be obtained from ethyl-4-bromocrotonate by nucleophilic displacement reactions shown in Scheme 6. Trisubstituted olefins as diplolarophiles can be obtained from ethylpropiolate by the cuprate chemistry (Scheme 7) according to the method described by Deslongchamps (<u>Synlett</u>, 660, 1994).

Scheme 6

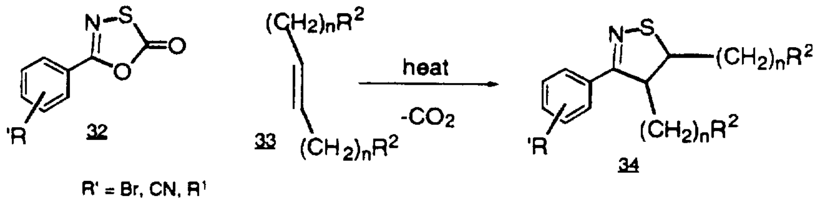


Scheme 7



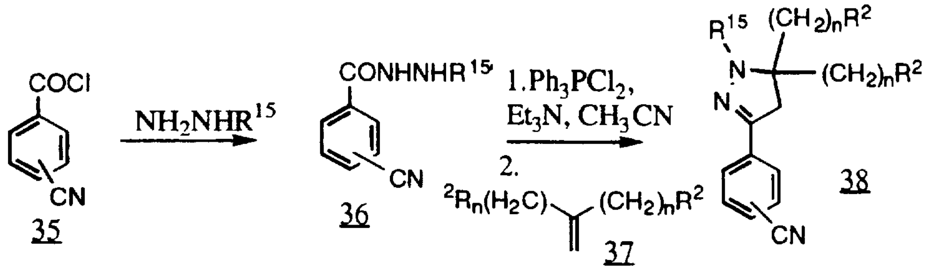
The isothiazoline compounds of this invention of formula (I) can be prepared by cycloaddition reaction of nitrile sulfides with olefins (Howe, J. Org. Chem., 43, 3742, 1978) as shown in Scheme 8. The nitrile sulfide is generated by thermolysis of 5-substituted 1,3,4-oxthiazol-2-one.

Scheme 8

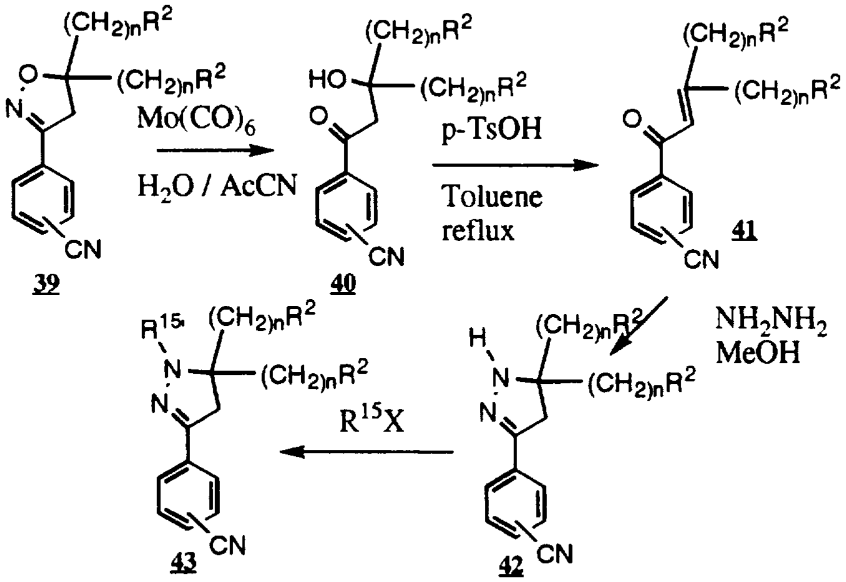


The pyrazoline compounds of this invention of formula (I) cab be prepared by the method described by Wahoff and Zahran (Synthesis, 876-879, 1987). An example of the synthesis is shown in Scheme 9. The hydrozine is coupled with the acyl chloride. The N-acylated hydrozine is reacted with dichlorotriphenylphosphorane and triethylamine. The nitrilimine generated in situ undergoes a 1,3-dipolar cycloaddition reaction with a suitable alkene to give the pyrazoline. The pyrazolines may also be prepared from isoxazolines as shown in Scheme 10. The isoxazoline was reacted with molybdenum hexacarbonyl in the conditions described by Baraldi (Synthesis, 276, 1987) provides the b-hydroxyketone. Dehydration of the b-hydroxyketone with p-toluenesulfonic acid yields the a,b-unsaturated ketone, which was then treated with hydrazine to afford the desired pyrazoline.

Scheme 9

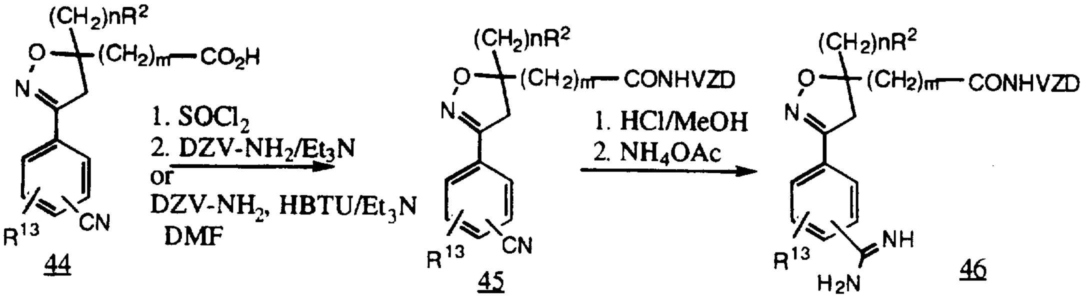


Scheme 10

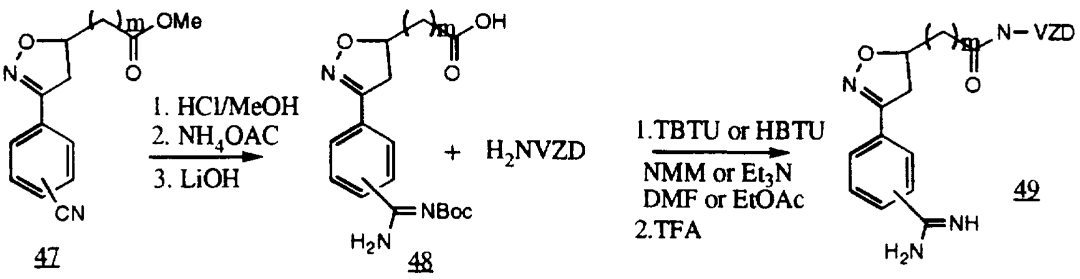


Compounds of this invention where U in formula (I) is CONH may be prepared using substituted acrylates, vinyl acetate, or crotonate as starting materials. The core ring structures can be synthesized as described above and the easter group is then coupled with an appropiate amine using standard conditions for the formation of amide bonds. The nitrile is then converted to the amidine *via* the imidate or thioimidate under standard conditions. Some of the compounds are prepared following the procedures described in copending commonly-assigned US. Patent application USSN 08/337920. An example of these compounds is shown in Scheme 11. The 3-substituted-isoxazoline-5-ylcarboxylic acids or 3-substituted-isoxazoline-5-ylacetic acids can be converted to the corresponding amidines first, followed by protection as the Boc-derivatives or CBZ-derivatives. They were then coupled with appropiate amines as exemplified in Scheme 12. Compounds of this invention where R^1 is NHCH(NR^5) in formula (I) may be prepared from amine derivatives by reaction of the amine with ethyl formimidate and N,N-dimethylpyridine in refluxing ethanol. Compounds of this invention where R^1 is NHC(NR^5)NR^5R^6 in formula (I) may be prepared from amine derivatives by reaction of the amine with either formamidine sulfonic acid and N,N-dimethylpyridine in refluxing ethanol (Kim, et al. Tet. Lett. 29, 3183, 1988), or Bocprotected pyrazole carboxamidine in DMF (Bernatowicz et al. Tet. Lett. 34, 3389, 1993).

Scheme 11

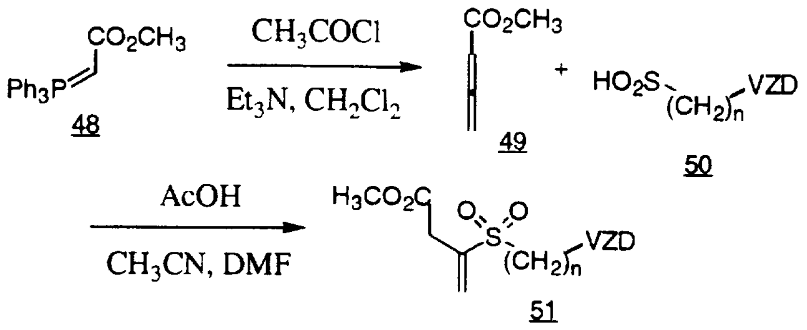


Scheme 12

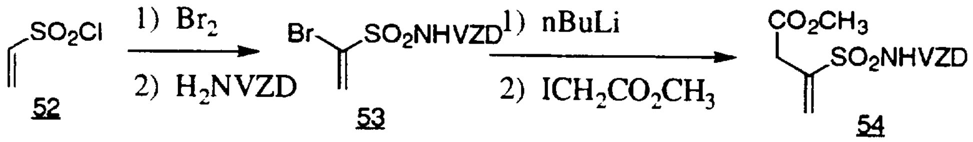


The sulfone derivatives where U is $-SO_2-(CH_2)_o-$ are prepared as exemplified by the reactions in Scheme 13. Methyl (triphenylphosphoranylidene)-acetate is reacted with acetyl chloride to give the desired allene. A sulfinic acid, prepared by hydrogen peroxide oxidation of the corresponding thiol, is added into the allene to give the desired alkene (Padwa, J. Org. Chem, 54, 4232, 1989). This alkene can be used in the previously described cycloaddition reactions. The sulfonamide derviatives where U is $-SO_2-NH-$ are prepared as exemplified by the reactions in Scheme 14. Vinyl sulfonyl chloride is brominated, then reacted with an amine (Barnett, Tet. Lett., 651, 1968). Halogen-metal exchange and alkylation with iodoacetate gives the desired substituted vinyl sulfonamide (Stetan, Chem. Ber., 122, 169, 1889) which can be used in the previously described cycloaddition reactions.

Scheme 13

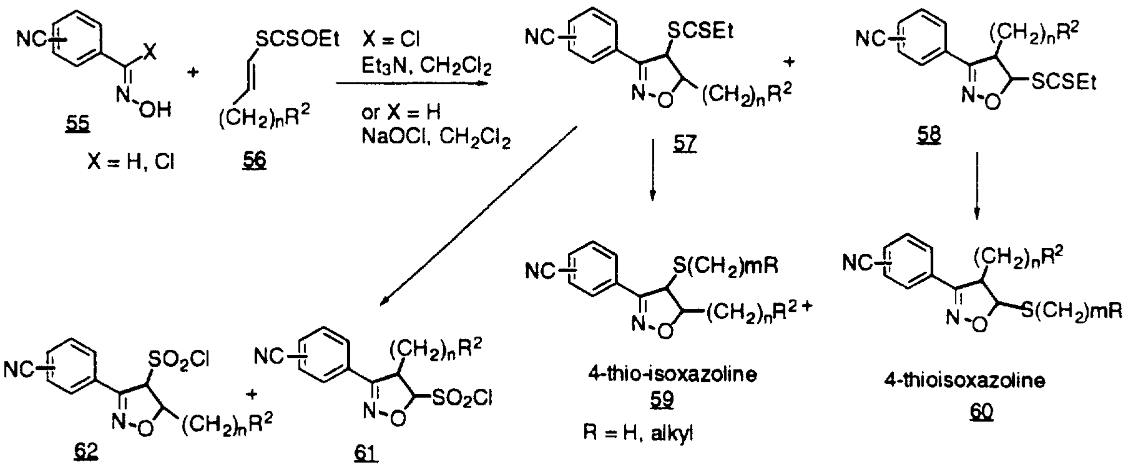


Scheme 14



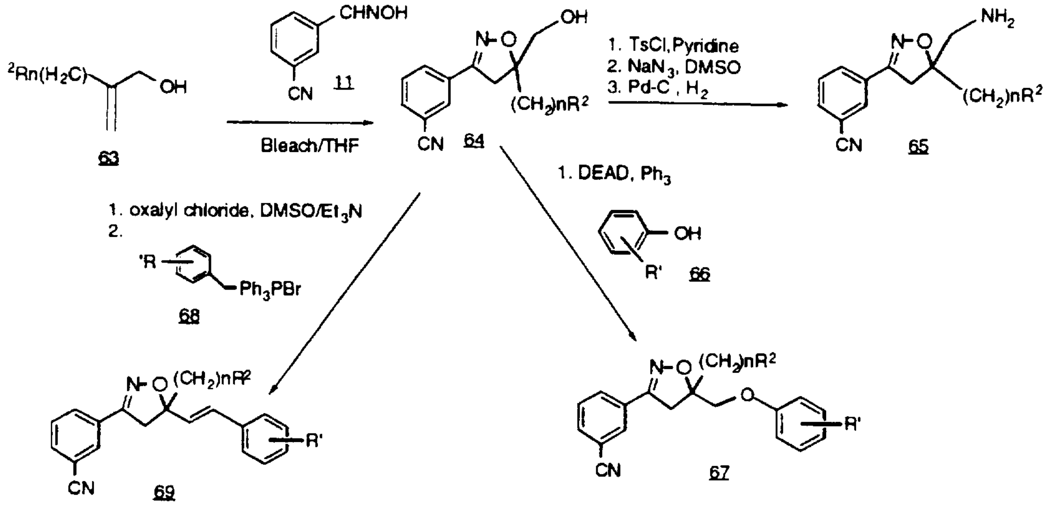
Isoxazoline compounds of the general formula I wherein U is thio, sulfonyl, or sulfonamide can also be prepared by the method outlined in scheme 15. The isoxazoline thioxanthate can be converted to the sulfonylchloride by treatement with chlorine in glacial acetic acid. The sulfonylchloride is then coupled with an appropriate amine to provide the desired sulfonamide. Alternatively the thioxanthate can be hydrolysed with sodium hydroxide in ethanol to the thiol followed by traping of the intermediate thiol with an appropriate benzylbromide to afford the thioalkylphenylanalog. Oxidation of the thio-compound with MCPBA or oxone affords the sulfoxide and or sulfone.

Scheme 15



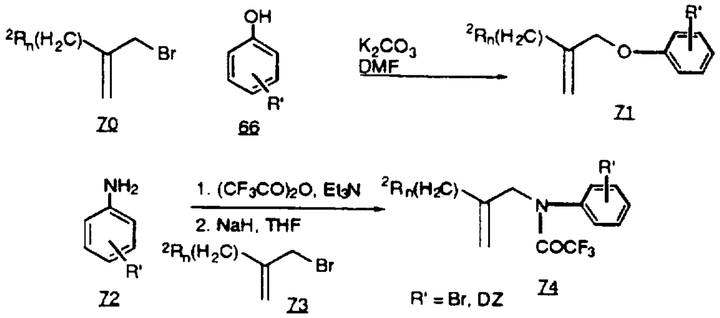
Compounds of this invention where U is alkene, ether, $-NHSO_2-$, ans -NHCO- can be prepared from the same intermediate as shown in Scheme 16. The 5-hydroxymethylisoxazoline is formed by the 1,3-dipolar cycloaddition described above. The alcohol can be oxidized to the corresponding aldehyde aand the converted to the alkene-linked compound by Wittig reaction. The alkene-linked compounds can then be reduced to the corresponding alkyl-linked compounds. The alkyl-linked compounds can also be prepared using Zinc and Copper organometallics shown by Knochel (Tet. Lett. 31, 4413-4416, 1990, see Scheme 4), The 5-hydroxymethyl group can be converted to the azide, and then reduced to the corresponding amine. This amine intermediate is the converted to compounds with $-NHSO_2-$, and -NHCO- using suitable sulfonyl or acyl chloride. The 5-hydroxymethylisoxazoline can be converted to the ether-linked compound by Mitsunobo reaction. The ether and amine linked compounds can also be prepared by displacement of the allyl bromide shown in Scheme 17.

Scheme 16


$^2Rn(H_2C)$
OH
63
CHNOH
CN
11
Bleach/THF
N-O
OH
$(CH_2)nR^2$
CN
64
1. TsCl, Pyridine
2. NaN_3, DMSO
3. Pd-C, H_2
NH_2
$(CH_2)nR^2$
CN
65
1. oxalyl chloride, DMSO/Et_3N
2.
'R
Ph_3PBr
68
1. DEAD, Ph_3
OH
R'
66
N-O
$(CH_2)nR^2$
R'
CN
69
N-O
$(CH_2)nR^2$
O
R'
CN
67

R' = Br, ZD

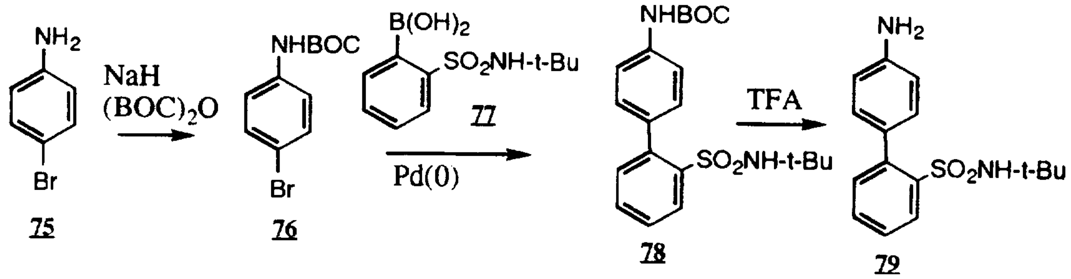
Scheme 17



Compounds of this invention where U is -CO- can be prepared by palladium-catalyzed coupling reactions of organozinc reagents with acid chlorides (Jackson, Synlett, 819-820, 1995 and Sato, Chem. Lett., 1135, 1981) or by organimetallics of Zinc and Copper described by Knochel (J. Org. Chem. 53, 5791-5793, 1988).

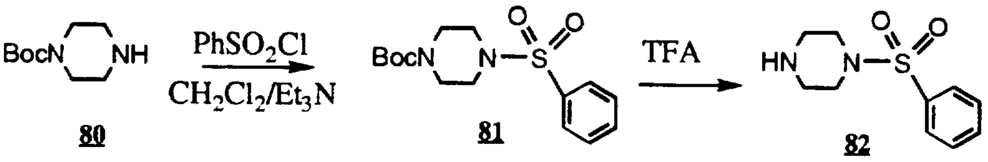
Compounds of this invention where Z is absent may be prepared as shown by an example in Scheme 18. 4-Bromoaniline is protected as Boc-derivative and the coupled to 2-(t-butylamino)sulfonylphenylboronic acid under Suzuki conditions. 2-(t-Butylamino)sulfonylphenylboronic acid is prepared by the method described by Rivero (Bioorg. Med. Chem. Lett., 189, 1994). Deprotection with TFA provides the aminobiphenyl compound. The aminobiphenyl is the coupled to the core ring structures first as described above. The Bromoaniline can be linked to the core ring structures first as described above, and then undergoes Suzuki reaction to give the desired product.

Scheme 18

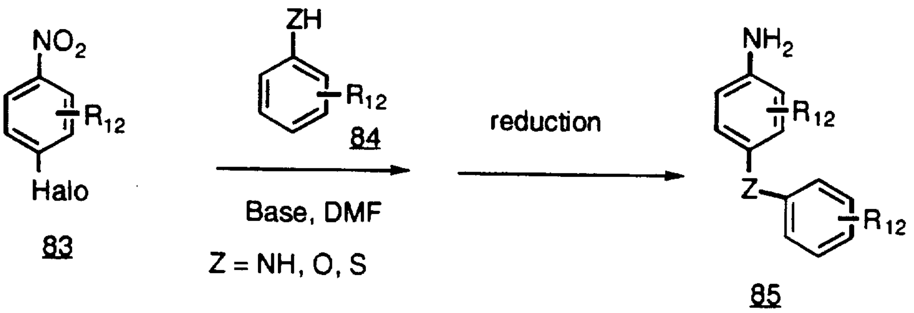


Compounds of this invention where -Z- is $-SO_2-$ are exemplified by the peperidine derivative shown in Scheme 19. Compounds of this invention where -Z- is -NH-, -O-, and -S- can be prepared by the methods described in Scheme 20.

Scheme 19



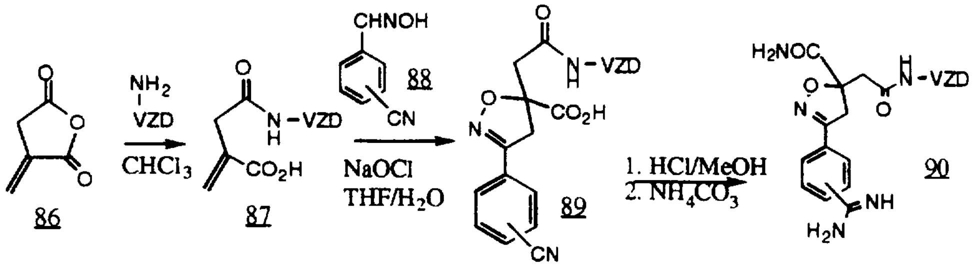
Scheme 20



Some of the compounds of this invention may also be prepared as shown in Scheme 21. Itaconic anhydride reacts with appropiate amine to give 3-carboxy-3-

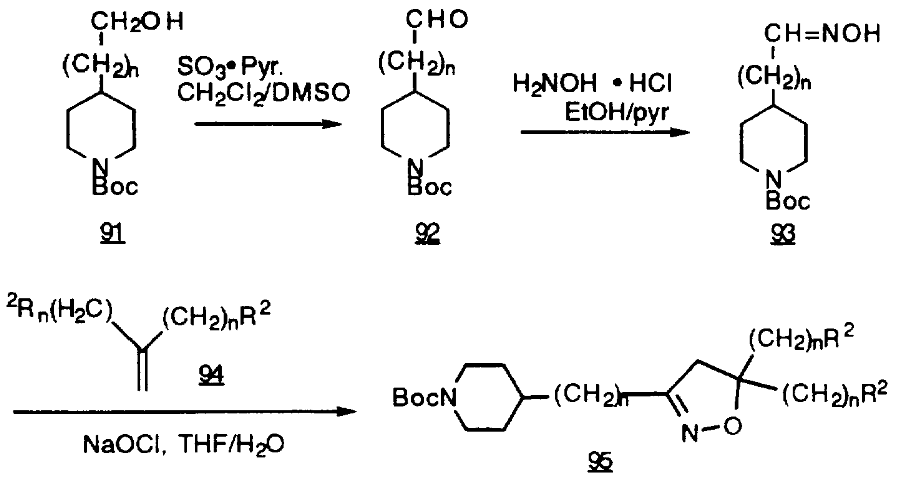
butenamide. The benzaldehyde oxime is oxidatively chlorinated and dehydrochlorinated. The resulting nitrile oxide then reacted with 3-carboxy-3-butenamide to yield the 3,5,5-trisubstituted isoxazoline which was then converted to the final benzamidine as described above.

Scheme 21



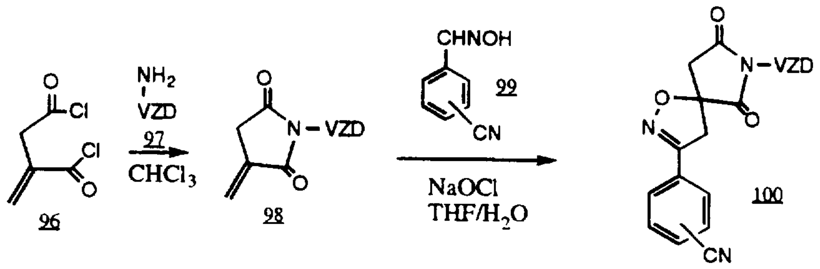
Compounds of this invention where Y is a piperidine derivative in formula (I) may be prepared from piperidine alcohols which are commercially available or prepared by coupling 4-brompyridine and appropiate length acetylenic alcohol followed by reduction. The piperidine alcohol is oxidized to the corresponding aldehyde under standard conditions. The aldehyde is converted to the isoxazoline by the same methods described above. An example of such a convertion is shown in Scheme 22 where n = 0-3.

Scheme 22

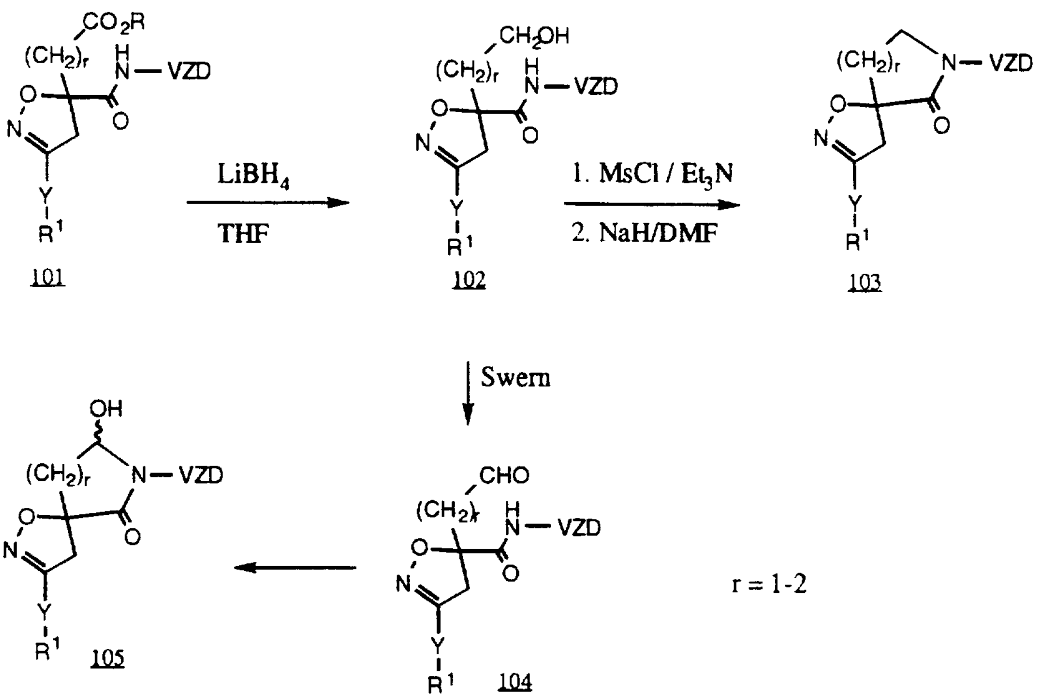


Some of the spiro-compounds of this invention in formula (II) may be prepared as shown in Scheme 23. Itaconyl chloride is reacted with appropiate amine to give the a-methylene-succinimide which then undergos 1,3-dipolar cycloaddition to yield the spiro-isoxazoline. Some of the spiro-compounds of this invention in formula (II) may be prepared from ester or acid intermediates. An example of this transformation is shown in Scheme 23. The ester or acid group in Scheme 24 can be reduced with LiBH4 in THF or other reducing agents to give the alcohol. The alcohol is then cyclized using a mesylate intermediate to afford the desired spiro-compound. The alcohol can also be oxidized under Swern oxidation conditions to generate the corresponding aldehyde, which can cyclized to give the spiro-compound.

Scheme 23



Scheme 24



As used herein, the term "compound of formula I " or "compounds of this invention" includes pharmaceutically acceptable salts and prodrug forms of the compounds of formula I.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula I are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of Formula I wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula I, and the like.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammoinum hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The compounds of this invention and their preparations can be understood further by the following examples which do not constitute a limitation of the invention. In these examples, unless otherwise indicated, all temperatures are in degrees centigrade and parts and percentages are by weight.

Example 1

3-amidinophenyl-5-(4-amidinophenyl)aminocarbonyl-5-carbomethoxymethyl-isoxazoline, Bistrifluoroacetic Acid Salt

Part A. Preparation of 3-cyanobenzaldehyde oxime

3-Cyanobenzaldehyde (25.0 g, 0.19 mol) and hydroxyamine hydrochloride (16.6 g, 0.24 mol) were added together with 100 mL of pyridine and 100 mL of ethanol. The mixture was stirred at room temperature under N_2 for 12h. The mixture was concentrated to half of its volume and 200 mL of water was added. A white precipitate formed. It was filtered and dried to afford 25.9 g of the oxime (93%). ^{1}HNMR (DMSO): d 7.61 (t, 1H); 7.85 (d, 1H); 7.96 (d, 1H); 8.00 (s, 1H); 8.21 (s, 1H); 11.61 (s, 1H).

Part B. Preparation of 3-(3-cyanophenyl)-5-carbomethoxy methyl-isoxazolin-5-ylcarboxylic acid

3-cyanobenzaldehyde oxime (26.9 g, 0.18 mol) and itaconic acid monomethyl ester (31.8 g, 0.22 mol) were added together with 600 mL of THF. To the above mixture was added bleach (467 mL of 0.67M aqueous solution) dropwise at room temperature. The reaction mixture was then stirred at RT under N_2 for 12h. The THF was removed in vacuo. The aqueous mixture was diluted with aqueous NaOH and then extracted with ethyl acetate. After residual organic solvents were removed from the aqueous mixture, it was acidified with aqueous HCl. A white precipitate formed and it was filtered and dried to give 39.4 g of the desired product (74%). ^{1}HNMR (DMSO): d 3.12 (m, 2H); 3.63 (s, 3H); 3.66 (d, 1H); 3.95 (d, 1H);7.68 (t, 1H); 7.85 (d, 1H); 7.95 (d, 1H); 8.04 (d, 1H); 8.12 (s, 1H).

Part C. Preparation of 3-(3-cyanophenyl)-5-(4-cyanophenyl)aminocarbonyl-5-carbomethoxymethyl-isoxazoline

3-(3-Cyanophenyl)-5-carbomethoxy methyl-isoxazolin-5-ylcarboxylic acid (1.00 g, 3.47 mmol), 4-cyanoaniline (0.41 g, 3.47 mmol), and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (1.11 g, 3.47 mmol) were added together with DMF (25 mL) and triethylamine (2 mL). The mixture was stirred at room temperature under N_2 for 48 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated. It was then purified by chromatography (silica gel, 30-50% EtOAc in hexane) to give 0.33 g of the desired product (24%). MS 406, $(M+NH_4)^+$. ^{1}HNMR ($CDCl_3$): d 3.06 (d, 1H); 3.32 (d, 1H); 3.69 (s, 3H); 3.78 (q, 2H), 7.51-7.62 (m, 3H); 7.71 (d, 2H); 7. 70 (s, 1H), 7.85 (d, 1H); 7.92 (s, 1H); 8.81 (s, 1H).

Part D. Preparation of 3-amidinophenyl-5-(4-amidinophenyl)-aminocarbonyl-5-carbomethoxymethyl-isoxazoline, Bistrifluoroacetic Acid Salt

3-(3-Cyanophenyl)-5-(4-cyanophenyl)aminocarbonyl-5-carbomethoxymethyl-isoxazoline (0.63 g, 1.62 mmol) was dissolved in 10 mL of anhydrous methanol and 30 mL of $CHCl_3$. The mixture was cooled in an ice-bath and HCl gas was bubbled-in until the solution was saturated. The reaction mixture was sealed and placed at 0°C for 12 h. The reaction mixture was concentrated to dryness, and dried under vacuum. The resulting solid was dissolved in 20 mL of anhydrous methanol and ammonium acetate (0.77 g, 10 mmol) was added. The reaction mixture was sealed and stirred at RT for 12 h. The mixture was concentrated and precipitated with ether. The precipitate was filtered and purified by HPLC (C18 reversed phased) eluted with 0.5% TFA in H_2O/CH_3CN to give 0.20 g of the bisbenzamidine TFA salt (20%). MS 423.2, $(M+H)^+$; 212.1, $(M+2H)^{2+}$. ^{1}HNMR (DMSO-d_6): d 3.20 (m, 2H); 3.58 (s, 3H); 3.70-4.02 (m, 2H); 7.65-8.09 (m, 8H); 9.04 (s, 2H); 9.18 (s, 2H), 9.30 (s, 1H); 9.40 (s, 2H); 10.49 (s, 1H).

Example 2

3-(3-Amidinophenyl)-5-[(2-naphthylsulfonyl)amino]methyl-isoxazoline Trifluoroacetic Acid Salt

Part A. Preparation of 3-(3-cyanophenyl)-5-hydroxymethyl-isoxazoline

3-Cyanobenzaldehyde oxime (27.57 g, 0.189 mol) and allyl alcohol (21.95 g, 0.378 mol) were added together with 1000 mL of THF. The reaction mixture was cooled to 0°C. To the above mixture was added bleach (480 mL of 0.67M aqueous solution) dropwise. The reaction mixture was allowed to slowly warm to RT under N_2 for 12h. The THF was removed *in vacuo*. The aqueous mixture was extracted with ethyl acetate. The combined organic extracts were triturated with diethyl ether. A white precipitate formed and it was filtered and dried to give 20.78 g of the desired product (54%). ^{1}HNMR (DMSO-d_6): d 3.16-3.56 (m, 5H), 4.74 (m, 1H), 4.98 (t, 3H), 7.62 (t, 1H), 7.86 (dd, 1H), 7.98 (m, 1H).

Part B. Preparation of 3-(3-cyanophenyl)-5-(4-methylphenylsulfonyloxy)methylisoxazoline

3-(3-Cyanophenyl)-5-hydroxymethylisoxazoline (1.0 g, 4.95 mmol) and p-toluenesulfonyl chloride (0.95 g, 4.98 mmol) were dissolved in 5 mL of pyridine and stirred at RT under N_2 for 12 h. After diluting with saturated aqueous sodium bicarbonate, the mixture was extracted with ethyl acetate. The combined organic extracted were back-extracted with water, dried with $MgSO_4$, and then the solvent was removed *in vacuo* to give 1.53 g (87%) of the desired compound as a white solid. ^{1}HNMR (DMSO-d_6): d 3.15 (dd, 1H), 3.51 (dd, 1H), 4.14 (m, 2H), 4.97 (m, 1H), 7.36 (m, 1H), 7.44 (d, 1H), 7.63 (t, 1H), 7.75 (m, 2H), 7.95 (m, 2H), 8.55 (d, 1H).

Part C. Preparation of 3-(3-cyanophenyl)-5-azidomethyl-isoxazoline

3-(3-Cyanophenyl)-5-(4-methylphenylsulfonyloxy)methylisoxazoline (1.00 g, 2.81 mmol) and sodium azide (0.55 g, 8.42 mmol) are dissolved in 10 mL of DMSO and stirred at RT under N_2 for 72 h. After diluting with water, the mixture was extracted with ethyl acetate, dried with $MgSO_4$, and then the solvent was removed *in vacuo* to give 0.64 g (100%) of the desired compound as a white solid. ^{1}HNMR ($CDCl_3$): d 3.24 (dd, 1H), 3.46 (m, 2H), 3.61 (dd, 1H), 5.00 (m, 1H), 7.56 (t, 1H), 7.67 (d, 1H), 7.95 (m, 2H).

Part D. Preparation of 3-(3-cyanophenyl)-5-aminomethylisoxazoline

3-(3-Cyanophenyl)-5-azidomethylisoxazoline (0.64 g, 2.81 mmol) and 10% palladium on carbon (0.10 g) are added to 50 mL of ethanol and stirred at RT under H_2 for 4 h. The reaction mixture was filtered through celite and then the solvent was removed *in vacuo* to give 0.57 g (100%) of the desired compound as a white solid. ^{1}HNMR ($CDCl_3$): d 2.90 (m, 1H), 3.06 (m, 1H), 3.18 (dd, 1H), 3.36 (dd, 1H), 4.88 (m, 1H), 7.32 (t, 1H), 7.48 (d, 1H), 7.95 (m, 2H).

Part E. Preparation of 3-(3-cyanophenyl)-5-[(2-naphthylsulfonyl)amino]methylisoxazoline

3-(3-Cyanophenyl)-5-aminomethylisoxazoline (0.56 g, 2.81 mmol) was dissolved in 20 mL of DMF and 2-naphthanenesulfonyl chloride (0.68 g, 3.00 mmol) and pyridine (0.48 mL, 6.2 mmol) were added. The reaction mixture was allowed to stir at RT under N_2 for 12h. After diluting with saturated aqueous sodium bicarbonate, the mixture was extracted with ethyl acetate, dried with $MgSO_4$, and then the solvent was removed *in vacuo*. The crude product mixture was chromatographed on silica gel eluted with ethyl acetate/hexane (1:3) to give 0.30 g (27%) of the desired compound as a white solid. ^{1}HNMR (DMSO-d_6): d 3.03 (m, 2H), 3.22 (dd, 1H), 3.49 (dd, 1H), 4.81 (m, 1H), 7.65 (m, 3H), 7.83-8.08 (m, 5H), 8.12 (m, 3H).

Part F. Preparation of 3-(3-amidinophenyl)-5-[(2-naphthylsulfonyl)amino]methylisoxazoline Trifluoroacetic Acid Salt

3-(3-Cyanophenyl)-5-[(2-naphthylsulfonyl)amino]methylisoxazoline (0.30g, 0.77 mmol) was dissolved in 50 mL of MeOH. The reaction mixture was cooled in an ice/salt bath (-5°C), and HCl gas was bubbled-in for 2h. The mixture was sealed, allowed to warm to RT, and stirred for 12h. The solvent was removed *in vacuo* and the resulting solid was dried and used in the next step.

The imidate formed above was added with ammonium carbonate (0.73 g, 7.6 mmol) to 50 mL of methanol. The mixture was sealed and stirred at RT for 12h. The crude benzamidine was purified by HPLC (C18 reverse phase) eluted with 0.5% TFA in H_2O/CH_3CN to give 0.03 g of the benzamidine TFA salt (9.5%). MS 409.3, $(M+H)^+$. ^{1}HNMR (DMSO-d_6): d 3.03 (t, 2H), 3.22-3.58 (m, 2H), 4.82 (m, 1H), 7.67-7.73 (m, 3H), 7.85 (m, 2H), 7.95 (d, 1H), 8.06 (m, 2H), 8.11-8.18 (m, 3H), 9.27 (s, 1H), 9.43 (s, 1H).

Example 3

4-amidinophenyl [3-(3-amidinophenyl)-5-Carbomethoxy-isoxazolin-5-yl]acetamide, Bistrifluoroacetic Acid Salt

Part A. Preparation of N-4-cyanophenyl 3-carboxy-3-butenamide

Itaconic anhydride (0.56 g, 5.0 mmol) and 4-cyanoaniline (0.71 g, 6.0 mmol) were added together with 25 mL of $CHCl_3$. The mixture was stirred at RT under N_2 for 1/2 h. It was then refluxed for 12 h. The mixture was cooled and the solid formed was filtered and dried (1.06 g, 92%). MS 248, $(M+NH_4)^+$.

Part B. Preparation of 4-cyanophenyl [3-(3-cyanophenyl)-5-carboxy-isoxazolin-5-yl]acetamide

N-4-cyanophenyl 3-carboxy-3-butenamide (1.06 g, 4.6 mmol) and 3-cyanobenzaldehyde oxime (0.67 g, 4.6 mmol) were dissolved in 50 mL THF. Bleach (12 mL of 0.67M solution) was added dropwise at RT under N_2. The mixture was stirred at RT for 12 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc. It was then washed with 0.1N HCl and brine, dried over $MgSO_4$ and concentrated to a solid. The solid was washed with CH_2Cl_2 to give 0.81 g off-solid (47%). MS 392, $(M+NH_4)^+$.

Part C. Preparation of 4-amidinophenyl [3-(3-amidinophenyl)-5-Carbometoxy-isoxazolin-5-yl]acetamide, Bistrifluoroacetic Acid Salt

4-cyanophenyl [3-(3-cyanophenyl)-5-carboxy-isoxazolin-5-yl]acetamide (0.30 g, 0.80 mmol) was dissolved in 20 mL of $CHCl_3$ and 10 mL of MeOH. It was cooled in an ice-bath and HCl gas was bubbled-in until the solution was saturated. It was sealed and stirred at RT for 12 h. The solvents were removed in vacuo and the resulting solid was then dried under vacuum. The solid was dissolved in 20 mL of MeOH and ammonium acetate (o.37 g) was added. The reaction mixture was sealed and stirred at RT for 12 h. It was concentrated and then precipitated with ether. the solid was filtered and then purified by HPLC (C18 reversed phased) eluted with 0.5% TFA in H_2O/CH_3CN to give 84 mg of the bisbenzamidine TFA salt (16%). MS 423.2, $(M+H)^+$. ^{1}HNMR (DMSO-d_6): d 3.72 (s, 3H); 3.60-4.09 (m, 4H); 7.70-8.10 (m, 8H); 8.90 (br.s, 1H); 8.95 (br.s, 1H), 9.20 (d, 2H); 9.40 (s, 1H); 10.68 (s, 1H).

Example 4

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline, Trifluoroacetic Acid Salt

Part A. Preparation of 2-(t-butylamino)sulfonylphenylboronic acid

To a solution of 34.0 g (0.16 mol) of benzene-N-(t-butylsulfonamide in 500 mL of THF under N_2 was added 160 mL (0.36 mol) of 2.25M n-butyllithium in hexane over 35 min, keeping the temperature between 0°-2°C. The reaction mixture was allowed to warm to room temperature over 1.5h, during which time a thick precipitate formed. Triisopropylborate (46 mL, 0.20 mol) was added, keeping the temperature below 35°C. After 1h, the reaction mixture was cooled, 1N HCl (260 mL) was added, and the mixture was stirred for 30 min. After diluted with 520 mL of water, the mixture was extracted with 3x400 mL of ether. The combined organic extracts were extracted with 3x250 mL of 1N NaOH. The aqueous extracts were acidified to pH 1 with 6N HCl, and then extracted with 3x250 mL of ether. The ether extracts were washed with 250 mL of brine, dried over $MgSO_4$, and the solvents were removed *in vacuo* to yield 45 g of a thick oil. After addition of Toluene (45 mL), the mixture was agitated for 1h on the rotary evaporator. A small quantity of solid formed, which was used to induce partial solidification of the remaining crude product. Addition toluene (150 mL) was added, and the mixture was reduced to 1/2 volume *in vacuo*, keeping the temperature from 0°-10°C. The resulting precipitate was collected and washed with hexane, then dried under vacuum to give 24.6 g (60%) of the title compound as white crystals. m.p. 118°-119°C.

^{1}HNMR ($CDCl_3$): d 1.18 (s, 9H); 5.13 (s, 1H); 6.29 (br s, 2H); 7.53 (m, 2H); 7.82 (d, 1H); 8.00 (d, 1H).

Part B. Preparation of 2'-t-butylaminosulfonyl-4-nitro-[1,1']-biphenyl

A mixture of 4.4 g (0.020 mol) of 1-bromo-4-nitrobenzene and 5.14 g (0.020 mol) of 2-(t-butylamino)sulfonylphenylboronic acid , 1.16 g of tetrakis(triphenylphosphine) palladium(0) (0.001 mol), 0.32 g of tetrabutylammonium bromide (0.001 mol), and 20 mL of 2M aqueous sodium carbonate were refluxed with 180 mL of benzene under N_2 for 5.5h. After cooling the mixture was diluted with methylene chloride and water. the two phases were separated and organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated. The resulting solid was recrystallized from EtOAc/hexane to afford 3.25 g of the desired biphenyl.(49%). ^{1}HNMR ($CDCl_3$): d 1.07(s, 9H); 3.60 (br s, 2H); 7.29 (d, 1H); 7.59 (m, 2H); 7.69 (d, 2H); 8.20 (d, 2H); 8.30 (d, 2H).

Part C. Preparation of 1-Bromo-4-t-butoxycarbonylaminobenzene

To a mixture of NaH (4.13, 0.14 mol) in THF was added 4-bromoaniline. The resulting mixture was refluxed under N_2 for 1h. It was then cooled and di-t-butyl dicarbonate (33 g, 0.15 mol) was added. After stirred for 1/2h, more NaH (4.13 g, 0.14 mol) was added and the reaction mixture was refluxed under N_2 overnight. The reaction mixture was cooled and carefully quenched with water. The mixture was extracted with ether. The combined organic solution was washed with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. It was then purified by chromatography on silica gel eluted with hexane to yield 27.2 g of the desired product (80%). ^{1}HNMR ($CDCl_3$): d 1.52 (s, 9H); 6.48 (br s, 1H); 7.27 (d, 2H); 7.40 (d, 2H).

Part D. Preparation of 2'-t-butylaminosulfonyl-4-amino-[1,1']-biphenyl

Method A:

A suspension of 3.00 g (0.009 mol) of 2'-t-butylaminosulfonyl-4-nitro-[1,1']-biphenyl and 0,30 g of 10% Pd/C in 90 mL of methanol was stirred at room temperature under $H_{2\ (gas)}$ (1 atm) for 1/2h. The solubility of the starting material was very poor in methanol, so 60 mL of ethyl acetate was added and the mixture was stirred for 4h. The reaction mixture was filtered through celite and the filtrate was concentrated. The crude product was recrystallized from benzene/hexane to give 2.32 g (85%) of the aniline. ^{1}HNMR ($CDCl_3$): d 0.99 (s, 9H); 3.72 (br s, 1H);3.83 (br s, 2H); 6.76 (d, 1H); 7.27 (d, 1H); 7.33 (d, 2H); 7.43 (t, 1H); 7.53 (t, 1H); 8.14 (d, 1H). MS m/e 305 $(M+H)^+$.

Method B:

A mixture of 12.8 g (0.047 mol) of 1-Bromo-4-t-butoxycarbonylaminobenzene and 12.3 g (0.048 mol) of 2-(t-butylamino)sulfonylphenylboronic acid , 3.0 g of tetrakis(triphenylphosphine) palladium(0) (0.0026 mol), 0.80 g of tetrabutylammonium bromide (0.0024 mol), and 13.8 g (0.10 mol, in 30 ml of water) potassium carbonate were refluxed with 300 mL of toluene under N_2 for 6h. The toluene was removed in vacuo and the residue was dissolved in methylene chloride and water. The two phases were separated and organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated. the crude product was purified by chromatography on silica gel eluted with EtOAc/hexane (1:3) to afford 12.66 g of the desired biphenyl.(67%).

The protected aminobiphenyl compound (2.80 g, 6.9 mmol) was stirred with 10 mL of triflouroacetic acid and 20 mL of methylene chloride at room temperature for 2h. The solvents were removed *in vacuo*. The residue was dissolved in methylene chloride and precipitated with hexane to give 1.20 g of the desired product as the TFA salt. ^{1}HNMR (DMSO-d_6): d 1.01(s, 9H); 6.80 (s, 1H); 7.20-7.68 (m, 8H);8.03 (d, 1H).

Part E. Preparation of 3-(3-cyanophenyl)-5-N-[2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline

3-(3-cyanophenyl)-5-carbomethoxy methyl-isoxazolin-5-ylcarboxylic acid (0.50 g, 1.73 mmol) was refluxed with 10 mL of acetonitrile and 0.76 mL (10.4 mmol) of thionyl chloride for 1h under N_2. The solvent was removed in vacuo. Residual thionyl chloride was removed by adding toluene and then evaporating to dryness. The resulting solid was dissolved in 20 mL of THF and 2'-t-butylaminosulfonyl-4-amino-[1,1']-biphenyl, TFA salt (0.60 g, 1.40 mmol) was added followed by triethylamine (1.5 mL, 10.4 mmol). The reaction mixture was stirred at RT and the reaction was completed in less than 30 min. The mixture was diluted with ethyl acetate and the solution was washed with water and brine. It was dried over $MgSO_4$ and concentrated. The crude product mixture was chromatographed on silica gel eluted with methylene chloride/ethyl acetate (9:1) to give 0.57 g of the desired product (71%). MS 575.2, $(M+H)^+$. ^{1}HNMR ($CDCl_3$): d 0.95 (s, 9H); 3.03 (d, 1H); 3.27 (d, 1H);3.60 (d, 1H); 3.66 (s, 3H); 3.78 (d, 1H); 7.19 (d, 1H); 7.39-7.71 (m, 8H); 7.83 (d, 1H); 7.92 (s, 1H); 8.09 (d, 1H); 8.68 (s, 1H).

Part F. Preparation of 3-(3-cyanophenyl)-5-N-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline

3-(3-Cyanophenyl)-5-N-[2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline (1.12 g, 1.95 mmol) was refluxed with 25 ml of trifluoroacetic acid under N_2 for 1/2h. The TFA was removed in vacuo, the residue was dissolved in methylene chloride and then precipitated with ether to give 1.0 g of white solid (99%). MS 519.2, $(M+H)^+$. ^{1}HNMR ($CDCl_3$): d 3.14 (d, 1H); 3.40 (d, 1H); 3.76 (s, 3H); 3.85 (dd, 2H); 4.40 (br s, 2H); 7.35 (d, 1H); 7.48-7.80 (m, 8H); 7.83 (d, 1H); 8.01 (s, 1H); 8.18 (d, 1H); 8.82 (s, 1H).

Part G. Preparation of 3-(3-amidinophenyl)-5-N-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline, Trifluoroacetic Acid Salt

3-(3-Cyanophenyl)-5-N-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline (1.2 g, 1.93 mmol) was dissolved in 90 mL of $CHCl_3$ and 20 mL of MeOH. The reaction mixture was cooled in an ice-bath, and HCl gas was bubbled-in for 30 min until the solution was saturated. The mixture was sealed and placed at 0°C for 12h. The solvents were removed in vacuo and the resulting solid was dried and used in the next step.

The imidate formed above was added with 0.92 g (12.0 mmol) of ammonium acetate and 30 mL of methanol. The mixture was sealed and stirred at RT for 12h. The crude benzamidine was purified by HPLC (C18 reversed phased) eluted with 0.5% TFA in H_2O/CH_3CN to give o.47 g of the benzamidine TFA salt (37%). MS 536.4, $(M+H)^+$. ^{1}HNMR

(DMSO-d_6): d 3.20 (m, 2H); 3.48 (s, 3H); 3.70-4.01(m, 2H); 7.20-7.32 (m, 4H); 7.52 (m, 2H); 7.72 (d, 2H); 7.88 (d, 1H); 7.98 (d, 1H); 8.05 (d, 1H); 8.07 (s, 1H); 9.24 (s, 2H); 9.40 (s, 2H); 10.05 (s, 1H).

Example 5 and Example 6

3-(3-amidinophenyl)-5-[[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)-methyl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline, trifluoroacetic acid salt **(Ex.5)**

3-(3-amidinophenyl)-7-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)methyl[1-oxa-2,7-diazaspiro[4,4]non-2-ene-6,8-diones,trifluoroacetic acid salt **(Ex.6)**

Part A. Preparation of 2'-t-butylaminosulfonyl-4-aminomethyl-[1,1']-biphenyl

2'-t-butylaminosulfonyl-4-methyl-[1,1']-biphenyl (prepared by the same method described in Part B of Exaple 1) (1.57 g, 5.18 mmol) was refluxed with N-bromosuccinamide (0.92 g, 5.18 mmol) and AIBN (0.10 g) in 50 mL of CCl_4 for 2h. The mixture was cooled and the precipitae was filtered-off. The filtrate was concentrated to an off-white solid. The resulting solid was dissovled in 20 mL of DMF and sodium azide (0.67 g, 10.3 mmol) was added. the mixture was heated to 100 °C for 6 h under N_2. The reaction mixture was cooled and pourted into water. It was extracted with EtOAc. The combined organic solution was washed with brine and dried over $MgSO_4$. It was the concentrated to a white solid. this solid was the added together with 0.2 g of Pd(OH), 0.5 mL of concentrated HCl, and 100 mL of MeOH. The mixture was placed under balloon H_2 for 5 h. The resulting mixture was filtered through celite and washed with MeOH. The filtrate was concentrated and precipitated with Et_2O to give 1.32 g of white solid (72 %). MS (DCI) 336 $(M+NH_4)^+$, 319 $(M+H)^+$.

Part B. Preparation of 3-(3-cyanophenyl)-5-N-[2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-methyl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline

This compound was prepared by the same method described in Part G of Example 4 using 2'-t-butylaminosulfonyl-4-aminomethyl-[1,1']-biphenyl and 3-(3-cyanophenyl)-5-carbomethoxy methyl-isoxazolin-5-ylcarboxylic acid as the starting materials. MS (DCI) 606 $(M+NH_4)^+$.

Part C. Preparation of 3-(3-amidinophenyl)-5-[[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)-methyl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline, trifluoroacetic acid salt (**EX 5**) and 3-(3-amidinophenyl)-7-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)methyl[1-oxa-2,7-diazaspiro[4,4]non-2-ene-6,8-diones,trifluoroacetic acid salt (**EX 6**).

3-(3-cyanophenyl)-5-N-[2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-methyl]aminocarbonyl-5-carbomethoxy methyl-isoxazoline was subjected to the Pinner - amidine reaction protocol described in Part D of Example 1. The crude product mixture was purified by HPLC (C18 reversed phased) eluted with 0.5 % TFA in H_2O and CH_3CN to give Compounds Ex 5 and Ex 6 as the TFA salts. Ex 5: MS (ESI) 518.4, $(M+H)^+$. Ex 6 : MS (ESI) 550.4, $(M+H)^+$.

Example 7

3-(3-amidinophenyl)-5-[(4-benzenesulfonylphenyl-1-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline, trifluoroacetic acid salt

Part A: Preparation of 4-aminodiphenylsulphone

To a suspension of 4-nitrodiphenylsulphone (1.00 g, 3.80 mmol) and Pd-C (61.6 mg, 5%) in MeOH (50 mL) was added 3N aqueous HCl (1.30 mL, 3.90 mmol). The mixture was placed under H_2 at 50 psi for 4h. It was filtered through celite and washed with MeOH. The filtrate was concentrated and preticipated with ether to give 0.79 g of pale orange solid (77%). MS 234.1, $(M+H)^+$. ^{1}HNMR (DMSO-d_6): d 6.61 (d, 2H); 6.85 (br. s, 2H); 7.55 (m, 5H), 7.81 (d, 2H).

Part B: Preparation of 3-(3-cyanophenyl)-5-[(4-benzenesulfonylphenyl-1-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

This compound was prepared by the method described in Part C of Example 1 using 3-(3-cyanophenyl)-5-carbomethoxy methyl-isoxazolin-5-ylcarboxylic acid and 4-aminodiphenylsulphone as starting materails. MS 504.2, $(M+H)^+$. ^{1}HNMR ($CDCl_3$): d 3.02-3.34 (m, 2H), 3.69 (s, 3H); 3.78 (m, 2H), 7.48 (t, 3H); 7.52 (t, 1H), 7.75 (d, 3H); 7.90 (m, 6H); 8.78 (br.s, 1H).

Part B: Preparation of 3-(3-amidinophenyl)-5-[(4-benzenesulfonylphenyl-1-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline, trifluoroacetic acid

This compound was prepared as described in Part D of Example 1. MS 521.2, $(M+H)^+$.

Example 8

3-(3-amidinophenyl)-5-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline, Trifluoroacetic Acid Salt

Part A. Preparation of 3-(3-cyanophenyl)-5-Carbomethoxy-5-(tetrazol-1-yl)methyl-isoxazoline

1*H*-Tetrazole(0.89 g, 14.0 mmol) and K_2CO_3 were added together with 50 mL of DMF. Methyl 2-(bromomethyl)acrylate (2.5 g, 14.0 mmol) was added. The mixture was stirred at room temperature under N_2 for 12h. The mixture was poured into water and extracted with EtOAc. The combined organic solution was washed with brine, dried over $MgSO_4$, and then concentrated to give 1.63 g of methyl 2-(tetrazolemethyl)acrylate. This crude product mixtre was added together with 3-cyanobenzaldehyde oxime prepared as described in Example 1 (1.42 g, 9.69 mmol) and THF (50 mL). To the above mixture was added dropwise bleach (25 mL of 0.67M solution). The resulting mixture was stirred at room temperature under N_2 for 3h. The THF was removed. The mixture was diluted with water and extracted with EtOAc. The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. It was purified by chromatography (silica gel, 5-15% EtOAc in CH_2Cl_2) to give 1.61 g of the desired product and 0.50 g of the regioisomer 3-(3-cyanophenyl)-5-Carbomethoxy-5-(tetrazol-2-yl)methyl-isoxazoline. ^{1}HNMR (DMSO-d_6): δ3.78 (s, 3H); 3.80-4.10 (q, 2H); 5.09-5.20 (q, 2H); 7.68 (t, 1H); 7.98 (d, 1H); 8.07 (s, 1H); 9.45 (s, 1H). MS(ES$^+$) 313.1 $(M+H)^+$.

Part B. Preparation of 3-(3-cyanophenyl)-5-Carboxylic acid-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-Cyanophenyl)-5-Carbomethoxy-5-(tetrazol-1-yl-methyl)-isoxazoline (1.60 g, 5.12 mmol) was added together with 75 mL of THF. LiOH (12 mL of 0.5 M aqueous solution) was added. The mixture was stirred at room temperature under N_2 for 1h. The THF was removed.

The mixture was diluted with water and acidified with concentrated HCl. It was extracted with EtOAc. The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated to a white solid (1.54 g). ^{1}HNMR (DMSO-d_6): δ 3.70-4.02 (q, 2H); 5.02-5.18 (q, 2H); 7.67 (t, 1H); 7.97 (d, 1H); 8.04 (s, 1H); 9.42 (s, 1H). MS(ES$^+$) 299 (M+H)$^+$.

Part C. Preparation of 3-(3-cyanophenyl)-5-[2'-t-Butylaminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-Cyanophenyl)-5-Carboxylic acid-5-(tetrazol-1-yl)methyl-isoxazoline (0.55 g, 1.84 mmol) was refluxed with CH_3CN (20 mL) and $SOCl_2$ (1.34 mL, 18.4 mmol) under N_2 for 1h. The solvent was removed. Residual $SOCl_2$ was removed by dissolving in toluene and then removing the solvent to dryness. The resulting solid was dissolved in CH_2Cl_2 (20 mL). 2'-t-Butylaminosulfonyl-4-amino-[1,1']-biphenyl prepared as described in Example 4 (0.28 g, 0.92 mmol) was added followed by Et_3N (1.5 mL, 18.4 mmol). The mixture was stirred at room temperature under N_2 for 1/2 h. It was diluted with CH_2Cl_2 and washed with water and brine. It was dried over $MgSO_4$ and concentrated. The desired product was the purified by chromatography (silica gel, 20% EtOAc in CH_2Cl_2) to give 0.59 g off-white solid. ^{1}HNMR (DMSO-d_6): δ1.01 (s, 9H); 3.90-4.10 (q, 2H); 5.08-5.16 (q, 2H); 6.70 (s, 1H), 7.24-7.38 (m, 3H), 7.50-7.77(m, 5H), 7.98-8,03 (m, 3H); 8.12 (s, 1H); 9.42 (s, 1H). MS(ES$^+$) 585.2 (M+H)$^+$.

Part D. Preparation of 3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline, Trifluoroacetic Acid Salt

3-(3-Cyanophenyl)-5-[2'-t-Butylaminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline (0.41 g, 0.70 mmol) was dissolved in anhydrous $CHCl_3$ (20 mL) and anhydrous CH_3OH (5 mL). HCl gas was bubbled-in until the solution was saturated (about 15 min). The reaction mixture was sealed and placed in a refrigerator for 12 h. The solvents were removed. The resulting solid was dried under vacuum. The imidate formed above was dissolved in 20 mL of anhydrous CH_3OH. Ammonium acetate (0.55 g, 7.0 mmol) was added. The mixture was sealed and stirred at room temperature for 12 h. The solvent was removed. The solid was dissolved in CH_3CN/H_2O/TFA, and purifed by reversed phase HPLC (C_{18} reversed phase column, 0.5% TFA in H_2O/CH_3CN) to give the desired TFA salt (0.15 g). ^{1}HNMR (DMSO-d_6): δ3.89-4.16 (q, 2H); 5.13-5.31 (q, 2H); 7.22-7.48 (m, 5H), 7.52-7.78(m, 5H), 7.91 (d, 1H); 8.00-8,08 (m, 3H); 9.12 (s, 2H); 9.41 (s, 2H); 9.43 (s, 1H). MS(ES$^+$) 546.3 $(M+H)^+$.

Example 9

3-(3-amidinophenyl)-5-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)oxymethyl-5-ethoxymethyl-isoxazoline, Trifluoroacetic Acid Salt

Part A. Preparation of 3-(3-cyanophenyl)-5-ethoxymethyl-5-(4-bromophenoxy)methyl-isoxazoline

Sodium hydride (0.74 g of 60% oil dispersion, 18.4 mmol) was washed with Petrolium ether and then suspended in 50 mL of THF. To it was added 4-bromophenol (2.89 g, 16.7 mmol). The mixture was stirred at room temperature for 15 min, and methyl 2-(bromomethyl)acrylate (2.99 g, 16.7 mmol) was added. The mixture was stirred at room temperature under N_2 for 12 h. The reaction was quenched with ethanol and the solvents were removed. The resulting material was dissovled in EtOAc and washed with water and brine. It was dried over $MgSO_4$ and concentrated to 3.93 g of methyl 2-[(4-bromophenoxy)methyl]acrylate.

Methyl 2-[(4-bromophenoxy)methyl]acrylate (2.01 g, 7.4 mmol) was dissolved in 50 mL of THF. The mixture was cooled at -78°C under N_2 and DIDAL-H (12.3 mL, 18.5 mmol) was added. The mixture was stirred for 1 h at -78°C and 1 h at -20°C, and then quenched carefully with ethanol and the solvents were removed. The resulting material was dissovled in EtOAc and washed with water and brine. It was dried over $MgSO_4$ and concentrated. Column chromatography on silica gel (4:1 hexane/EtOAc) gave 0.21 g of corresponding alcohol.

Sodium hydride (0.11 g of 60% oil dispersion, 4.4 mmol) was washed with Petrolium ether and then suspended in 30 mL of THF. The mixture was stirred at room temperature for 15 min, and ethyl iodide (0.62 g, 4.0 mmol) was added. The mixture was refluxed under N_2 for 12 h. The reaction was quenched with ethanol and the solvents were removed. The resulting material was dissovled in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, chromatographed on silica gel (4:1 hexane/EtOAc) to give 0.38 g of 2-[(4-bromophenoxy)methyl]-2-(ethoxymethyl)alkene.

2-[(4-Bromophenoxy)methyl]-2-(ethoxymethyl)alkene (0.38 g, 1.4 mmol) and 3-cyanobenzaldehyde oxime prepared as described in Example 1 (0.21 g, 1.4 mmol) were dissolved in THF (10 mL). Clorox bleach (3.6 mL of o.67M) was added dropwise. The mixture was stirred at room temperature under N_2 for 12 h. It was diluted with EtOAc and washed with brine. The organic mixture was dried over $MgSO_4$, concentrated, and recrystalized from EtOAc/hexane to give 0.48 g of 3-(3-cyanophenyl)-5-ethoxymethyl-5-(4-bromophenoxy)methyl-isoxazoline.

Part B. Preparation of 3-(3-cyanophenyl)-5-[2'-t-Butylaminosulfonyl-[1,1']-biphenyl-4-yl]oxymethyl-5-ethoxymethyl-isoxazoline

3-(3-Cyanophenyl)-5-ethoxymethyl-5-(4-bromophenoxy)methyl-isoxazoline (0.48 g, 1.15 mmol), 2-(t-butylaminosulfonylphenyl boronic acid prepared as described in Example 4 (0.38 g, 1.49 mmol), tetrabutyl ammonium bromide (0.062 g, 0.054 mmol), sodium carbonate (0.36 g, 3.4 mmol), water (3.0 mL), and benzene (50 mL) were added. Nitrogen gas was bubbled through the mixture for 5 min and tetrakis(triphenylphosphine)palladium was added. The mixture was refluxed under N_2 for 12 h. The solvents were removed. The resulting material was dissovled in EtOAc and washed with water and brine. It was dried over $MgSO_4$, concentrated, chromatographed on silica gel (3:1 hexane/EtOAc) to give 0.18 g of the desired product. ^{1}HNMR ($CDCl_3$): δ 1.00 (s, 9H); 1.21(t, 3H); 3.43 (m, 2H); 3.73-3.80 (m, 5H); 4.20 (m, 2H); 7.00 (d, 2H); 7.27 (d, 1H); 7.42 (d, 2H); 7.46-7.58 (m, 3H); 7.71 (d, 1H); 7.98 (m, 2H); 8.15 (d, 1H).

Part C. Preparation of 3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]oxymethyl-5-ethoxymethyl-isoxazoline, trifluoroacetic acid salt.

3-(3-Cyanophenyl)-5-[2'-t-Butylaminosulfonyl-[1,1']-biphenyl-4-yl]oxymethyl-5-ethoxymethyl-isoxazoline (0.18 g, 0.32 mmol) was dissolved in 50 mL of anhydrous methanol. It was cooled to -20°C and HCl gas was bubbled in until the solution was saturated. The mixture was sealed and allowed to stand at 0°C for 12h. The solvent was removed and the solid was dried under vacuum. The resulting solid was dissolved in 50 mL of anhydrous methanol, and ammonium carbonate (0.15 g, 1.6 mmol) was added. The mixture was stirred for 48 h. The solvent was removed. The solid was purified by by reversed phase HPLC (C_{18} reversed phase column, 0.5% TFA in H_2O/CH_3CN) to give 0.13 g of the desired TFA salt (0.15 g). ^{1}HNMR (DMSO-d_6): δ 1.09 (s, 3H); 3.40-3.58 (m, 4H); 3.68 (q, 2H); 4.17 (q, 2H);6.93 (d 2H); 7.15 (s, 2H); 7.28(m, 3H), 7.46-7.59(m, 2H), 7.68 (t, 1H); 7.83 (d, 1H); 7.82-8.10 (m, 3H); 9.30 (s, 2H); 9.39 (s, 2H). MS(ES$^+$) 509.4 $(M+H)^+$.

Example 10 and Example 11

3-(3-amidinophenyl)-4-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-methyl-isoxazoline, Trifluoroacetic Acid Salt

3-(3-amidinophenyl)-5-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-4-methyl-isoxazoline, Trifluoroacetic Acid Salt

Part A. Preparation of 3-(3-cyanophenyl)-5-Carbomethoxy-4-methyl-isoxazoline and 3-(3-cyanophenyl)-4-Carbomethoxy-5-methyl-isoxazoline

To a dichloromethane (100mL) solution of 3-cyanophenyl-oximinochloride (2.30 g, 13.65 mmol) and methyl crotonate (1.71 g, 17.05 mmol) was added triethylamine (1.39 g, 13.65 mmol) in dichloromethane (5mL) dropwise over 0.5 h. The reaction mixture was stirred at room temperature for 12 h. It was then concentrated to a viscous oil. Chromatography (silica gel, hexane : ethyl acetate 8:2) afforded the desired 4-methylcarboxylate-isoxazoline (0.82g, 25% yield) as a colorless oil. ^{1}HNMR($CDCl_3$) δ 1.47 (d, J = 9Hz, 3H), 3.77 (s, 3H), 4.09 (d, J = 4.2Hz, 1H), 5.15 (m, 1H), 7.54 (t, 1H), 7.68 (d, J = 7.8Hz, 2H), 7.94 (d, J = 8Hz, 2H). MS(ESI) 245, $(M+H)^+$. The 5-methylcarboxylate isoxazoline was also obtained (0.53g, 16% yield) as a colorless oil. ^{1}HNMR(CDCl$_3$) δ 1.42 (d, J = 8.5Hz, 3H), 3.81 (s, 3H), 3.96 (m, 1H), 4.83 (d, J = 4.5Hz, 1H), 7.55 (t, 1H), 7.70 (d, J = 8.0Hz, 2H), 7.95 (d, J = 7.9Hz, 2H). MS(ESI) 245, (M+H)$^+$.

Part B. Preparation of 3-(3-cyanophenyl)-4-Carboxylic acid-5-methyl-isoxazoline

The 4-isoxazoline ester was then carefully hydrolyzed (LiOH, 1eq.) in THF:water (4:1, 20 mL) to the carboxylic acid (0.75g, 97% yield). ^{1}HNMR(CDCl$_3$) δ 1.50 (d, J = 8Hz, 3H), 4.07 (d, J = 7 Hz, 1H), 5.18, (m, 1H), 7.50 (t, 1H), 7.68 (d, J = 8Hz, 2H), 7.97 (d, J = 8Hz, 2H). MS(ESI) 231 (M+H)$^+$.

Part C. Preparation of 3-(3-cyanophenyl)-4-(2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-methyl-isoxazoline

Treatment of the acid from Part C with oxalyl chloride (1eq) in dichloromethane followed by addition of a drop of DMF. Reaction mixture was stirred at room temperature for 1.5h and then concentrated to a yelloow oil. This was then redissolved in dichloromethane followed by treatment with 2'-t-Butylaminosulfonyl-4-amino-[1,1']-biphenyl prepared as described in Example 4 (1 eq) and triethyl amine (3 eq.). The reaction mixture was stirred at room temperature overnight The reaction mixture was poured into water (100mL) and then extracted with ethyl acetate (2X100mL), It was washed with brine (50mL) and dried (magnesium sulfate). Evaporation of the solvent afforded crude amide which was purified (column chromatography, silica gel CH$_2$Cl$_2$:MeOH, 9:1) to give 0.35 g (20% yield) colorless oil. ^{1}HNMR(CDCl$_3$) δ 1.01 (s, 9H), 1.52 (d, J = 6.5Hz, 3H), 3.70 (s, 1H), 4.18 (d, J = 5.4Hz, 1H), 5.18 (m, 1H), 7.27 (dd, J = 3 and 8Hz, 1H), 7.43-7.54 (m, 7H), 7.68 (d, J = 8.5Hz, 1H), 8.03 (ds, 2H), 8.17 (sd, 2H). MS (DCI-NH_3) 534 $(M+NH_4)^+$.

Part D. Preparation of 3-(3-amidinophenyl)-4-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-methyl-isoxazoline

The nitrile obtained in Part D was then subjected to the Pinner - amidine reaction protocol described previously to afford 0.15g (colorless crystals) of the desired benzamidine compound after reversed phase HPLC purification. ^{1}HNMR(DMSO d_6) δ 1.44 (d, J = 7.5Hz, 3H), 4.53 (d, J = 6Hz, 1H), 5.02 (m, 1H), 7.27-7.38 (m, 5H), 7.55-7.63 (m, 3H), 7.70 (t, 1H0, 7.80 (d, J = 8.5Hz, 1H), 7.91 (d, J = 8.2hz, 1H), 8.00 (dd, J = 1.8 and 7.9Hz, 1H), 9.10 (bs, 2H), 9.44 (bs, 2H), 10.30 (s, 1H). MS (ESI) 478.3, $(M+H)^+$.

Part E. Preparation of 3-(3-amidinophenyl)-5-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-4-methyl-isoxazoline

This compound was obtained by the same procedure described above using 3-(3-cyanophenyl)-4-Carbomethoxy-5-methyl-isoxazoline as starting material. ^{1}HNMR(DMSO d_6) δ 1.38 (d, J = 7.7Hz, 3H), 4.31 (m, 1H), 5.08 (d, J = 5.4Hz, 1H), 7.23-7.38 (m, 5H), 7.55-7.66 (m, 2H), 7.69-7.70 (m, 2H), 7.88 (d, j = 8Hz, 1H), 8.00 (d, j = 8 Hz, 1H), 8.10 (ds, 2H), 9.20 (bs, 2H0, 9.40 (bs, 2H), 10.3 (s, 1H). MS(ESI) 478.4, $(M+H)^+$.

Example 12

3-(3-amidinophenyl)-5-[(4-(2'-nitrophenoxy))phenyl-1-yl]aminocarbonyl-5-methyl-isoxazoline, Trifluoroacetic Acid Salt

Part A. Preparation of 4-(2'-nitrophenoxy)aniline

To a stirred DMF (10 mL) solution of p-aminophenol (0.89 g, 8.16 mmol) was added anhydrous potassium carbonate (6.76 g, 48.96 mmol). The reaction mixture was stirred at room temperature for 1h and then 2-fluoronitrobenzene (1.152 g, 8.16 mmol) aws added. The reddish brown solution was refluxed for 24h. The reaction mixture was cooled and then quenched with water (200mL). It was extracted with EtOAc, washed with brine(50mL), and dried with magnesium sulfate. Evaporation of the solvent provided a crude material which was purified via column chromatography (silica gel 9 : 1, hexane : ethyl acetate) to a colorless oil 1.10 g (58% yield); ^{1}HNMR($CDCl_3$) δ 3.60 (bs, 2H), 6.65 (d, J = 8.2Hz, 2H), 6.88 (d, J = 8.0Hz, 2H), 7.06 (t, 1H), 7.40 (t, 1H), 7.98 (d, J = 8.0Hz, 1H). MS ($DCI-NH_3$) 248 ($M+NH_4$, 100).

Part B. Preparation of 3-(3-amidinophenyl)-5-[(4-(2'-nitrophenoxy))phenyl-1-yl]aminocarbonyl-5-methyl-isoxazoline

3-(3-Cyanophenyl)-5-carboxylic acid-5-methyl-isoxazoline prepared by the same procedures described above aws coupled to 4-(2-nitrophenoxy)aniline from Part A as previously described. The resulting product was subjected to standard Pinner reaction to give the desired amidine. ^{1}HNMR(DMSO d_6) δ 7.74 (s, 3H), 3.48 (d, J = 19Hz, 1H), 4.04 (d, J = 19Hz, 1H), 7.04 (dd, J = 2.5 and 8Hz, 3H), 7.33 (t, 1H), 7.64-7.77 (m, 3H), 7.78 (d, J = 8.5Hz, 1H), 7.87 (d, J = 7.5Hz, 1H), 8.03 (t, 3H), 9.20 (bs, 2H), 9.41 (bs, 2H), 10.2(s, 1H). MS(ESI) 460.2, (M+H, 100).

Example 13

3-(3-amidinophenyl)-5-(3-[NN-ethyl(pyrid-2-yl-methyl)]aminophenyl-1-yl)aminocarbonyl-5-methyl-isoxazoline, Trifluoroacetic Acid Salt

Part A. Preparation of 3-[NN-ethyl(pyrid-2-yl-methyl)]aniline

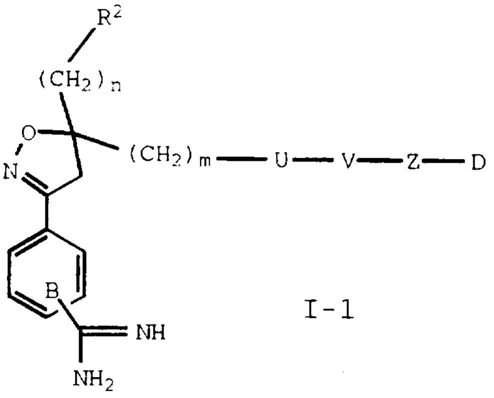
The title compound was prepared in three step sequence via a sequential reductive amination of 3-nitroaniline with 2-pyridine carboxaldehyde and acetaldehyde with sodium cycanoborohydride in methanol, followed by catalytic (Pd/C) hydrogenation in 29% overall yield. ^{1}HNMR(CDCl$_3$) δ 1.30 (t, 3H), 3.60 (q, 2H), 4.70 (s, 2H), 6.91 (dd, 1H), 7.05-7.30 (m, 3H), 7.50 (m, 2H), 7.65 (t, 1H), 8.60 (d, 1H). MS(ESI) 258, (M+H, 100).

Part B. Preparation of 3-(3-amidinophenyl)-5-(3-[NN-ethyl(pyrid-2-yl-methyl)]aminophenyl-1-yl)aminocarbonyl-5-methyl-isoxazoline, Trifluoroacetic Acid Salt

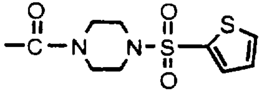
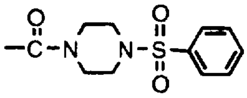
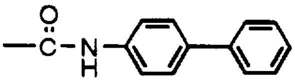
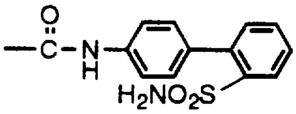
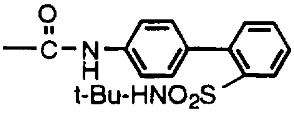
3-(3-Cyanophenyl)-5-carboxylic acid-5-methyl-isoxazoline prepared by the same procedures described above was coupled to 3-[NN-ethyl(pyrid-2-yl-methyl)]aniline from Part A as previously described. The resulting product was subjected standard Pinner reaction to give the desired amidine. ^{1}HNMR(DMSO d$_6$) δ 1.12 (t, 3H), 1.70 (s, 3H), 3.40 (-3.49(dm, J = 19.6Hz, 3H), 4.00 (d, J = 19.6 Hz, 1H), 4.60 (s, 2H), 6.34 (dd, J = 2.5 and 8Hz, 1H), 6.99 (t, 1H), 7.04 (d, J = 8.6Hz, 1H), 7.19 (s, 1H), 7.40 (d, J = 8.4Hz, 1H), 7.36 (m, 1H), 7.70 (t, 1H), 7.80 (m, 2H), 8.05 (ds, 2H), 8.58 (d, J = 4.4Hz, 1H), 9.06 (bs, 2H), 9.40 (bs, 2H), 9.80 (s, 1H). High resolution mass spectrum calcd. for $C_{26}H_{29}N_6O_2$ 457.235199, found 457.233965.

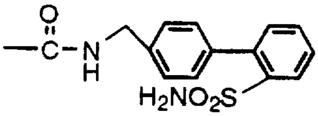
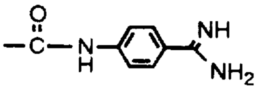
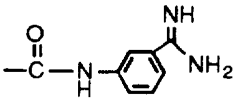
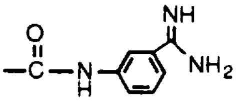
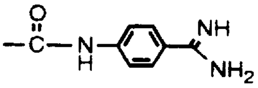
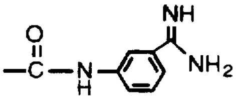
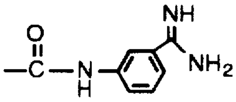
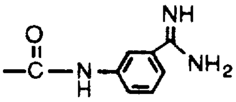
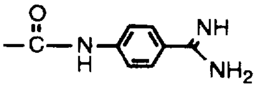
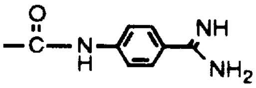
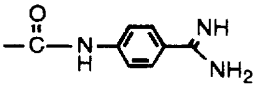
The compounds of Tables 1-6 were prepared by the methods of Examples 1-13. The compounds in Tables 1-6 which have asymmetric centers are racemates except where indicated otherwise by (+) or (-) in the column headed o.r. (for optical rotation) in Table 2.

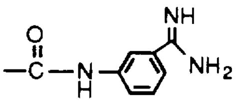
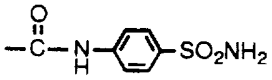
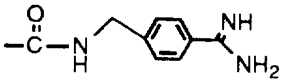
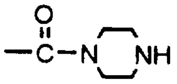
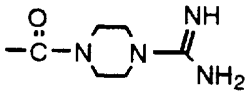
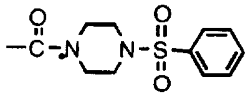
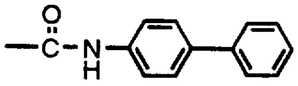
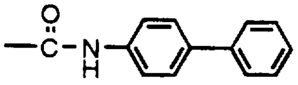
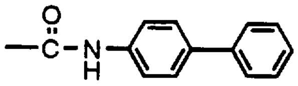
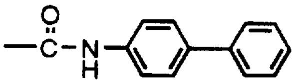
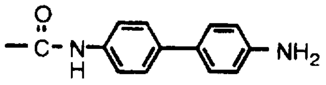
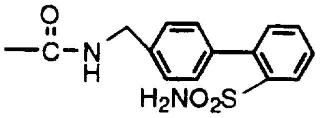
TABLE 1

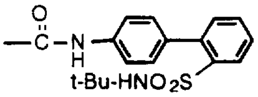
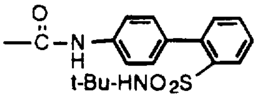
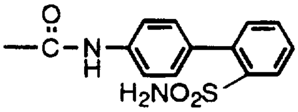
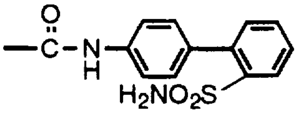
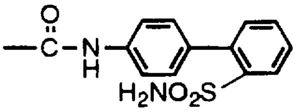
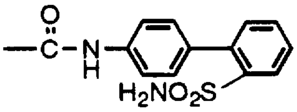
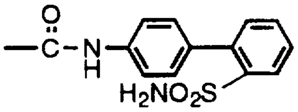
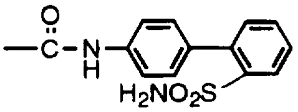
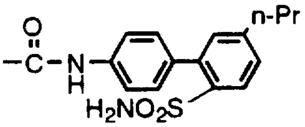
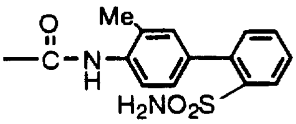


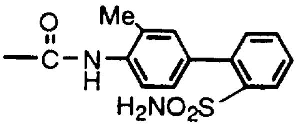
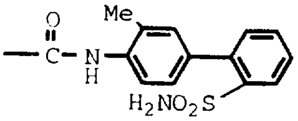
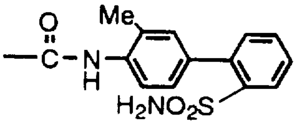
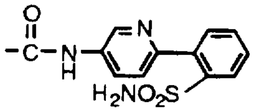
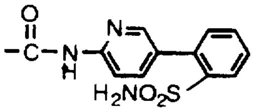
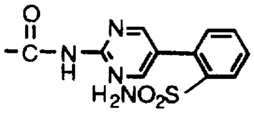
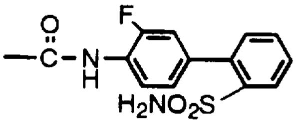
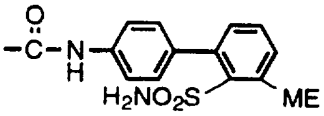
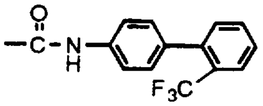
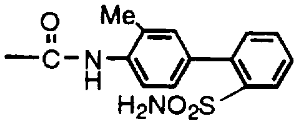
I-1

EX#	B	m	$(CH_2)_nR^2$	-U-V-Z-D	MS $(M+H)^+$
14	*p*	1	H		462
15	*p*	1	H		456
16	*p*	1	H		399.0
17	*p*	1	H		478.3
18	*p*	1	H		534.3

19	*p*	1	H		492.0
20	*p*	1	H		365.2
21	*p*	1	H		365.3
22	*m*	1	H		365.3
23	*m*	1	H		365.3
24	*p*	1	$CONH_2$		408.2
25	*m*	0	CH_2CO_2Me		423.3
26	*m*	0	CH_2CO_2H		409.2
27	*m*	0	H		351.3
28	*m*	0	$CH_2CONHCH_2CO_2Me$		480.5
29	*m*	0	CH_2CO_2H		409.3

30	*p*	0	CO_2Me		423.3
31	*m*	0	CH_2CO_2Me		460.3
32	*m*	0	CH_2CO_2Me		219.2 $(M+2H)^{2+}$
33	*m*	0	CH_2CO_2Me		374.2
34	*m*	0	CH_2CO_2Me		416.4
359	*m*	0	CH_2CO_2Me		514.3
36	*m*	0	CH_2CO_2Me		457.4
37	*m*	0	CH_2CO_2H		443.4
38	*m*	0	CH_2CONH_2		442.4
39	*m*	0	CH_2CH_2OH		429.3
40	*m*	0	CH_2CO_2Me		236.8 $(M+2H)^{2+}$
41	*m*	0	CH_2CONH_2		535.4

42	*m*	0	CH_2CO_2Me		592.5
43	*m*	0	CH_2CONH_2		577.5
44	*m*	0	CH_2CO_2H		522.4
45	*m*	0	CH_2CONH_2		521.4
46	*m*	0	CH_2CH_2OH		508.2
47	*m*	0	CH_2CH_2OMe		
48	*m*	0	$CH_2CONHCH_2CO_2Me$		593.3
49	*m*	0	$CH_2CONH(CH_2)_2$-4-imidazole		308.2 $(M+2H)^{2+}$
50	*m*	0	CH_2CO_2Me		578.3
51	*m*	0	CH_2CO_2Me		550.3

52	*m*	0	CH_2CO_2H		536.5
53	*m*	0	CH_2CONH_2		535.3
54	*m*	0	$CH_2CONHCH_2CO_2Me$		607.3
55	*m*	0	CH_2CO_2Me		537.2
56	*m*	0	CH_2CO_2Me		537.2
57	*m*	0	CH_2CO_2Me		538.2
58	*m*	0	CH_2CO_2Me		554.2
59	*m*	0	CH_2CO_2Me		
60	*m*	0	CH_2CO_2Me		525.3
61	*m*	0	$CH=CHCO_2Me$		562.3

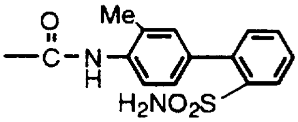
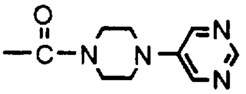
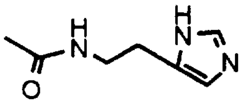
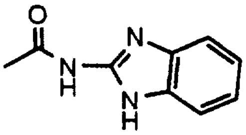
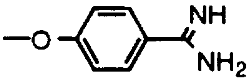
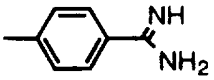
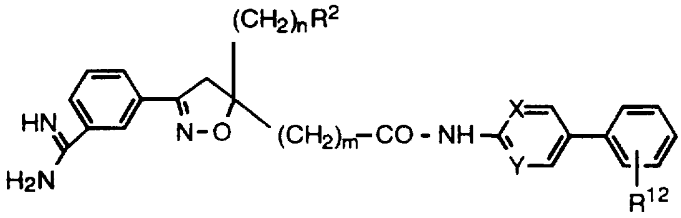
62	*m*	0	$CH_2CH_2CO_2Me$		564.2
63	*m*	0	CH_2CO_2Me		226.7 $(M+2H)^{2+}$
64	*m*	0	CH_2CO_2Me		200.2 $(M+2H)^{2+}$
65	*m*	0	CH_2CO_2Me		211.2 $(M+2H)^{2+}$
66	*m*	1	H		169.1 $(M+2H)^{2+}$
67	*m*	2	H		168.6 $(M+2H)^{2+}$

TABLE 2



I-2

EX #	o.r.	m	X	Y	$(CH_2)_nR^2$	R^{12}	MS $(M+H)^+$
68		0	N	N	CH_2CO_2Me	*o*-SO_2NH_2	538.2
69		0	CH	N	CH_2CO_2Me	*o*-SO_2NH_2	537.2
70	(+)	0	N	N	CH_2CO_2Me	*o*-SO_2NH_2	538.2
71	(-)	0	N	N	CH_2CO_2Me	*o*-SO_2NH_2	538.2

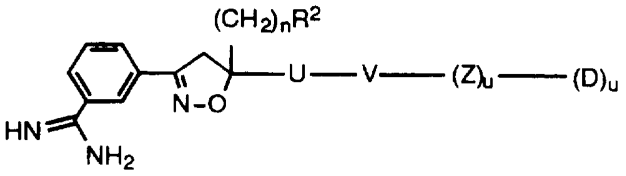
72		0	CF	CH	CH_2CO_2Me	*o*-SO_2NH_2	554.2
73		0	CF	CH	CH_2CO_2H	*o*-SO_2NH_2	540.2
74		0	CH	CH	H	*o*-SO_2NH_2	464.2
75		0	CH	N	CH_3	*o*-SO_2NH_2	479.3
76		0	CH	CH	CH_3	*o*-SO_2NH_2	478.2
77		0	CH	N	CH_2OMe	*o*-SO_2NH_2	509.2
78		0	N	N	CH_2SEt	*o*-SO_2NH_2	540.3
79		0	N	N	CH_2SO_2Et	*o*-SO_2NH_2	572.4
80		0	CH	N	CH_2SO_2Et	*o*-SO_2NH_2	571.3
81		0	CH	CH	CH_2SO_2Et	*o*-SO_2NH_2	570.4
8		0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	546.3
82		0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH-t-Bu	602.3
83		0	CH	CH	CH_2-tetrazol-2-yl	*o*-SO_2NH_2	546.5
84		0	CH	CH	CH_2-tetrazol-2-yl	*o*-SO_2NH-t-Bu	602.6
85		0	CH	N	CH_2CO_2H	*o*-SO_2NH_2	523.1
86	(-)	0	CH	N	CH_2CO_2Me	*o*-SO_2NH_2	537.1
87	(+)	0	CH	N	CH_2CO_2Me	*o*-SO_2NH_2	537.3
88		0	N	N	CH_2OMe	*o*-SO_2NH_2	510.3
89		0	N	N	CH_2OEt	*o*-SO_2NH_2	524.3
90		0	CH	N	CH_2OEt	*o*-SO_2NH_2	523.3
91		0	CH	CH	CH_2CONH_2	*o*-SO_2NH_2	520.6
92		0	CH	CH	CH_2OMe	*o*-SO_2NH_2	508.3
93		0	CH	CH	CH_2OEt	*o*-SO_2NH_2	522.3
94	(-)	0	CH	CH	CH_2OEt	*o*-SO_2NH_2	522.4
95	(+)	0	CH	CH	CH_2OEt	*o*-SO_2NH_2	522.4
96	(+)	0	CH	CH	CH_2OEt	*o*-SO_2NH-t-Bu	578.5
97		0	CH	N	CH_2CO_2H	*o*-SO_2NH_2	524.4

98		0	CH	CH	CH_2O-i-Pen	*o*-SO_2NH_2	564.4
99		0	CH	CH	CH_2Br	*o*-SO_2NH_2	556.3
100		0	CH	CH	CH_2Br	*o*-SO_2NH-t-Bu	612.4
101		0	CH	CH	CH_2OEt	*o*-SO_2NHMe	536.4
102	(-)	0	CH	N	CH_2OEt	*o*-SO_2NH_2	523.3
103	(-)	0	CH	N	CH_2OEt	*o*-SO_2NH-t-Bu	579.3
104		0	CH	CH	CH_2O-n-Pr	*o*-SO_2NH_2	536.4
105		0	CH	CH	CH_2O-n-Bu	*o*-SO_2NH_2	550.5
106		0	CH	N	CH_2SEt	*o*-SO_2NH_2	539.3
107		0	CH	CH	CF_3	*o*-SO_2NH-t-Bu	588.2
108		0	CH	CH	CF_3	*o*-SO_2NH_2	532.3
109	(-)	0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	546.4
110	(+)	0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	546.2
111	(-)	0	CCl	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	580.1
112		0	CCl	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	580.1
113		0	CF	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	564.4
114	(-)	0	CF	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	564.4
115		0	CH	N	CH_2-tetrazol-1-yl	*o*-SO_2NH-t-Bu	603.5
116		0	CH	N	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	547.4
117	(-)	0	CH	N	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	547.4
118		0	CH	CH	CH_2CH_2OMe	*o*-SO_2NH_2	522.4
119		0	CH	CH	CH_2CH_2OMe	*o*-SO_2NH-t-Bu	578.5
120	(-)	0	CH	N	CH_2-tetrazol-1-yl	*o*-SO_2NH-t-Bu	603.6
121		0	CH	CH	CH_2Ph	*o*-SO_2NH_2	554.3
122		0	CH	CH	CH_2O-i-Pr	*o*-SO_2NH_2	536.3
123	(-)	0	CH	N	CH_2OMe	*o*-SO_2NH_2	509.3
124	(-)	0	CH	N	CH_2OMe	*o*-SO_2NH-t-Bu	565.4

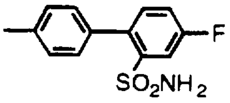
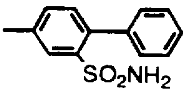
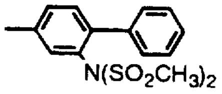
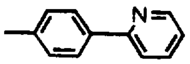
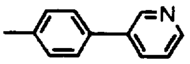
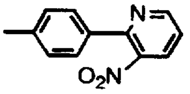
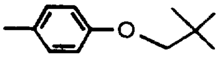
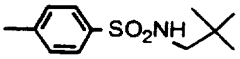
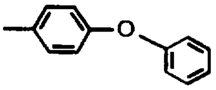
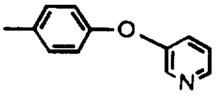
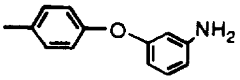
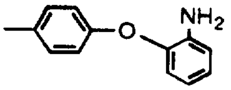
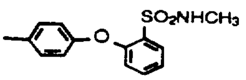
125		0	CH	N	CH_2-tetrazol-1-yl	*o*-SO_2NHMe	561.6
126	(-)	0	CH	N	CH_2-tetrazol-1-yl	*o*-SO_2NHMe	561.6
127	(-)	0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH-n-Pr	588.6
128		0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NH-n-Pr	588.4
129	(-)	0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2NHMe	560.4
130		0	CH	CH	CH_2I	*o*-SO_2NH_2	604.3
131		0	CH	CH	CH_2-1-(4,5-dichloroimidazole)	*o*-SO_2NHMe	612.2
132		0	N	N	CH_2-tetrazol-1-yl	*o*-SO_2NH_2	548.4
133		1	CH	CH	CO_2Me	*o*-SO_2NH_2	536.3
134		1	CH	CH	CO_2Me	*o*-SO_2NH-t-Bu	592.4
135		1	CH	N	CO_2H	*o*-SO_2NH_2	523.4
136	(-)	1	N	N	CO_2H	*o*-SO_2NH_2	524.3
137	(-)	1	CH	N	CO_2H	*o*-SO_2NH_2	523.4
138		1	N	N	CO_2H	*o*-SO_2NH_2	524.4
139		0	CH	CH	CH_2CO_2Me	*o*-OMe	487.3
140		0	CH	CH	CH_2CO_2Me	*m*-OMe	487.3
141		0	CH	CH	CH_2CONH_2	*o*-OMe	472.2
142		0	CH	CH	CH_2CONH_2	*m*-OMe	472.2
143		0	CH	CH	CH_2CO_2Me	*m*-CF_3	525.2
144		0	CH	CH	CH_2CONH_2	*m*-CF_3	510.2
145		0	CH	CH	CH_2CONH_2	*m*-SO_2Me	535.3
146		0	CH	CH	CH_2CONH_2	*o*-Me	456.5
147		0	CH	CH	CH_2CO_2Me	*o*-Me	471.5
148		0	CH	CH	CH_2CONH_2	*m*-Me	456.5
149		0	CH	CH	CH_2CO_2Me	*m*-Me	471.5
150		0	CH	CH	CH_2CO_2Me	*m*-SO_2NH_2	536.5

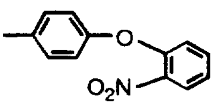
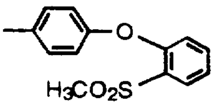
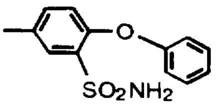
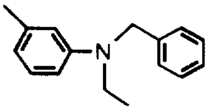
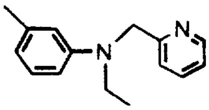
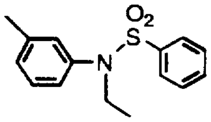
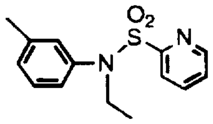
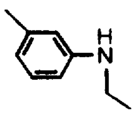
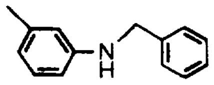
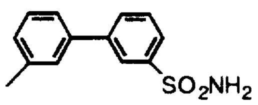
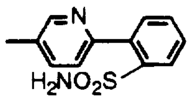
151		0	CH	CH	CH_2CONH_2	*o*-SO_2NMe_2	549.4
152		0	CH	CH	CH_2CONH_2	*o*-SO_2NHMe	535.4
153		0	CH	CH	CH_2CO_2Me	*o*-SMe	503.4
154		0	CH	CH	CH_2CO_2Me	*o*-SO_2Me	535.4
155		1	CH	CH	CO_2Me	*o*-SO_2Me	535.4
156		0	CH	CH	CH_2CONH_2	*o*-CO_2Me	500.3
157		0	CH	CH	CH_2CO_2Me	*o*-CO_2Me	515.4
158		0	CH	CH	CH_2CONH_2	*o*-SOMe	488.3
159		0	CH	CH	CH_2OMe	*o*-SO_2Me	507.4
160		0	CH	CH	CH_2OMe	*o*-SO_2Et	521.4
161		0	CH	CH	CH_2OMe	*o*-SO_2-n-Pr	535.4
162		0	CH	CH	CH_2OMe	*o*-SO_2-i-Bu	549.5
163		0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2Me	545.2
164		0	CH	CH	CH_2-tetrazol-1-yl	*o*-SO_2CF_3	
165	(-)	0	CH	CH	CH_2-tetrazol-1-yl	*o*-CF_3	535.4
166	(-)	0	N	CH	CH_2-tetrazol-1-yl	*o*-CF_3	536.3
167		0	N	N	CH_2-tetrazol-1-yl	*o*-CF_3	
168		0	CCl	CH	CH_2-tetrazol-1-yl	*o*-CF_3	
169		0	CF	CH	CH_2-tetrazol-1-yl	*o*-CF_3	
170		0	CH	CH	CH_2-imidazol-1-yl	*o*-CF_3	
171		0	CH	CH	CH_2-imidazol-1-yl	*o*-SO_2NH_2	

TABLE 3



I-3

EX#	U	$(CH_2)_nR^2$	V-(Z)u-(D)u	MS $(M+H)^+$
172	CONH	CH_2OMe		526.4
173	CONH	CH_3		478.3
174	CONH	CH_3		570.3
175	CONH	CH_3		400.3
176	CONH	CH_3		400.2
177	CONH	CH_3		445.4
178	CONH	CH_3		409.3
179	CONH	CH_3		472.4
180	CONH	CH_3		415.3
181	CONH	CH_3		416.4
182	CONH	CH_3		430.3
183	CONH	CH_3		430.3
184	CONH	CH_3		508.4

12	CONH	CH_3		462.2
185	CONH	CH_2OCH_3		523.3
186	CONH	CH_2OCH_3		494.3
187	CONH	CH_3		456.4
13	CONH	CH_3		457.4
188	CONH	CH_3		506.4
189	CONH	CH_3		507.4
190	CONH	CH_3		366.2
191	CONH	CH_3		429.4
192	CONH	CH_2CO_2Me		536.2
193	CONH	CH_2CO_2Me		537.2

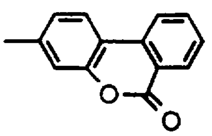
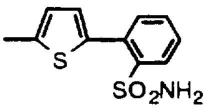
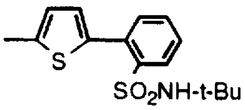
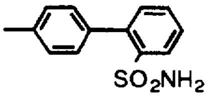
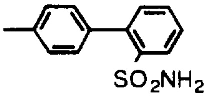
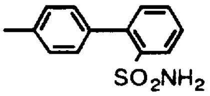
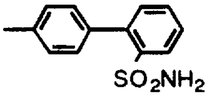
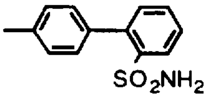
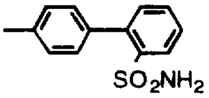
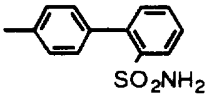
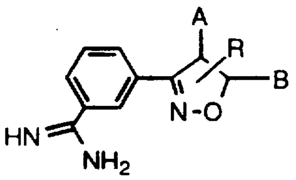
194	CONH	CH_2CO_2Me		499.1
195	CONH	CH_2OEt		528.3
196	CONH	CH_2OEt		584.4
197	CH_2	CH_2OEt		493.2
198	CH_2O	H		451.2
9	CH_2O	CH_2OEt		509.2
199	CH_2CH_2O	H		465.4
200	CH_2NH	H		450.3
201	CH_2NCOCF_3	H		563.3
202	CH_2CO	H		463.3

TABLE 4



I-4

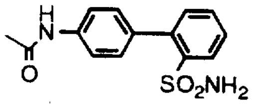
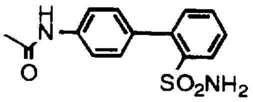
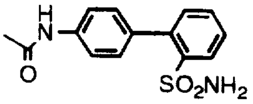
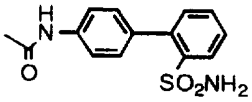
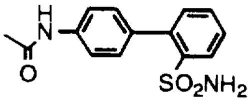
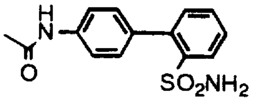
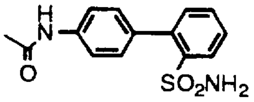
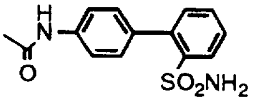
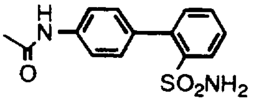
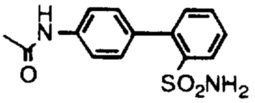
EX#	R	A	B	MS (M+H)+
10	H		CH_3	478.3
203	H		CH_3OCH_2	508.4
204	H		tetrazole-1-yl-CH_2-	546.4
205	H		CF_3	532.3
206	H		$Si(Et)_2Me$	564.4
207	4-CH_2OCH_3		CH_3	522.3
11	H	CH_3		478.3
208	H	CH_3OCH_2		508.4
209	H	CF_3		532.3
210	5-CH_2OCH_3	CH_3		522.3

TABLE 5

EX#	Structures	MS (M+H)+

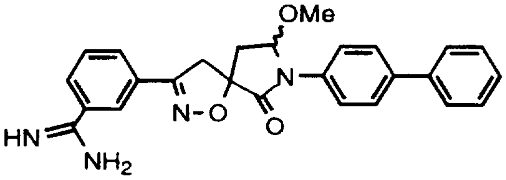
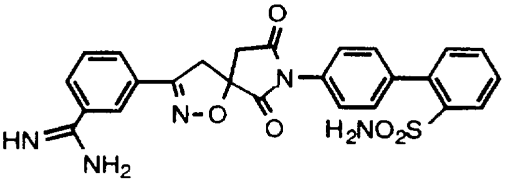
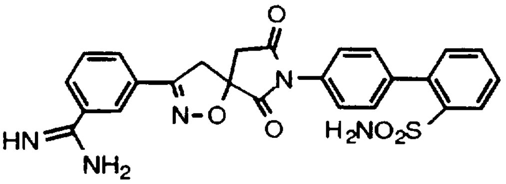
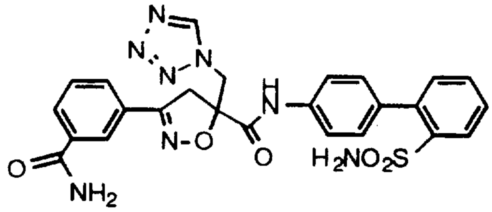
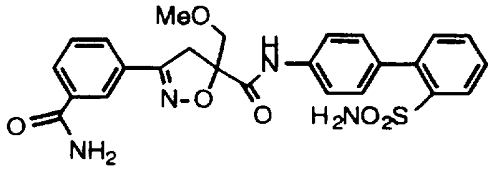
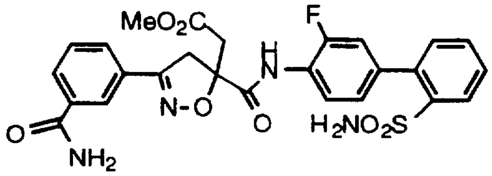
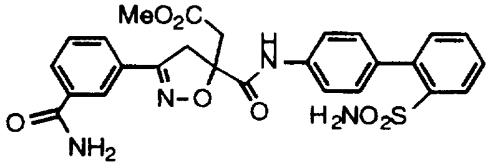
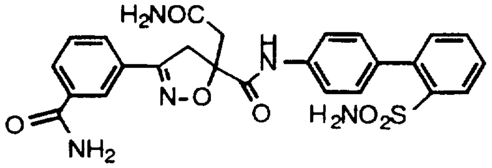
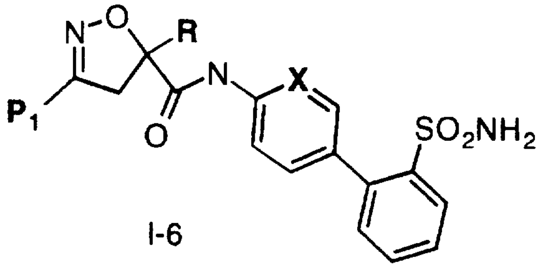
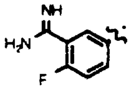
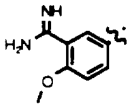
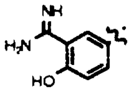
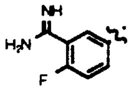
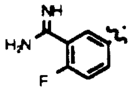
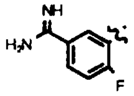
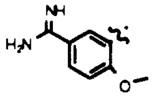
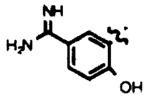
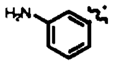
211		441.3
212		504.3
213		504.3
214		
215		
216		
217		
218		

TABLE 6



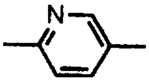
I-6

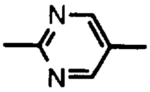
EX#	P1	R	X	MP(^{0}C)	MS(M+H)$^+$
219		$-CH_3$	CH	140	496.3
220		$-CH_3$	CH	240	508.3 (69%)
221		$-CH_3$	CH	235	494.3
222		CH_2OCH_3	N	81	528.4
223		CH_2OCH_3	CH	175	526.4
224		CH_2OCH_3	CH	215	526.3
225		$-CH_3$	CH	245	508.4
226		$-CH_3$	CH	238	494.2
227		$-CH_3$	CH	207	451.4

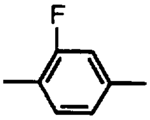
Tables 7-15 identify additional representative compounds of this invention which can be prepared by the methods described above.

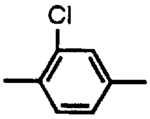
The divalent radicals V in the compounds of Tables 7-11 have the following structures

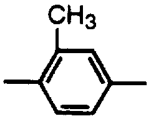
1,4-phenylene 

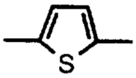
pyridin-2,5-diyl 

pyrimidin-2,5-diyl 

2-fluoro-1,4-phenylene 

2-chloro-1,4-phenylene 

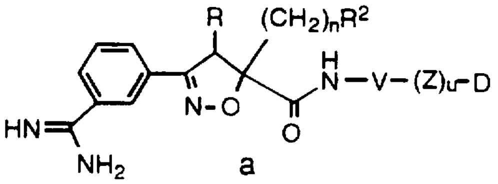
2-methyl-1,4-phenylene 

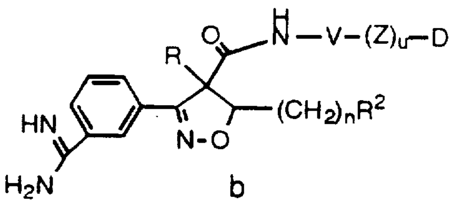
2,5-thiophene 

The pyridin-2,5-diyl and pyrimidin-2,5-diyl radicals are bonded to the $(Z)_u$-D moiety at the 5 position. The 2-substituted-1,4-phenylene radicals are bonded to the $(Z)_u$-D moiety at the 4 position.

The compounds of Tables 7-11 have the structures indicated by the formula "a" under each table heading. The corresponding compounds having the structures of formula "b" under each table heading can be obtained by substituting the appropriate starting material, as illustrated in Examples 10 and 11.

TABLE 7


a


b

Part	Cpd	R	$(CH_2)_nR^2$	V	$(Z)_u$-D
A1	1	CH_2OCH_3	CH_2OMe	1-4-phenylene	2-aminosulfonylphenyl
	2	CH_2OCH_3	CH_2OEt	1-4-phenylene	2-aminosulfonylphenyl
	3	CH_2OCH_3	CH_2O-n-Pr	1-4-phenylene	2-aminosulfonylphenyl
	4	CH_2OCH_3	CH_2O-i-Pr	1-4-phenylene	2-aminosulfonylphenyl
	5	CH_2OCH_3	CH_2O-n-Bu	1-4-phenylene	2-aminosulfonylphenyl
	6	CH_2OCH_3	CH_2O-i-Bu	1-4-phenylene	2-aminosulfonylphenyl
	7	CH_2OCH_3	CH_2Ph	1-4-phenylene	2-aminosulfonylphenyl
	8	CH_2OCH_3	CH_2-pyrazol-1-yl	1-4-phenylene	2-aminosulfonylphenyl
	9	CH_2OCH_3	CH_2-imidazol-1-yl	1-4-phenylene	2-aminosulfonylphenyl
	10	CH_2OCH_3	CH_2-tetrazol-1-yl	1-4-phenylene	2-aminosulfonylphenyl
	11	CH_2OCH_3	CH_2-tetrazol-2-yl	1-4-phenylene	2-aminosulfonylphenyl
	12	CH_2OCH_3	CH_2-triazol-1-yl	1-4-phenylene	2-aminosulfonylphenyl
	13	CH_2OCH_3	CH_2SEt	1-4-phenylene	2-aminosulfonylphenyl
	14	CH_2OCH_3	CH_2SO_2Et	1-4-phenylene	2-aminosulfonylphenyl
	15	CH_2OCH_3	CF_3	1-4-phenylene	2-aminosulfonylphenyl
	16	CH_2OCH_3	CH_3	1-4-phenylene	2-aminosulfonylphenyl
	17	CH_2OCH_3	H	1-4-phenylene	2-aminosulfonylphenyl
A2	1	CH_2OCH_3	CH_2OMe	pyridin-2,5-diyl	2-aminosulfonylphenyl
	2	CH_2OCH_3	CH_2OEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	3	CH_2OCH_3	CH_2O-n-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl

	4	CH_2OCH_3	CH_2O-i-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	5	CH_2OCH_3	CH_2O-n-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	6	CH_2OCH_3	CH_2O-i-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	7	CH_2OCH_3	CH_2Ph	pyridin-2,5-diyl	2-aminosulfonylphenyl
	8	CH_2OCH_3	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	9	CH_2OCH_3	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	10	CH_2OCH_3	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	11	CH_2OCH_3	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	12	CH_2OCH_3	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	13	CH_2OCH_3	CH_2SEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	14	CH_2OCH_3	CH_2SO_2Et	pyridin-2,5-diyl	2-aminosulfonylphenyl
	15	CH_2OCH_3	CF_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	16	CH_2OCH_3	CH_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	17	CH_2OCH_3	H	pyridin-2,5-diyl	2-aminosulfonylphenyl
A3	1	CH_2OCH_3	CH_2OMe	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	2	CH_2OCH_3	CH_2OEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	3	CH_2OCH_3	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	4	CH_2OCH_3	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl

	5	CH_2OCH_3	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	6	CH_2OCH_3	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	7	CH_2OCH_3	CH_2Ph	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	8	CH_2OCH_3	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	9	CH_2OCH_3	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	10	CH_2OCH_3	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	11	CH_2OCH_3	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	12	CH_2OCH_3	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	13	CH_2OCH_3	CH_2SEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	14	CH_2OCH_3	CH_2SO_2Et	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	15	CH_2OCH_3	CF_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	16	CH_2OCH_3	CH_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	17	CH_2OCH_3	H	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
A4	1	CH_2OCH_3	CH_2OMe	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	2	CH_2OCH_3	CH_2OEt	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	3	CH_2OCH_3	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	4	CH_2OCH_3	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	5	CH_2OCH_3	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl

	6	CH_2OCH_3	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	7	CH_2OCH_3	CH_2Ph	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	8	CH_2OCH_3	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	9	CH_2OCH_3	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	10	CH_2OCH_3	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	11	CH_2OCH_3	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	12	CH_2OCH_3	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	13	CH_2OCH_3	CH_2SEt	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	14	CH_2OCH_3	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	15	CH_2OCH_3	CF_3	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	16	CH_2OCH_3	CH_3	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	17	CH_2OCH_3	H	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
A5	1	CH_2OCH_3	CH_2OMe	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	2	CH_2OCH_3	CH_2OEt	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	3	CH_2OCH_3	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	4	CH_2OCH_3	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	5	CH_2OCH_3	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	6	CH_2OCH_3	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-aminosulfonylphenyl

	7	CH_2OCH_3	CH_2Ph	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	8	CH_2OCH_3	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	9	CH_2OCH_3	CH_2-imidazol-1-yl	2-chloro-1,4-phenylenel	2-aminosulfonylphenyl
	10	CH_2OCH_3	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	11	CH_2OCH_3	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	12	CH_2OCH_3	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	13	CH_2OCH_3	CH_2SEt	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	14	CH_2OCH_3	CH_2SO_2Et	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	15	CH_2OCH_3	CF_3	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	16	CH_2OCH_3	CH_3	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	17	CH_2OCH_3	H	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
B1	1	CH_3	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	CH_3	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	CH_3	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	CH_3	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	CH_3	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	CH_3	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	CH_3	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	CH_3	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	CH_3	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	CH_3	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl

	11	CH_3	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	CH_3	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	CH_3	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	CH_3	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	CH_3	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	CH_3	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	CH_3	H	1,4-phenylene	2-aminosulfonylphenyl
B2	1	CH_3	CH_2OMe	pyridin-2,5-diyl	2-aminosulfonylphenyl
	2	CH_3	CH_2OEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	3	CH_3	CH_2O-n-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	4	CH_3	CH_2O-i-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	5	CH_3	CH_2O-n-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	6	CH_3	CH_2O-i-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	7	CH_3	CH_2Ph	pyridin-2,5-diyl	2-aminosulfonylphenyl
	8	CH_3	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	9	CH_3	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	10	CH_3	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	11	CH_3	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	12	CH_3	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	13	CH_3	CH_2SEt	pyridin-2,5-diyl	2-aminosulfonylphenyl

	14	CH_3	CH_2SO_2Et	pyridin-2,5-diyl	2-aminosulfonylphenyl
	15	CH_3	CF_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	16	CH_3	CH_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	17	CH_3	H	pyridin-2,5-diyl	2-aminosulfonylphenyl
B3	1	CH_3	CH_2OMe	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	2	CH_3	CH_2OEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	3	CH_3	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	4	CH_3	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	5	CH_3	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	6	CH_3	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	7	CH_3	CH_2Ph	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	8	CH_3	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	9	CH_3	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	10	CH_3	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	11	CH_3	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	12	CH_3	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	13	CH_3	CH_2SEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	14	CH_3	CH_2SO_2Et	pyrimidin-2,5-diyl	2-aminosulfonylphenyl

	15	CH_3	CF_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	16	CH_3	CH_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	17	CH_3	H	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
B4	1	CH_3	CH_2OMe	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	2	CH_3	CH_2OEt	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	3	CH_3	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	4	CH_3	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	5	CH_3	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	6	CH_3	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	7	CH_3	CH_2Ph	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	8	CH_3	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	9	CH_3	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	10	CH_3	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	11	CH_3	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	12	CH_3	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	13	CH_3	CH_2SEt	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	14	CH_3	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	15	CH_3	CF_3	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl

	16	CH_3	CH_3	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	17	CH_3	H	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
B5	1	CH_3	CH_2OMe	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	2	CH_3	CH_2OEt	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	3	CH_3	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	4	CH_3	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	5	CH_3	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	6	CH_3	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	7	CH_3	CH_2Ph	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	8	CH_3	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	9	CH_3	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	10	CH_3	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	11	CH_3	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	12	CH_3	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	13	CH_3	CH_2SEt	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	14	CH_3	CH_2SO_2Et	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	15	CH_3	CF_3	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	16	CH_3	CH_3	2-chloro-1,4-phenylene	2-aminosulfonylphenyl

	17	CH_3	H	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
C1	1	H	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	H	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	H	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	H	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	H	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	H	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	H	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	H	H	1,4-phenylene	2-aminosulfonylphenyl
C2	1	H	CH_2OMe	pyridin-2,5-diyl	2-aminosulfonylphenyl
	2	H	CH_2OEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl

	7	H	CH_2Ph	pyridin-2,5-diyl	2-aminosulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	9	H	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	13	H	CH_2SEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	pyridin-2,5-diyl	2-aminosulfonylphenyl
	15	H	CF_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	16	H	CH_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	17	H	H	pyridin-2,5-diyl	2-aminosulfonylphenyl
C3	1	H	CH_2OMe	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	2	H	CH_2OEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	7	H	CH_2Ph	pyrimidin-2,5-diyl	2-aminosulfonylphenyl

	8	H	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	9	H	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	13	H	CH_2SEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	15	H	CF_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	16	H	CH_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	17	H	H	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
C4	1	H	CH_2OMe	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	2	H	CH_2OEt	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	7	H	CH_2Ph	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl

	9	H	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	13	H	CH_2SEt	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	15	H	CF_3	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	16	H	CH_3	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
	17	H	H	2-fluoro-1,4-phenylene	2-aminosulfonylphenyl
C5	1	H	CH_2OMe	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	2	H	CH_2OEt	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	7	H	CH_2Ph	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	9	H	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl

	10	H	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	13	H	CH_2SEt	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	15	H	CF_3	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	16	H	CH_3	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
	17	H	H	2-chloro-1,4-phenylene	2-aminosulfonylphenyl
C6	1	H	CH_2OMe	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	2	H	CH_2OEt	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	7	H	CH_2Ph	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	9	H	CH_2-imidazol-1-yl	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	2-methyl-1,4-phenylene	2-aminosulfonylphenyl

	11	H	CH_2-tetrazol-2-yl	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	13	H	CH_2SEt	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	15	H	CF_3	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	16	H	CH_3	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
	17	H	H	2-methyl-1,4-phenylene	2-aminosulfonylphenyl
D1	1	H	CH_2OMe	1,4-phenylene	2-trifluoromethylphenyl
	2	H	CH_2OEt	1,4-phenylene	2-trifluoromethylphenyl
	3	H	CH_2O-n-Pr	1,4-phenylene	2-trifluoromethylphenyl
	4	H	CH_2O-i-Pr	1,4-phenylene	2-trifluoromethylphenyl
	5	H	CH_2O-n-Bu	1,4-phenylene	2-trifluoromethylphenyl
	6	H	CH_2O-i-Bu	1,4-phenylene	2-trifluoromethylphenyl
	7	H	CH_2Ph	1,4-phenylene	2-trifluoromethylphenyl
	8	H	CH_2-pyrazol-1-yl	1,4-phenylene	2-trifluoromethylphenyl
	9	H	CH_2-imidazol-1-yl	1,4-phenylene	2-trifluoromethylphenyl
	10	H	CH_2-tetrazol-1-yl	1,4-phenylene	2-trifluoromethylphenyl
	11	H	CH_2-tetrazol-2-yl	1,4-phenylene	2-trifluoromethylphenyl

	12	H	CH_2-triazol-1-yl	1,4-phenylene	2-trifluoromethylphenyl
	13	H	CH_2SEt	1,4-phenylene	2-trifluoromethylphenyl
	14	H	CH_2SO_2Et	1,4-phenylene	2-trifluoromethylphenyl
	15	H	CF_3	1,4-phenylene	2-trifluoromethylphenyl
	16	H	CH_3	1,4-phenylene	2-trifluoromethylphenyl
	17	H	H	1,4-phenylene	2-trifluoromethylphenyl
D2	1	H	CH_2OMe	pyridin-2,5-diyl	2-trifluoromethylphenyl
	2	H	CH_2OEt	pyridin-2,5-diyl	2-trifluoromethylphenyl
	3	H	CH_2O-n-Pr	pyridin-2,5-diyl	2-trifluoromethylphenyl
	4	H	CH_2O-i-Pr	pyridin-2,5-diyl	2-trifluoromethylphenyl
	5	H	CH_2O-n-Bu	pyridin-2,5-diyl	2-trifluoromethylphenyl
	6	H	CH_2O-i-Bu	pyridin-2,5-diyl	2-trifluoromethylphenyl
	7	H	CH_2Ph	pyridin-2,5-diyl	2-trifluoromethylphenyl
	8	H	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-trifluoromethylphenyl
	9	H	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-trifluoromethylphenyl
	10	H	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-trifluoromethylphenyl
	11	H	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-trifluoromethylphenyl
	12	H	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-trifluoromethylphenyl

	13	H	CH_2SEt	pyridin-2,5-diyl	2-trifluoromethylphenyl
	14	H	CH_2SO_2Et	pyridin-2,5-diyl	2-trifluoromethylphenyl
	15	H	CF_3	pyridin-2,5-diyl	2-trifluoromethylphenyl
	16	H	CH_3	pyridin-2,5-diyl	2-trifluoromethylphenyl
	17	H	H	pyridin-2,5-diyl	2-trifluoromethylphenyl
D3	1	H	CH_2OMe	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	2	H	CH_2OEt	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	3	H	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	4	H	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	5	H	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	6	H	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	7	H	CH_2Ph	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	8	H	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	9	H	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	10	H	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	11	H	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	12	H	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	13	H	CH_2SEt	pyrimidin-2,5-diyl	2-trifluoromethylphenyl

	14	H	CH_2SO_2Et	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	15	H	CF_3	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	16	H	CH_3	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
	17	H	H	pyrimidin-2,5-diyl	2-trifluoromethylphenyl
D4	1	H	CH_2OMe	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	2	H	CH_2OEt	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	3	H	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	4	H	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	5	H	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	6	H	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	7	H	CH_2Ph	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	8	H	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	9	H	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	10	H	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	11	H	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	12	H	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	13	H	CH_2SEt	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	14	H	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl

	15	H	CF_3	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	16	H	CH_3	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl
	17	H	H	2-fluoro-1,4-phenylene	2-trifluoromethylphenyl

D5	1	H	CH_2OMe	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	2	H	CH_2OEt	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	3	H	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	4	H	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	5	H	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	6	H	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	7	H	CH_2Ph	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	8	H	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	9	H	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	10	H	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	11	H	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	12	H	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	13	H	CH_2SEt	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	14	H	CH_2SO_2Et	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	15	H	CF_3	2-chloro-1,4-phenylene	2-trifluoromethylphenyl

	16	H	CH_3	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
	17	H	H	2-chloro-1,4-phenylene	2-trifluoromethylphenyl
D6	1	H	CH_2OMe	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	2	H	CH_2OEt	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	3	H	CH_2O-n-Pr	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	4	H	CH_2O-i-Pr	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	5	H	CH_2O-n-Bu	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	6	H	CH_2O-i-Bu	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	7	H	CH_2Ph	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	8	H	CH_2-pyrazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	9	H	CH_2-imidazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	10	H	CH_2-tetrazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	11	H	CH_2-tetrazol-2-yl	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	12	H	CH_2-triazol-1-yl	2-methyl-1,4-phenylenel	2-trifluoromethylphenyl
	13	H	CH_2SEt	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	14	H	CH_2SO_2Et	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	15	H	CF_3	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
	16	H	CH_3	2-methyl-1,4-phenylene	2-trifluoromethylphenyl

	17	H	H	2-methyl-1,4-phenylene	2-trifluoromethylphenyl
E1	1	H	CH_2OMe	1,4-phenylene	2-trifluoromethoxyphenyl
	2	H	CH_2OEt	1,4-phenylene	2-trifluoromethoxyphenyl
	3	H	CH_2O-n-Pr	1,4-phenylene	2-trifluoromethoxyphenyl
	4	H	CH_2O-i-Pr	1,4-phenylene	2-trifluoromethoxyphenyl
	5	H	CH_2O-n-Bu	1,4-phenylene	2-trifluoromethoxyphenyl
	6	H	CH_2O-i-Bu	1,4-phenylene	2-trifluoromethoxyphenyl
	7	H	CH_2Ph	1,4-phenylene	2-trifluoromethoxyphenyl
	8	H	CH_2-pyrazol-1-yl	1,4-phenylene	2-trifluoromethoxyphenyl
	9	H	CH_2-imidazol-1-yl	1,4-phenylene	2-trifluoromethoxyphenyl
	10	H	CH_2-tetrazol-1-yl	1,4-phenylene	2-trifluoromethoxyphenyl
	11	H	CH_2-tetrazol-2-yl	1,4-phenylene	2-trifluoromethoxyphenyl
	12	H	CH_2-triazol-1-yl	1,4-phenylene	2-trifluoromethoxyphenyl
	13	H	CH_2SEt	1,4-phenylene	2-trifluoromethoxyphenyl
	14	H	CH_2SO_2Et	1,4-phenylene	2-trifluoromethoxyphenyl
	15	H	CF_3	1,4-phenylene	2-trifluoromethoxyphenyl
	16	H	CH_3	1,4-phenylene	2-trifluoromethoxyphenyl
	17	H	H	1,4-phenylene	2-trifluoromethoxyphenyl

E2	1	H	CH_2OMe	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	2	H	CH_2OEt	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	3	H	CH_2O-n-Pr	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	4	H	CH_2O-i-Pr	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	5	H	CH_2O-n-Bu	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	6	H	CH_2O-i-Bu	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	7	H	CH_2Ph	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	8	H	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	9	H	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	10	H	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	11	H	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	12	H	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	13	H	CH_2SEt	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	14	H	CH_2SO_2Et	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	15	H	CF_3	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	16	H	CH_3	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
	17	H	H	pyridin-2,5-diyl	2-trifluoromethoxyphenyl
E3	1	H	CH_2OMe	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl

	2	H	CH_2OEt	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	3	H	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	4	H	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	5	H	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	6	H	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	7	H	CH_2Ph	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	8	H	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	9	H	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	10	H	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	11	H	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	12	H	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	13	H	CH_2SEt	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	14	H	CH_2SO_2Et	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	15	H	CF_3	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	16	H	CH_3	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
	17	H	H	pyrimidin-2,5-diyl	2-trifluoromethoxyphenyl
E4	1	H	CH_2OMe	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	2	H	CH_2OEt	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl

	3	H	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	4	H	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	5	H	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	6	H	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	7	H	CH_2Ph	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	8	H	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	9	H	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	10	H	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	11	H	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	12	H	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	13	H	CH_2SEt	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	14	H	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	15	H	CF_3	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	16	H	CH_3	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
	17	H	H	2-fluoro-1,4-phenylene	2-trifluoromethoxyphenyl
E5	1	H	CH_2OMe	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	2	H	CH_2OEt	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	3	H	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl

	4	H	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	5	H	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	6	H	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	7	H	CH_2Ph	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	8	H	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	9	H	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	10	H	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	11	H	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	12	H	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	13	H	CH_2SEt	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	14	H	CH_2SO_2Et	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	15	H	CF_3	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	16	H	CH_3	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
	17	H	H	2-chloro-1,4-phenylene	2-trifluoromethoxyphenyl
E6	1	H	CH_2OMe	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	2	H	CH_2OEt	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	3	H	CH_2O-n-Pr	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	4	H	CH_2O-i-Pr	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl

	5	H	CH$_2$O-n-Bu	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	6	H	CH$_2$O-i-Bu	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	7	H	CH$_2$Ph	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	8	H	CH$_2$-pyrazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	9	H	CH$_2$-imidazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	10	H	CH$_2$-tetrazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	11	H	CH$_2$-tetrazol-2-yl	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	12	H	CH$_2$-triazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	13	H	CH$_2$SEt	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	14	H	CH$_2$SO$_2$Et	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	15	H	CF$_3$	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	16	H	CH$_3$	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
	17	H	H	2-methyl-1,4-phenylene	2-trifluoromethoxyphenyl
F1	1	H	CH$_2$OMe	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	2	H	CH$_2$OEt	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	3	H	CH$_2$O-n-Pr	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	4	H	CH$_2$O-i-Pr	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	5	H	CH$_2$O-n-Bu	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl

	6	H	CH_2O-i-Bu	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	7	H	CH_2Ph	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	8	H	CH_2-pyrazol-1-yl	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	9	H	CH_2-imidazol-1-yl	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	10	H	CH_2-tetrazol-1-yl	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	11	H	CH_2-tetrazol-2-yl	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	12	H	CH_2-triazol-1-yl	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	13	H	CH_2SEt	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	14	H	CH_2SO_2Et	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	15	H	CF_3	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	16	H	CH_3	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	17	H	H	1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
F2	1	H	CH_2OMe	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	2	H	CH_2OEt	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	3	H	CH_2O-n-Pr	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	4	H	CH_2O-i-Pr	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	5	H	CH_2O-n-Bu	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	6	H	CH_2O-i-Bu	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl

	7	H	CH_2Ph	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	8	H	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	9	H	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	10	H	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	11	H	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	12	H	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	13	H	CH_2SEt	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	14	H	CH_2SO_2Et	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	15	H	CF_3	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	16	H	CH_3	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	17	H	H	pyridin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
F3	1	H	CH_2OMe	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	2	H	CH_2OEt	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	3	H	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	4	H	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	5	H	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	6	H	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	7	H	CH_2Ph	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl

	8	H	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	9	H	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	10	H	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	11	H	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	12	H	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	13	H	CH_2SEt	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	14	H	CH_2SO_2Et	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	15	H	CF_3	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	16	H	CH_3	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
	17	H	H	pyrimidin-2,5-diyl	2-trifluoromethyl-sulfonyl-phenyl
F4	1	H	CH_2OMe	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	2	H	CH_2OEt	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	3	H	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	4	H	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	5	H	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	6	H	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	7	H	CH_2Ph	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	8	H	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl

	9	H	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	10	H	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	11	H	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	12	H	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	13	H	CH_2SEt	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	14	H	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	15	H	CF_3	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	16	H	CH_3	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	17	H	H	2-fluoro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
F5	1	H	CH_2OMe	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	2	H	CH_2OEt	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	3	H	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	4	H	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	5	H	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	6	H	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	7	H	CH_2Ph	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	8	H	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl
	9	H	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethylsulfonyl-phenyl

	10	H	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	11	H	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	12	H	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	13	H	CH_2SEt	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	14	H	CH_2SO_2Et	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	15	H	CF_3	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	16	H	CH_3	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	17	H	H	2-chloro-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
F6	1	H	CH_2OMe	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	2	H	CH_2OEt	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	3	H	CH_2O-n-Pr	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	4	H	CH_2O-i-Pr	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	5	H	CH_2O-n-Bu	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	6	H	CH_2O-i-Bu	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	7	H	CH_2Ph	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	8	H	CH_2-pyrazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	9	H	CH_2-imidazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	10	H	CH_2-tetrazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl

	11	H	CH_2-tetrazol-2-yl	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	12	H	CH_2-triazol-1-yl	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	13	H	CH_2SEt	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	14	H	CH_2SO_2Et	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	15	H	CF_3	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	16	H	CH_3	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
	17	H	H	2-methyl-1,4-phenylene	2-trifluoromethyl-sulfonyl-phenyl
G1	1	H	CH_2OMe	phenyl	2-methoxyphenyl
	2	H	CH_2OEt	phenyl	2-methoxyphenyl
	3	H	CH_2O-n-Pr	phenyl	2-methoxyphenyl
	4	H	CH_2O-i-Pr	phenyl	2-methoxyphenyl
	5	H	CH_2O-n-Bu	phenyl	2-methoxyphenyl
	6	H	CH_2O-i-Bu	phenyl	2-methoxyphenyl
	7	H	CH_2Ph	phenyl	2-methoxyphenyl
	8	H	CH_2-pyrazol-1-yl	phenyl	2-methoxyphenyl
	9	H	CH_2-imidazol-1-yl	phenyl	2-methoxyphenyl
	10	H	CH_2-tetrazol-1-yl	phenyl	2-methoxyphenyl
	11	H	CH_2-tetrazol-2-yl	phenyl	2-methoxyphenyl
	12	H	CH_2-triazol-1-yl	phenyl	2-methoxyphenyl
	13	H	CH_2SEt	phenyl	2-methoxyphenyl
	14	H	CH_2SO_2Et	phenyl	2-methoxyphenyl
	15	H	CF_3	phenyl	2-methoxyphenyl
	16	H	CH_3	phenyl	2-methoxyphenyl
	17	H	H	phenyl	2-methoxyphenyl

G2	1	H	CH_2OMe	pyridin-2,5-diyl	2-methoxyphenyl
	2	H	CH_2OEt	pyridin-2,5-diyl	2-methoxyphenyl
	3	H	CH_2O-n-Pr	pyridin-2,5-diyl	2-methoxyphenyl
	4	H	CH_2O-i-Pr	pyridin-2,5-diyl	2-methoxyphenyl
	5	H	CH_2O-n-Bu	pyridin-2,5-diyl	2-methoxyphenyl
	6	H	CH_2O-i-Bu	pyridin-2,5-diyl	2-methoxyphenyl
	7	H	CH_2Ph	pyridin-2,5-diyl	2-methoxyphenyl
	8	H	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-methoxyphenyl
	9	H	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-methoxyphenyl
	10	H	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-methoxyphenyl
	11	H	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-methoxyphenyl
	12	H	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-methoxyphenyl
	13	H	CH_2SEt	pyridin-2,5-diyl	2-methoxyphenyl
	14	H	CH_2SO_2Et	pyridin-2,5-diyl	2-methoxyphenyl
	15	H	CF_3	pyridin-2,5-diyl	2-methoxyphenyl
	16	H	CH_3	pyridin-2,5-diyl	2-methoxyphenyl
	17	H	H	pyridin-2,5-diyl	2-methoxyphenyl
G3	1	H	CH_2OMe	pyrimidin-2,5-diyl	2-methoxyphenyl

	2	H	CH_2OEt	pyrimidin-2,5-diyl	2-methoxyphenyl
	3	H	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-methoxyphenyl
	4	H	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-methoxyphenyl
	5	H	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-methoxyphenyl
	6	H	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-methoxyphenyl
	7	H	CH_2Ph	pyrimidin-2,5-diyl	2-methoxyphenyl
	8	H	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-methoxyphenyl
	9	H	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-methoxyphenyl
	10	H	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-methoxyphenyl
	11	H	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-methoxyphenyl
	12	H	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-methoxyphenyl
	13	H	CH_2SEt	pyrimidin-2,5-diyl	2-methoxyphenyl
	14	H	CH_2SO_2Et	pyrimidin-2,5-diyl	2-methoxyphenyl
	15	H	CF_3	pyrimidin-2,5-diyl	2-methoxyphenyl
	16	H	CH_3	pyrimidin-2,5-diyl	2-methoxyphenyl
	17	H	H	pyrimidin-2,5-diyl	2-methoxyphenyl
G4	1	H	CH_2OMe	2-fluoro-1,4-phenylene	2-methoxyphenyl
	2	H	CH_2OEt	2-fluoro-1,4-phenylene	2-methoxyphenyl

	3	H	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-methoxyphenyl
	4	H	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-methoxyphenyl
	5	H	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-methoxyphenyl
	6	H	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-methoxyphenyl
	7	H	CH_2Ph	2-fluoro-1,4-phenylene	2-methoxyphenyl
	8	H	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-methoxyphenyl
	9	H	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-methoxyphenyl
	10	H	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-methoxyphenyl
	11	H	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-methoxyphenyl
	12	H	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-methoxyphenyl
	13	H	CH_2SEt	2-fluoro-1,4-phenylene	2-methoxyphenyl
	14	H	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-methoxyphenyl
	15	H	CF_3	2-fluoro-1,4-phenylene	2-methoxyphenyl
	16	H	CH_3	2-fluoro-1,4-phenylene	2-methoxyphenyl
	17	H	H	2-fluoro-1,4-phenylene	2-methoxyphenyl
G5	1	H	CH_2OMe	2-chloro-1,4-phenylene	2-methoxyphenyl
	2	H	CH_2OEt	2-chloro-1,4-phenylene	2-methoxyphenyl
	3	H	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-methoxyphenyl

	4	H	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-methoxyphenyl
	5	H	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-methoxyphenyl
	6	H	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-methoxyphenyl
	7	H	CH_2Ph	2-chloro-1,4-phenylene	2-methoxyphenyl
	8	H	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-methoxyphenyl
	9	H	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-methoxyphenyl
	10	H	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-methoxyphenyl
	11	H	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-methoxyphenyl
	12	H	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-methoxyphenyl
	13	H	CH_2SEt	2-chloro-1,4-phenylene	2-methoxyphenyl
	14	H	CH_2SO_2Et	2-chloro-1,4-phenylene	2-methoxyphenyl
	15	H	CF_3	2-chloro-1,4-phenylene	2-methoxyphenyl
	16	H	CH_3	2-chloro-1,4-phenylene	2-methoxyphenyl
	17	H	H	2-chloro-1,4-phenylene	2-methoxyphenyl
G6	1	H	CH_2OMe	2-methyl-1,4-phenylene	2-methoxyphenyl
	2	H	CH_2OEt	2-methyl-1,4-phenylene	2-methoxyphenyl
	3	H	CH_2O-n-Pr	2-methyl-1,4-phenylene	2-methoxyphenyl
	4	H	CH_2O-i-Pr	2-methyl-1,4-phenylene	2-methoxyphenyl

	5	H	CH_2O-n-Bu	2-methyl-1,4-phenylene	2-methoxyphenyl
	6	H	CH_2O-i-Bu	2-methyl-1,4-phenylene	2-methoxyphenyl
	7	H	CH_2Ph	2-methyl-1,4-phenylene	2-methoxyphenyl
	8	H	CH_2-pyrazol-1-yl	2-methyl-1,4-phenylene	2-methoxyphenyl
	9	H	CH_2-imidazol-1-yl	2-methyl-1,4-phenylene	2-methoxyphenyl
	10	H	CH_2-tetrazol-1-yl	2-methyl-1,4-phenylene	2-methoxyphenyl
	11	H	CH_2-tetrazol-2-yl	2-methyl-1,4-phenylene	2-methoxyphenyl
	12	H	CH_2-triazol-1-yl	2-methyl-1,4-phenylene	2-methoxyphenyl
	13	H	CH_2SEt	2-methyl-1,4-phenylene	2-methoxyphenyl
	14	H	CH_2SO_2Et	2-methyl-1,4-phenylene	2-methoxyphenyl
	15	H	CF_3	2-methyl-1,4-phenylene	2-methoxyphenyl
	16	H	CH_3	2-methyl-1,4-phenylene	2-methoxyphenyl
	17	H	H	2-methyl-1,4-phenylene	2-methoxyphenyl
H1	1	H	CH_2OMe	phenyl	2-methylsulfonylphenyl
	2	H	CH_2OEt	phenyl	2-methylsulfonylphenyl
	3	H	CH_2O-n-Pr	phenyl	2-methylsulfonylphenyl
	4	H	CH_2O-i-Pr	phenyl	2-methylsulfonylphenyl
	5	H	CH_2O-n-Bu	phenyl	2-methylsulfonylphenyl

	6	H	CH_2O-i-Bu	phenyl	2-methylsulfonylphenyl
	7	H	CH_2Ph	phenyl	2-methylsulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	phenyl	2-methylsulfonylphenyl
	9	H	CH_2-imidazol-1-yl	phenyl	2-methylsulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	phenyl	2-methylsulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	phenyl	2-methylsulfonylphenyl
	12	H	CH_2-triazol-1-yl	phenyl	2-methylsulfonylphenyl
	13	H	CH_2SEt	phenyl	2-methylsulfonylphenyl
	14	H	CH_2SO_2Et	phenyl	2-methylsulfonylphenyl
	15	H	CF_3	phenyl	2-methylsulfonylphenyl
	16	H	CH_3	phenyl	2-methylsulfonylphenyl
	17	H	H	phenyl	2-methylsulfonylphenyl
H2	1	H	CH_2OMe	pyridin-2,5-diyl	2-methylsulfonylphenyl
	2	H	CH_2OEt	pyridin-2,5-diyl	2-methylsulfonylphenyl
	3	H	CH_2O-n-Pr	pyridin-2,5-diyl	2-methylsulfonylphenyl
	4	H	CH_2O-i-Pr	pyridin-2,5-diyl	2-methylsulfonylphenyl
	5	H	CH_2O-n-Bu	pyridin-2,5-diyl	2-methylsulfonylphenyl
	6	H	CH_2O-i-Bu	pyridin-2,5-diyl	2-methylsulfonylphenyl

	7	H	CH_2Ph	pyridin-2,5-diyl	2-methylsulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-methylsulfonylphenyl
	9	H	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-methylsulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-methylsulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-methylsulfonylphenyl
	12	H	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-methylsulfonylphenyl
	13	H	CH_2SEt	pyridin-2,5-diyl	2-methylsulfonylphenyl
	14	H	CH_2SO_2Et	pyridin-2,5-diyl	2-methylsulfonylphenyl
	15	H	CF_3	pyridin-2,5-diyl	2-methylsulfonylphenyl
	16	H	CH_3	pyridin-2,5-diyl	2-methylsulfonylphenyl
	17	H	H	pyridin-2,5-diyl	2-methylsulfonylphenyl
H3	1	H	CH_2OMe	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	2	H	CH_2OEt	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	3	H	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	4	H	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	5	H	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	6	H	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	7	H	CH_2Ph	pyrimidin-2,5-diyl	2-methylsulfonylphenyl

	8	H	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	9	H	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	12	H	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	13	H	CH_2SEt	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	14	H	CH_2SO_2Et	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	15	H	CF_3	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	16	H	CH_3	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
	17	H	H	pyrimidin-2,5-diyl	2-methylsulfonylphenyl
H4	1	H	CH_2OMe	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	2	H	CH_2OEt	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	3	H	CH_2O-n-Pr	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	4	H	CH_2O-i-Pr	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	5	H	CH_2O-n-Bu	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	6	H	CH_2O-i-Bu	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	7	H	CH_2Ph	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl

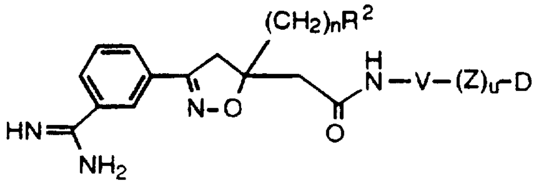
	9	H	CH_2-imidazol-1-yl	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	12	H	CH_2-triazol-1-yl	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	13	H	CH_2SEt	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	14	H	CH_2SO_2Et	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	15	H	CF_3	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	16	H	CH_3	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
	17	H	H	2-fluoro-1,4-phenylene	2-methylsulfonylphenyl
H5	1	H	CH_2OMe	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	2	H	CH_2OEt	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	3	H	CH_2O-n-Pr	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	4	H	CH_2O-i-Pr	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	5	H	CH_2O-n-Bu	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	6	H	CH_2O-i-Bu	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	7	H	CH_2Ph	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	9	H	CH_2-imidazol-1-yl	2-chloro-1,4-phenylene	2-methylsulfonylphenyl

	10	H	CH_2-tetrazol-1-yl	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	12	H	CH_2-triazol-1-yl	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	13	H	CH_2SEt	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	14	H	CH_2SO_2Et	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	15	H	CF_3	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	16	H	CH_3	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
	17	H	H	2-chloro-1,4-phenylene	2-methylsulfonylphenyl
H6	1	H	CH_2OMe	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	2	H	CH_2OEt	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	3	H	CH_2O-n-Pr	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	4	H	CH_2O-i-Pr	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	5	H	CH_2O-n-Bu	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	6	H	CH_2O-i-Bu	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	7	H	CH_2Ph	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	9	H	CH_2-imidazol-1-yl	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	2-methyl-1,4-phenylene	2-methylsulfonylphenyl

	11	H	CH_2-tetrazol-2-yl	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	12	H	CH_2-triazol-1-yl	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	13	H	CH_2SEt	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	14	H	CH_2SO_2Et	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	15	H	CF_3	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	16	H	CH_3	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
	17	H	H	2-methyl-1,4-phenylene	2-methylsulfonylphenyl
I1	1	H	CH_2OMe	1,4-phenylene	2-nitrophenoxy
	2	H	CH_2OEt	1,4-phenylene	2-nitrophenoxy
	3	H	CH_2O-n-Pr	1,4-phenylene	2-nitrophenoxy
	4	H	CH_2O-i-Pr	1,4-phenylene	2-nitrophenoxy
	5	H	CH_2O-n-Bu	1,4-phenylene	2-nitrophenoxy
	6	H	CH_2O-i-Bu	1,4-phenylene	2-nitrophenoxy
	7	H	CH_2Ph	1,4-phenylene	2-nitrophenoxy
	8	H	CH_2-pyrazol-1-yl	1,4-phenylene	2-nitrophenoxy
	9	H	CH_2-imidazol-1-yl	1,4-phenylene	2-nitrophenoxy
	10	H	CH_2-tetrazol-1-yl	1,4-phenylene	2-nitrophenoxy
	11	H	CH_2-tetrazol-2-yl	1,4-phenylene	2-nitrophenoxy
	12	H	CH_2-triazol-1-yl	1,4-phenylene	2-nitrophenoxy
	13	H	CH_2SEt	1,4-phenylene	2-nitrophenoxy
	14	H	CH_2SO_2Et	1,4-phenylene	2-nitrophenoxy
	15	H	CF_3	1,4-phenylene	2-nitrophenoxy
	16	H	CH_3	1,4-phenylene	2-nitrophenoxy
	17	H	H	1,4-phenylene	2-nitrophenoxy

J1	1	H	CH_2OMe	2,5-thiophene	2-aminosulfonylphenyl
	2	H	CH_2OEt	2,5-thiophene	2-aminosulfonylphenyl
	3	H	CH_2O-n-Pr	2,5-thiophene	2-aminosulfonylphenyl
	4	H	CH_2O-i-Pr	2,5-thiophene	2-aminosulfonylphenyl
	5	H	CH_2O-n-Bu	2,5-thiophene	2-aminosulfonylphenyl
	6	H	CH_2O-i-Bu	2,5-thiophene	2-aminosulfonylphenyl
	7	H	CH_2Ph	2,5-thiophene	2-aminosulfonylphenyl
	8	H	CH_2-pyrazol-1-yl	2,5-thiophene	2-aminosulfonylphenyl
	9	H	CH_2-imidazol-1-yl	2,5-thiophene	2-aminosulfonylphenyl
	10	H	CH_2-tetrazol-1-yl	2,5-thiophene	2-aminosulfonylphenyl
	11	H	CH_2-tetrazol-2-yl	2,5-thiophene	2-aminosulfonylphenyl
	12	H	CH_2-triazol-1-yl	2,5-thiophene	2-aminosulfonylphenyl
	13	H	CH_2SEt	2,5-thiophene	2-aminosulfonylphenyl
	14	H	CH_2SO_2Et	2,5-thiophene	2-aminosulfonylphenyl
	15	H	CF_3	2,5-thiophene	2-aminosulfonylphenyl
	16	H	CH_3	2,5-thiophene	2-aminosulfonylphenyl
	17	H	H	2,5-thiophene	2-aminosulfonylphenyl

TABLE 8



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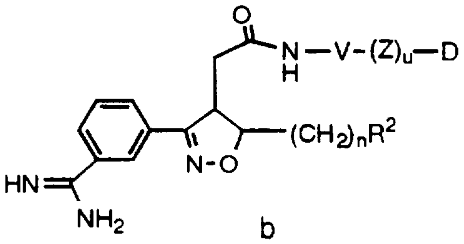


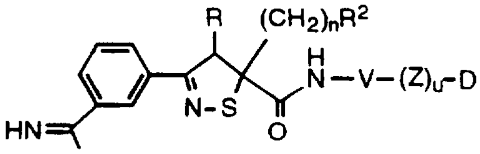
b

Part	Cpd	$(CH_2)_nR^2$	V	$(Z)_u$-D
A	1	CH_2OMe	phenyl	2-aminosulfonylphenyl
	2	CH_2OEt	phenyl	2-aminosulfonylphenyl

	3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
	4	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
	5	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
	6	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
	7	CH_2Ph	phenyl	2-aminosulfonylphenyl
	8	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
	9	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
	10	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
	11	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
	12	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
	13	CH_2SEt	phenyl	2-aminosulfonylphenyl
	14	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
	15	CF_3	phenyl	2-aminosulfonylphenyl
	16	CH_3	phenyl	2-aminosulfonylphenyl
	17	H	phenyl	2-aminosulfonylphenyl
B	1	CH_2OMe	pyridin-2,5-diyl	2-aminosulfonylphenyl
	2	CH_2OEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	3	CH_2O-n-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	4	CH_2O-i-Pr	pyridin-2,5-diyl	2-aminosulfonylphenyl
	5	CH_2O-n-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	6	CH_2O-i-Bu	pyridin-2,5-diyl	2-aminosulfonylphenyl
	7	CH_2Ph	pyridin-2,5-diyl	2-aminosulfonylphenyl
	8	CH_2-pyrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	9	CH_2-imidazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	10	CH_2-tetrazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	11	CH_2-tetrazol-2-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	12	CH_2-triazol-1-yl	pyridin-2,5-diyl	2-aminosulfonylphenyl
	13	CH_2SEt	pyridin-2,5-diyl	2-aminosulfonylphenyl
	14	CH_2SO_2Et	pyridin-2,5-diyl	2-aminosulfonylphenyl
	15	CF_3	pyridin-2,5-diyl	2-aminosulfonylphenyl

	16	CH_3	pyridin-2,5-diyl	2-aminosulfonylphenyl
	17	H	pyridin-2,5-diyl	2-aminosulfonylphenyl
C	1	CH_2OMe	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	2	CH_2OEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	3	CH_2O-n-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	4	CH_2O-i-Pr	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	5	CH_2O-n-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	6	CH_2O-i-Bu	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	7	CH_2Ph	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	8	CH_2-pyrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	9	CH_2-imidazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	10	CH_2-tetrazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	11	CH_2-tetrazol-2-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	12	CH_2-triazol-1-yl	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	13	CH_2SEt	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	14	CH_2SO_2Et	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	15	CF_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	16	CH_3	pyrimidin-2,5-diyl	2-aminosulfonylphenyl
	17	H	pyrimidin-2,5-diyl	2-aminosulfonylphenyl

TABLE 9



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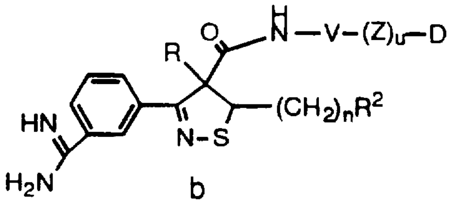


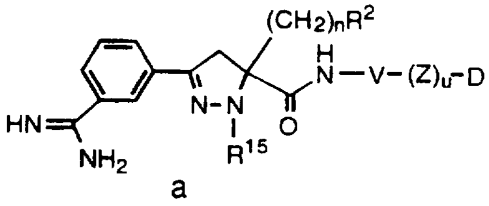
b

Part	Cpd	R	$(CH_2)_nR^2$	V	$(Z)_u$-D
A	1	CH_3	CH_2OMe	phenyl	2-aminosulfonylphenyl

	2	CH_3	CH_2OEt	phenyl	2-aminosulfonylphenyl
	3	CH_3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
	4	CH_3	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
	5	CH_3	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
	6	CH_3	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
	7	CH_3	CH_2Ph	phenyl	2-aminosulfonylphenyl
	8	CH_3	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
	9	CH_3	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
	10	CH_3	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
	11	CH_3	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
	12	CH_3	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
	13	CH_3	CH_2SEt	phenyl	2-aminosulfonylphenyl
	14	CH_3	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
	15	CH_3	CF_3	phenyl	2-aminosulfonylphenyl
	16	CH_3	CH_3	phenyl	2-aminosulfonylphenyl
	17	CH_3	H	phenyl	2-aminosulfonylphenyl
B	1	H	CH_2OMe	phenyl	2-aminosulfonylphenyl
	2	H	CH_2OEt	phenyl	2-aminosulfonylphenyl

3	H	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
4	H	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
5	H	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
6	H	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
7	H	CH_2Ph	phenyl	2-aminosulfonylphenyl
8	H	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
9	H	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
10	H	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
11	H	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
12	H	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
13	H	CH_2SEt	phenyl	2-aminosulfonylphenyl
14	H	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
15	H	CF_3	phenyl	2-aminosulfonylphenyl
16	H	CH_3	phenyl	2-aminosulfonylphenyl
17	H	H	phenyl	2-aminosulfonylphenyl

TABLE 10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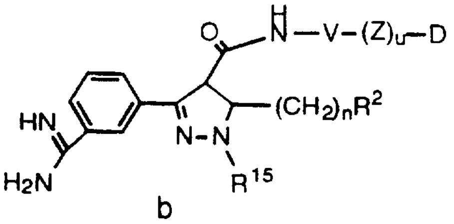
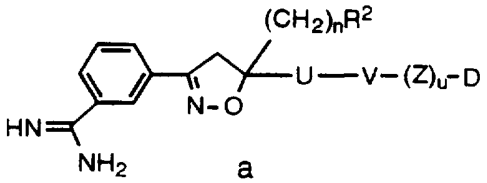

b

Cpd	R^{15}	$(CH_2)_nR^2$	V	$(Z)_u$-D
1	CH_3	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
2	CH_3	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
3	CH_3	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
4	CH_3	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
5	CH_3	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
6	CH_3	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
7	CH_3	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
8	CH_3	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
9	CH_3	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
10	CH_3	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
11	CH_3	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
12	CH_3	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
13	CH_3	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
14	CH_3	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl

15	CH_3	CF_3	1,4-phenylene	2-aminosulfonylphenyl
16	CH_3	CH_3	1,4-phenylene	2-aminosulfonylphenyl
17	CH_3	H	1,4-phenylene	2-aminosulfonylphenyl
18	CH_2CF_3	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
19	CH_2CF_3	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
20	CH_2CF_3	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
21	CH_2CF_3	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
22	CH_2CF_3	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
23	CH_2CF_3	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
24	CH_2CF_3	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
25	CH_2CF_3	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
26	CH_2CF_3	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
27	CH_2CF_3	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
28	CH_2CF_3	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
29	CH_2CF_3	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
30	CH_2CF_3	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
31	CH_2CF_3	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
32	CH_2CF_3	CF_3	1,4-phenylene	2-aminosulfonylphenyl

33	CH_2CF_3	CH_3	1,4-phenylene	2-aminosulfonylphenyl
34	CH_2CF_3	H	1,4-phenylene	2-aminosulfonylphenyl

TABLE 11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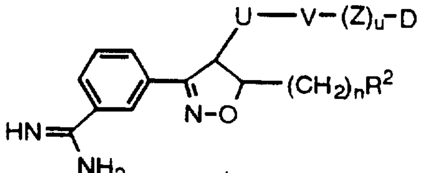

b

Part	Cpd	U	$(CH_2)_nR^2$	V	$(Z)_u$-D
A	1	CH_2NH	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	CH_2NH	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	CH_2NH	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	CH_2NH	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	CH_2NH	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	CH_2NH	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	CH_2NH	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	CH_2NH	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	CH_2NH	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	CH_2NH	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	11	CH_2NH	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	CH_2NH	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	CH_2NH	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	CH_2NH	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	CH_2NH	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	CH_2NH	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	CH_2NH	H	1,4-phenylene	2-aminosulfonylphenyl

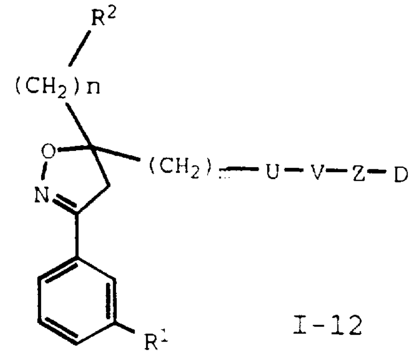
B	1	CH_2CO	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	CH_2CO	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	CH_2CO	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	CH_2CO	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	CH_2CO	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	CH_2CO	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	CH_2CO	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	CH_2CO	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	CH_2CO	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	CH_2CO	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	11	CH_2CO	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	CH_2CO	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	CH_2CO	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	CH_2CO	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	CH_2CO	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	CH_2CO	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	CH_2CO	H	1,4-phenylene	2-aminosulfonylphenyl
C	1	CH_2CH_2	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	CH_2CH_2	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	CH_2CH_2	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	CH_2CH_2	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	CH_2CH_2	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	CH_2CH_2	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	CH_2CH_2	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	CH_2CH_2	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	CH_2CH_2	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	CH_2CH_2	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl

	11	CH_2CH_2	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	CH_2CH_2	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	CH_2CH_2	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	CH_2CH_2	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	CH_2CH_2	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	CH_2CH_2	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	CH_2CH_2	H	1,4-phenylene	2-aminosulfonylphenyl
D	1	SO_2NH	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	SO_2NH	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	SO_2NH	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	SO_2NH	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	SO_2NH	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	SO_2NH	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	SO_2NH	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	SO_2NH	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	SO_2NH	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	SO_2NH	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	11	SO_2NH	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	SO_2NH	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	SO_2NH	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	SO_2NH	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	SO_2NH	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	SO_2NH	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	SO_2NH	H	1,4-phenylene	2-aminosulfonylphenyl
E	1	SO_2CH_2	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	SO_2CH_2	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	SO_2CH_2	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	SO_2CH_2	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	SO_2CH_2	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl

	6	SO_2CH_2	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	SO_2CH_2	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	SO_2CH_2	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	SO_2CH_2	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	SO_2CH_2	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	11	SO_2CH_2	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	SO_2CH_2	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	SO_2CH_2	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	SO_2CH_2	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl
	15	SO_2CH_2	CF_3	1,4-phenylene	2-aminosulfonylphenyl
	16	SO_2CH_2	CH_3	1,4-phenylene	2-aminosulfonylphenyl
	17	SO_2CH_2	H	1,4-phenylene	2-aminosulfonylphenyl
F	1	CH_2O	CH_2OMe	1,4-phenylene	2-aminosulfonylphenyl
	2	CH_2O	CH_2OEt	1,4-phenylene	2-aminosulfonylphenyl
	3	CH_2O	CH_2O-n-Pr	1,4-phenylene	2-aminosulfonylphenyl
	4	CH_2O	CH_2O-i-Pr	1,4-phenylene	2-aminosulfonylphenyl
	5	CH_2O	CH_2O-n-Bu	1,4-phenylene	2-aminosulfonylphenyl
	6	CH_2O	CH_2O-i-Bu	1,4-phenylene	2-aminosulfonylphenyl
	7	CH_2O	CH_2Ph	1,4-phenylene	2-aminosulfonylphenyl
	8	CH_2O	CH_2-pyrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	9	CH_2O	CH_2-imidazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	10	CH_2O	CH_2-tetrazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	11	CH_2O	CH_2-tetrazol-2-yl	1,4-phenylene	2-aminosulfonylphenyl
	12	CH_2O	CH_2-triazol-1-yl	1,4-phenylene	2-aminosulfonylphenyl
	13	CH_2O	CH_2SEt	1,4-phenylene	2-aminosulfonylphenyl
	14	CH_2O	CH_2SO_2Et	1,4-phenylene	2-aminosulfonylphenyl

15	CH_2O	CF_3	1,4-phenylene	2-aminosulfonylphenyl
16	CH_2O	CH_3	1,4-phenylene	2-aminosulfonylphenyl
17	CH_2O	H	1,4-phenylene	2-aminosulfonylphenyl

TABLE 12



I-12

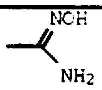
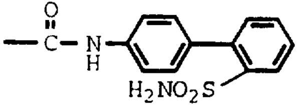
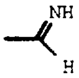
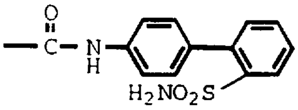
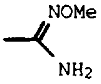
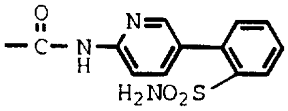
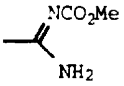
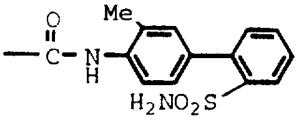
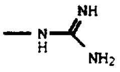
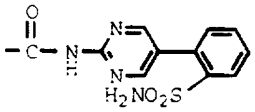
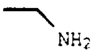
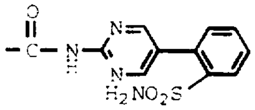
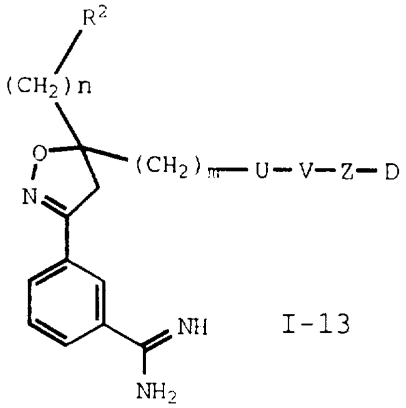
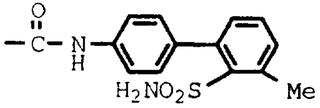
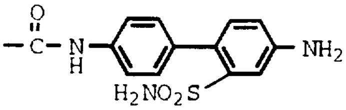
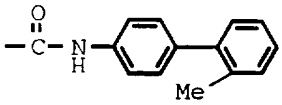
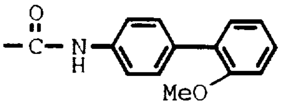
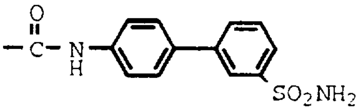
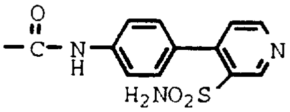
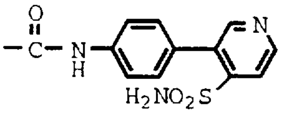
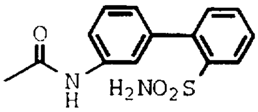
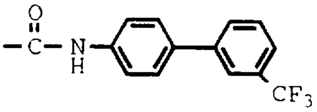
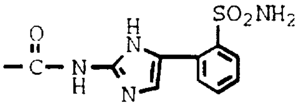
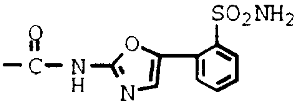
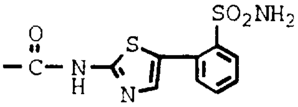
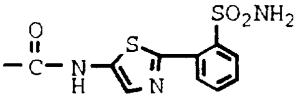
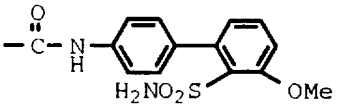
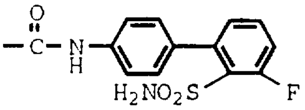
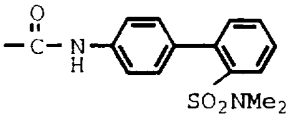
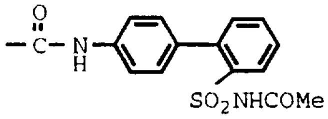
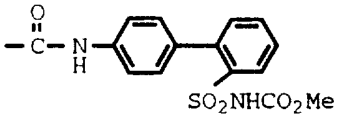
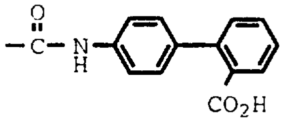
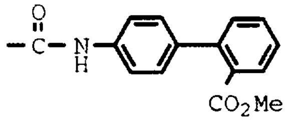
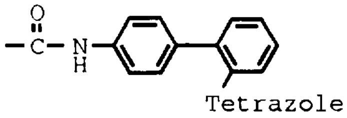
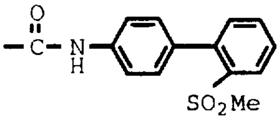
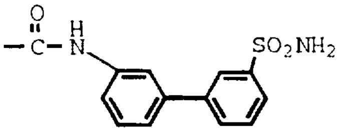
Cpd.#	R^1	n	m	R^2	-U-V-Z-D
1		1	0	CO_2Me	
2		1	0	CO_2Me	
3		1	0	CO_2Me	
4		1	0	CO_2Me	
5		1	0	CO_2Me	
6		1	0	CO_2Me	

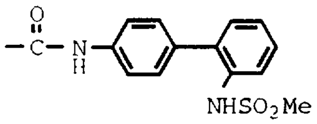
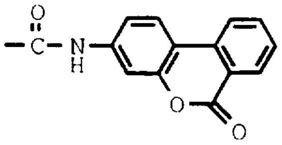
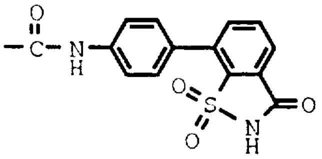
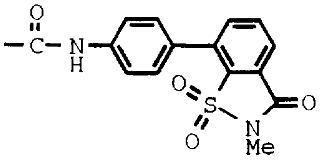
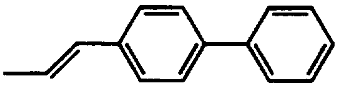
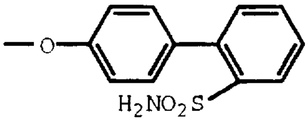
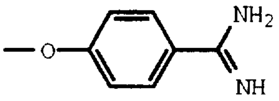
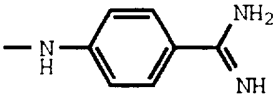
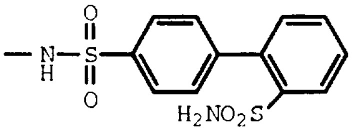
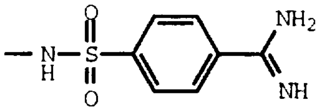
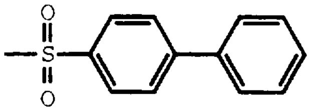
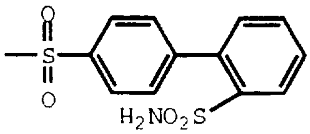
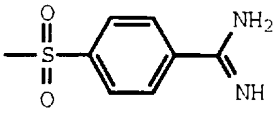
TABLE 13



I-13

Cpd. #	n	m	R^2	-U-V-Z-D
1	1	0	CO_2Me	
2	1	0	CO_2Me	
3	1	0	CO_2Me	
4	1	0	CO_2Me	
5	1	0	CO_2Me	
6	1	0	CO_2Me	
7	1	0	CO_2Me	
8	1	0	CO_2Me	
9	1	0	CO_2Me	

10	1	0	CO_2Me	
11	1	0	CO_2Me	
12	1	0	CO_2Me	
13	1	0	CO_2Me	
14	1	0	CO_2Me	
15	1	0	CO_2Me	
16	1	0	CO_2Me	
17	1	0	CO_2Me	
18	1	0	CO_2Me	
19	1	0	CO_2Me	
20	1	0	CO_2Me	
21	1	0	CO_2Me	
22	1	0	CO_2Me	
23	1	0	CO_2Me	

24	1	0	CO_2Me	
25	1	0	CO_2Me	
26	1	0	CO_2Me	
27	1	0	CO_2Me	
28	0	0	H	
29	0	0	$CONHCH_2CO_2Me$	
30	0	0	$CONHCH_2CO_2H$	
31	0	0	CH_2OMe	
32	0	0	$CH=CH_2$	
33	0	0	$CH=CHCO_2Me$	
34	0	0	$CH=CHCO_2H$	
35	0	0	$CH=CHCONH_2$	
36	0	0	$CH=CHCONH-CH_2CO_2Me$	

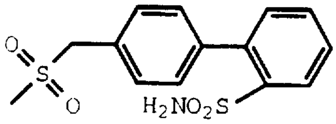
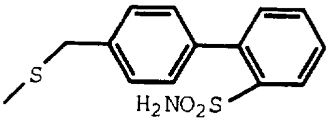
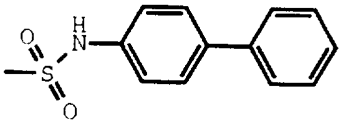
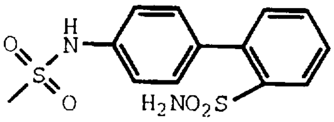
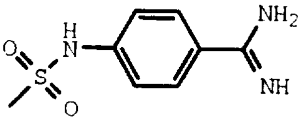
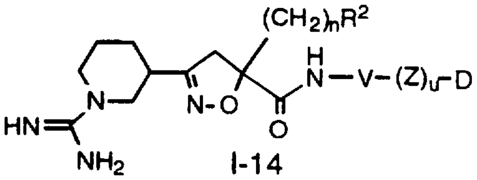
37	0	0	$CH=CHCONH-(CH_2)_2$-4-imidazole	
38	0	0	$CH=CHCH_2OH$	
39	0	0	$CH=CHCH_2OMe$	
40	1	0	CO_2Me	
41	1	0	CO_2Me	

TABLE 14

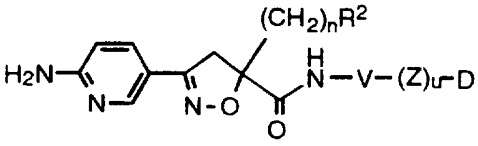


I-14

Cpd	$(CH_2)_nR^2$	V	$(Z)_u$-D
1	CH_2OMe	phenyl	2-aminosulfonylphenyl
2	CH_2OEt	phenyl	2-aminosulfonylphenyl
3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
4	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
5	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
6	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
7	CH_2Ph	phenyl	2-aminosulfonylphenyl
8	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
9	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
10	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
11	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
12	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
13	CH_2SEt	phenyl	2-aminosulfonylphenyl

14	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
15	CF_3	phenyl	2-aminosulfonylphenyl
16	CH_3	phenyl	2-aminosulfonylphenyl
17	H	phenyl	2-aminosulfonylphenyl

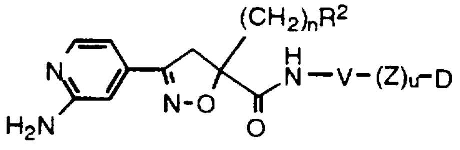
TABLE 15



I-15

Cpd	$(CH_2)_nR^2$	V	$(Z)_u$-D
1	CH_2OMe	phenyl	2-aminosulfonylphenyl
2	CH_2OEt	phenyl	2-aminosulfonylphenyl
3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
4	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
5	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
6	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
7	CH_2Ph	phenyl	2-aminosulfonylphenyl
8	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
9	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
10	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
11	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
12	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
13	CH_2SEt	phenyl	2-aminosulfonylphenyl
14	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
15	CF_3	phenyl	2-aminosulfonylphenyl
16	CH_3	phenyl	2-aminosulfonylphenyl
17	H	phenyl	2-aminosulfonylphenyl

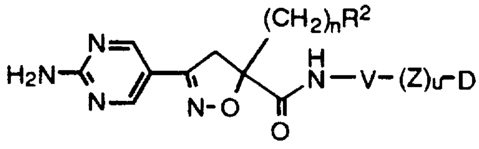
TABLE 16



I-16

Cpd	$(CH_2)_nR^2$	V	$(Z)_u$-D
1	CH_2OMe	phenyl	2-aminosulfonylphenyl
2	CH_2OEt	phenyl	2-aminosulfonylphenyl
3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
4	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
5	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
6	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
7	CH_2Ph	phenyl	2-aminosulfonylphenyl
8	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
9	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
10	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
11	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
12	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
13	CH_2SEt	phenyl	2-aminosulfonylphenyl
14	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
15	CF_3	phenyl	2-aminosulfonylphenyl
16	CH_3	phenyl	2-aminosulfonylphenyl
17	H	phenyl	2-aminosulfonylphenyl

5 **TABLE 17**

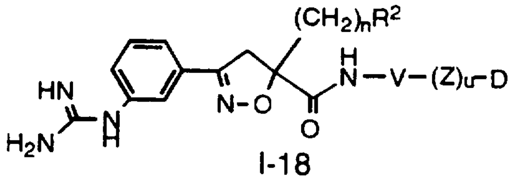


I-17

Cpd	$(CH_2)_nR^2$	V	$(Z)_u$-D
1	CH_2OMe	phenyl	2-aminosulfonylphenyl
2	CH_2OEt	phenyl	2-aminosulfonylphenyl
3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
4	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl

5	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
6	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
7	CH_2Ph	phenyl	2-aminosulfonylphenyl
8	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
9	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
10	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
11	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
12	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
13	CH_2SEt	phenyl	2-aminosulfonylphenyl
14	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl
15	CF_3	phenyl	2-aminosulfonylphenyl
16	CH_3	phenyl	2-aminosulfonylphenyl
17	H	phenyl	2-aminosulfonylphenyl

TABLE 18



I-18

Cpd	$(CH_2)_nR^2$	V	$(Z)_u$-D
1	CH_2OMe	phenyl	2-aminosulfonylphenyl
2	CH_2OEt	phenyl	2-aminosulfonylphenyl
3	CH_2O-n-Pr	phenyl	2-aminosulfonylphenyl
4	CH_2O-i-Pr	phenyl	2-aminosulfonylphenyl
5	CH_2O-n-Bu	phenyl	2-aminosulfonylphenyl
6	CH_2O-i-Bu	phenyl	2-aminosulfonylphenyl
7	CH_2Ph	phenyl	2-aminosulfonylphenyl
8	CH_2-pyrazol-1-yl	phenyl	2-aminosulfonylphenyl
9	CH_2-imidazol-1-yl	phenyl	2-aminosulfonylphenyl
10	CH_2-tetrazol-1-yl	phenyl	2-aminosulfonylphenyl
11	CH_2-tetrazol-2-yl	phenyl	2-aminosulfonylphenyl
12	CH_2-triazol-1-yl	phenyl	2-aminosulfonylphenyl
13	CH_2SEt	phenyl	2-aminosulfonylphenyl
14	CH_2SO_2Et	phenyl	2-aminosulfonylphenyl

15	CF_3	phenyl	2-aminosulfonylphenyl
16	CH_3	phenyl	2-aminosulfonylphenyl
17	H	phenyl	2-aminosulfonylphenyl

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, pulmonary embolisms.

The anticoagulant effect of compounds of this invention is due to inhibition of Factor Xa. The activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (Factor Xa, Factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of Factor Xa can generate 138 molecules of thrombin (*Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII COomplex: Probable role of the complex in the amplification of blood coagulation. Thromb. Res. 1979, 15, 617-629*), inhibition of factor Xa may be more efficient that inactivation of thrombin in interrupting the blood coagulation system.

The effectiveness of the compounds of the invention as inhibitors of Factor Xa was determined using purified human Factor Xa and synthetic substrate. The rate of Factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25 °C using the method of Lineweaver and Burk.

Values of K_i were determined by allowing 0.2 - 0.5 nM human Factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM - 1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values.

$$\frac{v_o - v_s}{v_s} = \frac{I}{K_i\ (1 + S/K_m)}$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;
I is the concentration of inhibitor;
K_i is the dissociation constant of the enzyme: inhibitor complex;
S is the concentration of substrate;
K_m is the Michaelis constant.

The antithrombotic effect of the compounds of this invention can be demonstrated in a rat vena cava thrombosis model. In this model Male Sprague-Dawley rats weighing 350-450 grams anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (110 mg/kg i.m.) are used. A carotid artery, a jugular vein and a femoral vein are cannulated for blood sampling, drug infusion and hypotonic saline injection, respectively. The abdominal vena cava is isolated and all its side-branches are ligated beneath the left renal vein. Thrombus formation is induced by rapid injection of 1 ml hypotonic saline (0.225%) into the vena cava. This is followed 15 seconds later by a 15-minute stasis of an isolated segment (about 1 cm) of the vena cava. The formed thrombus in the vena cava is removed and immediately weighed.

Test compounds or vehicle are given as continuous intravenous infusions or orally starting 1 hour before the injection of hypotonic saline. Arterial blood samples (1.5 ml) for the determination of clotting times are collected before and 1 hour after the infusion or oral dosing of test compounds or vehicle. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of this invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other Factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. Such inhibitors include boroarginine derivatives and boropeptides, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471 651 A2, the disclosures of which are hereby incorporated herein by reference, in their entirety.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosures of which are hereby incorporated herein by reference herein, in their entirety. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of Factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving Factor Xa. The compounds of the present invention may also be used in diagnostic assays involving Factor Xa.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

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

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

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

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

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

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

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

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

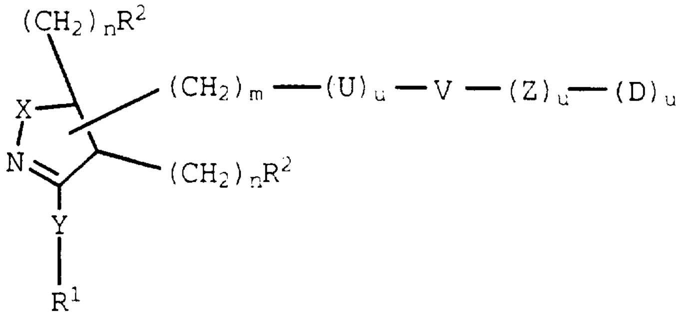
Where the compounds of Formula I are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

WE CLAIM:

1. Compounds of Formula I:



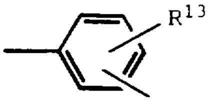
(I)

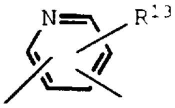
including pharmaceutically acceptable salts and prodrug forms thereof, and all stereoisomeric forms thereof and mixtures of such stereoisomeric forms, wherein:

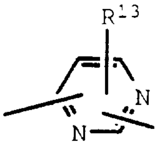
U when present (i.e., when u=1) is selected from
$-CO-NH-(CH_2)_o-$
$-CO-(CH_2)_o-$
$-SO_2-NH-(CH_2)_o-$
$-SO_2-(CH_2)_o-$
$-NHSO_2-(CH_2)_o-$, provided $m \neq 0$
$-NHCO-(CH_2)_o-$, provided $m \neq 0$
$-NH-(CH_2)_o-$, provided $m \neq 0$
$-O-(CH_2)_o-$, provided $m \neq 0$
$-S-(CH_2)_o-$, provided $m \neq 0$
$-CH=CH-(CH_2)_o-$

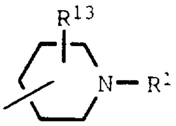
X is O, S, NR^{15}

Y is selected from









R^1 is selected from

$(CH_2)_pNR^5R^6$

$C(NR^{14})NR^5R^6$

$NHC(NR^{14})NR^5R^6$

$NHC(NR^{14})H$

$CONR^5R^6$

R^2 is selected from

H

C_1-C_6 alkyl

C_1-C_6 alkoxy

CO_2R^5

$CONHR^5$

$CONHCH_2CO_2R^5$

$CONH(CH_2)_q$-R^{10}

R^{10}

CO-R^5

$COCO_2R^5$

$COCONHR^5$

SO_nR^5

SO_2NHR^5

NHR^7

$CH=CHCO_2R^5$

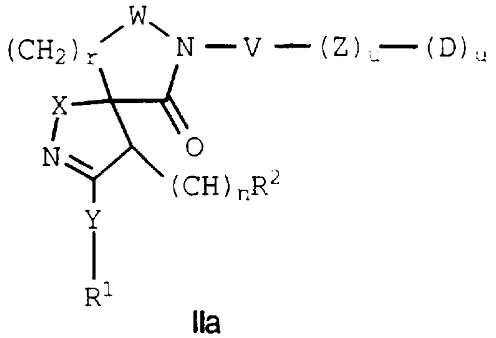
$CH=CHCONHR^5$

O-$(CH_2)_n$-R^{10}

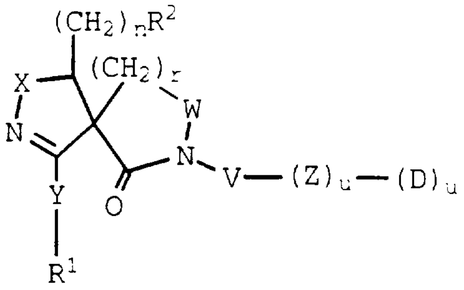
SO_n-$(CH_2)_n$-R^{10}

NH-$(CH_2)_n$-R^{10}

U and R^2 taken together provide a spiro compound of formula IIa and IIb, or a compound of formula IIIa or IIIb:

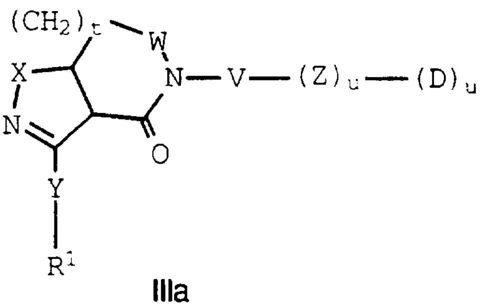


IIa

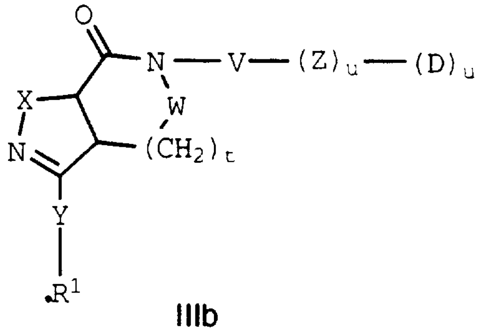


IIb

where W = CO, CH_2, $CHOR^5$ and r = 1-3



IIIa

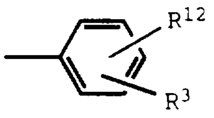


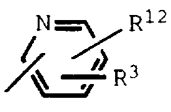
IIIb

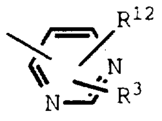
where W = CO, CH_2, $CHOR^5$ and t = 0-2

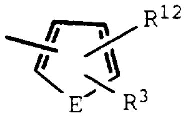
R^3 is selected from
$(CH_2)_sNR^5R^6$
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$
$NHC(NR^{14})H$
$CONR^5R^6$

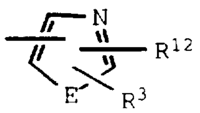
V is selected from the following when Z and D are both absent:

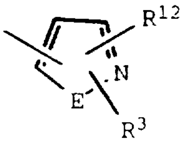


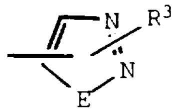


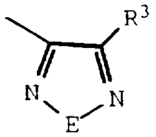


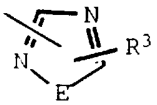


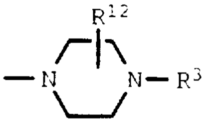


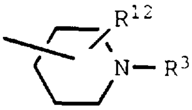


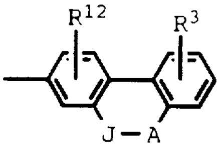


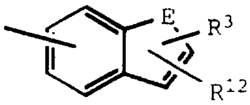


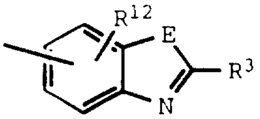


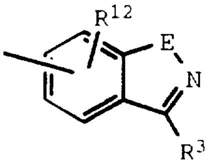


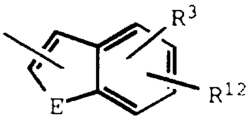


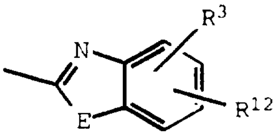


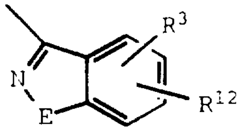


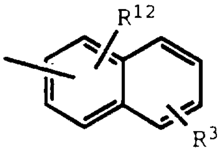












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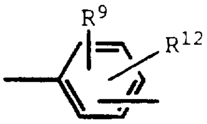
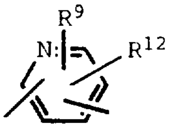
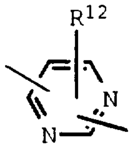
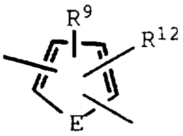
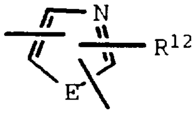
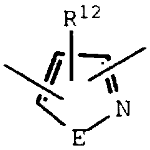


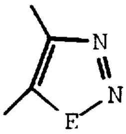


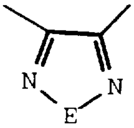


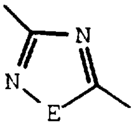


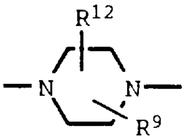


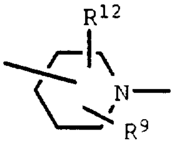


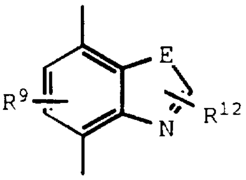


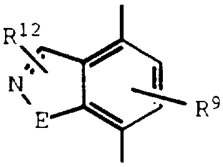


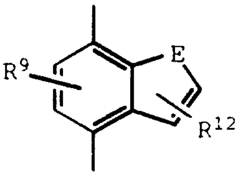


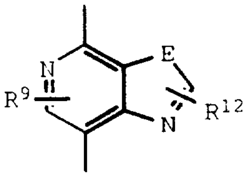


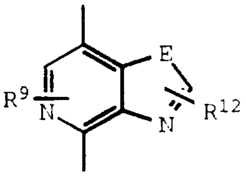


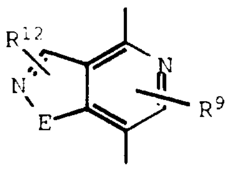


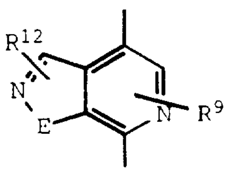


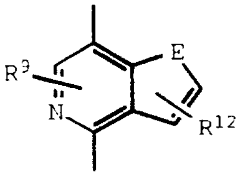


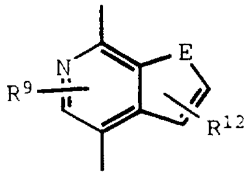


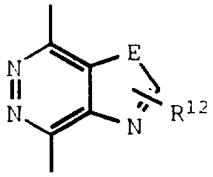


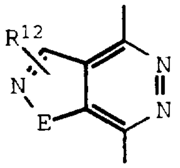


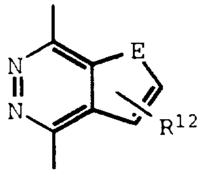












Z when present (i.e., when u = 1) is selected from a single bond,

-CO-,

-$(CH_2)_t$-,

-SO_n-,

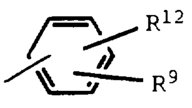
-SO_2NHR^4, provided D is absent

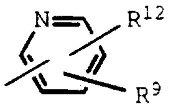
-NH-,

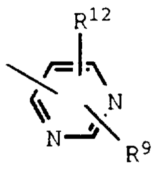
-NR^7-,

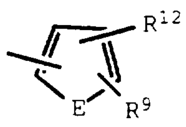
-O-

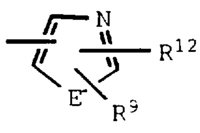
D when present (i.e., when u = 1) is selected from

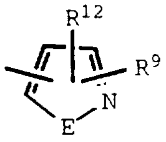


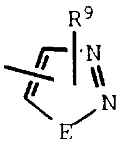


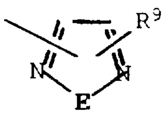


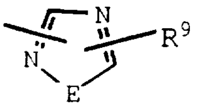


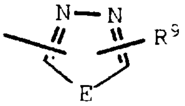


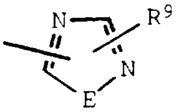


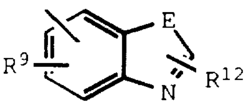


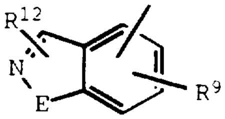


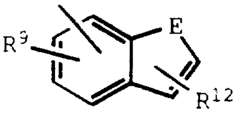


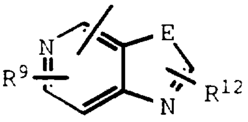


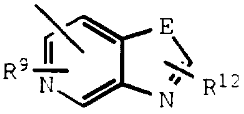


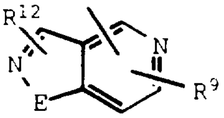


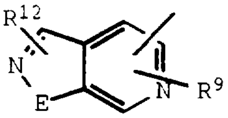


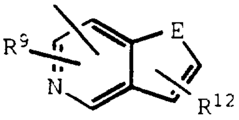


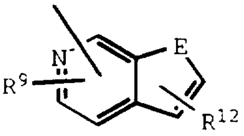


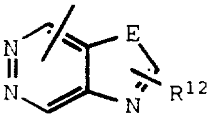


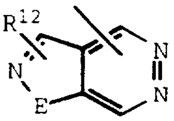


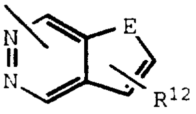












E is selected from N, NR^5, O, S;

J is selected from O, NR^7;

A is selected from CO, CH$_2$, SO, SO$_2$

R^4 is selected from
- H
- C$_1$-C$_6$ alkyl
- (CH$_2$)$_n$-phenyl
- (CH$_2$)$_n$-CONHR^5
- (CH$_2$)$_n$-CONHR^{5}CH$_2$CO$_2$R^5

R^5 and R^6 at each appearance are independently
- H
- C$_1$-C$_6$ alkyl
- (CH$_2$)$_n$-phenyl

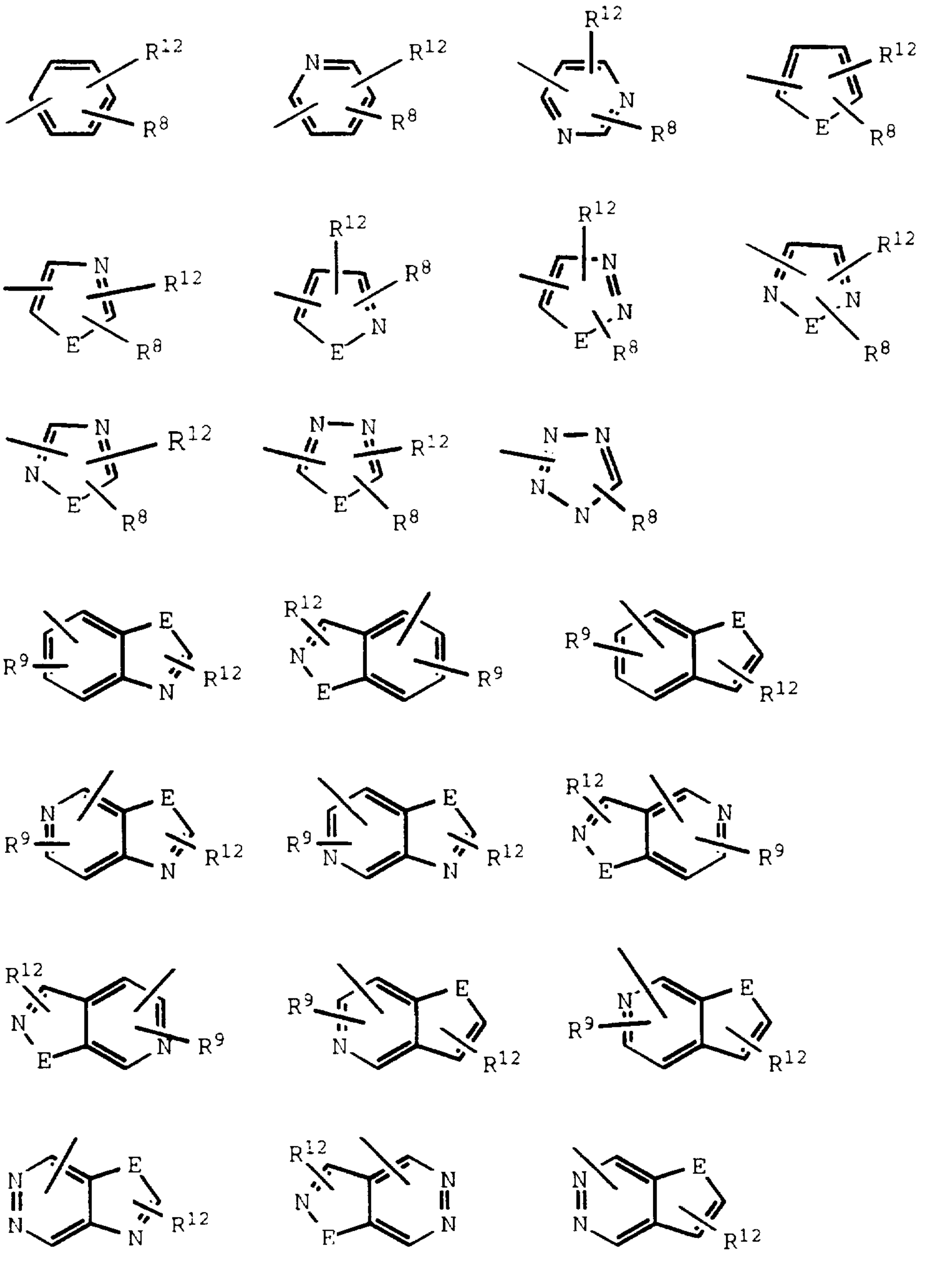
R^7 is selected from
H
C_1-C_6 alkyl
SO_2R^5
COR^5
$(CH_2)_r$-R^{10}
$(CH_2)_n$-phenyl

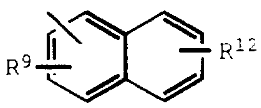
R^8 is selected from
H
C_1-C_6 alkyl
halogen
NO_2
CF_3
OR^5

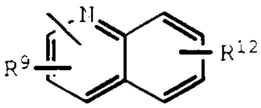
R^9 is selected from
H
C_1-C_6 alkyl
halogen
NO_2
NHR^7
SO_2NHR^{11}
CF_3
OR^5
CO_2R^5
$CONR^5R^7$
CN
$(CH_2)_pNR^5R^6$
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$
$NHC(NR^{14})H$
SO_n-R^5
SO_n-CF_3

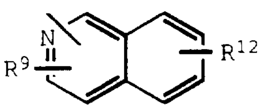
imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole and tetrazole, each optionally substituted with CF_3, halogen, NO_2, C_1-C_5 alkyl, or C_1-C_5 alkoxy;

R^{10} is selected from









R^{11} is selected from

H

C_1-C_6 alkyl

$(CH_2)_n$-phenyl

COR^5

CO_2R^5

R^{12} is selected from

H

C_1-C_6 alkyl

C_1-C_6 alkoxy

halogen

NO_2

NHR^7

CN

CF_3

$SONHR^{11}$

R^{13} is selected from

H

OH

C_1-C_{10} alkyl

C_1-C_{10} alkoxy

nitro

halo

CF_3

R^{14} is selected from

H

OH

C_1-C_{10} alkyl

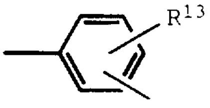
C_1-C_{10} alkoxy

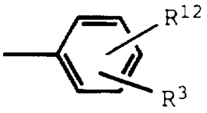
CO_2-C_1-C_{10} alkyl
CO-C_1-C_{10} alkyl
CONH-C_1-C_{10} alkyl
CONH-phenyl
$CO_2(CH_2)_n$-phenyl;

R^{15} is selected from
H
C_1-C_6 alkyl,
C_1-C_6 alkoxy
CO_2R^{14}
$CONHR^{14}$
$CONHCH_2CO_2R^5$
$CONH(CH_2)_q$-R^{10}
$(CH_2)_nR^{10}$
CO-R^5
$COCO_2R^5$
$COCONHR^5$
SO_2NHR^5

at each appearance each of the following are independently:
m = 0-2
n = 0-4, except that in -SO_n-, n = 0-2;
o = 0-2
p = 0-1
q = 0-4
r = 1-2
s = 0-2
t = 0-2
u = 0-1,

provided that, when X is NR^{15}, Z and D are both absent,

Y is 

and V is 

,

then at least one of R^1 and R^3 must be

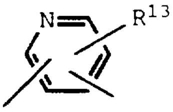
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$ or
$NHC(NR^{14})H$.

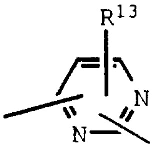
2. Compounds of claim 1 wherein:

U is present and is selected from
$-CO-NH-(CH_2)_o-$
$-CO-(CH_2)_o-$
$-SO_2-NH-(CH_2)_o-$
$-SO_2-(CH_2)_o-$
$-NH-(CH_2)_o-$
$-O-(CH_2)_o-$

X is O

Y is selected from



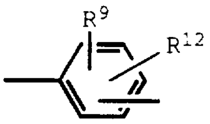


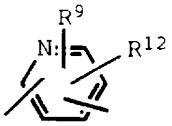
R^1 is selected from
$C(NR^{14})NR^5R^6$
$NHC(NR^{14})NR^5R^6$

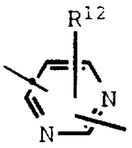
R^2 is selected from
H
C_1-C_6 alkyl
C_1-C_6 alkoxy
CO_2R^5
$CONHR^5$
$CONHCH_2CO_2R^5$
$CONH(CH_2)_q-R^{10}$
R^{10}
$CO-R^5$

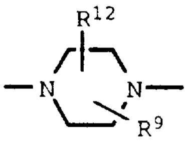
$COCO_2R^5$
$COCONHR^5$
SO_nR^5
SO_2NHR^5
NHR^7
$CH{=}CHCO_2R^5$
$CH{=}CHCONHR^5$
$O\text{-}(CH)_n\text{-}R^{10}$
$SO_n\text{-}(CH)_n\text{-}R^{10}$
$NH\text{-}(CH)_n\text{-}R^{10}$

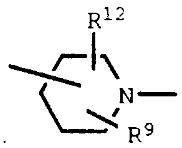
V is selected from the following when Z and/or D are present:

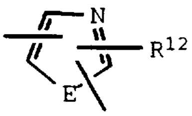




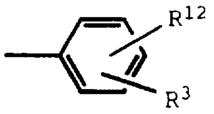


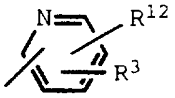


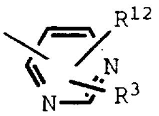


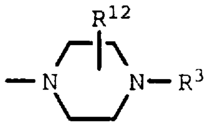


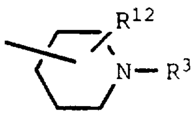
V is selected from the following when Z and D are both absent:

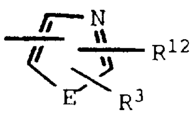




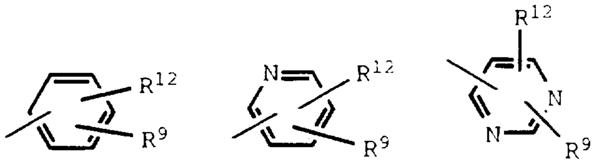




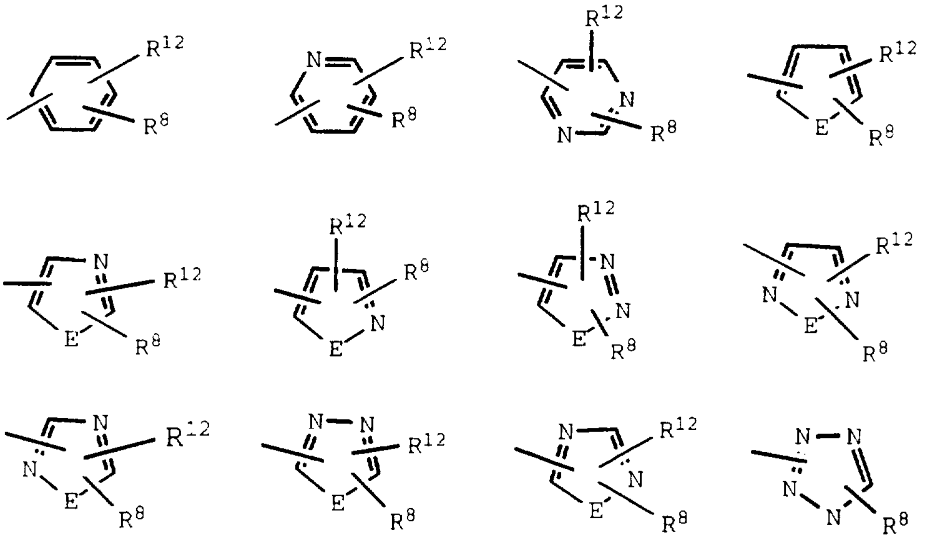




D when present (i.e., when u = 1) is selected from



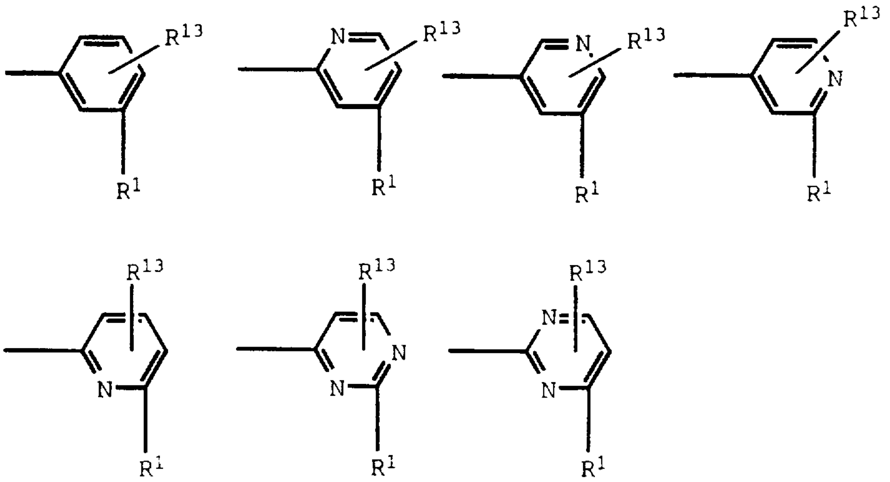
R^{10} is selected from



3. Compounds of claim 2 wherein:

U is $-CO-NH-(CH_2)_o-$

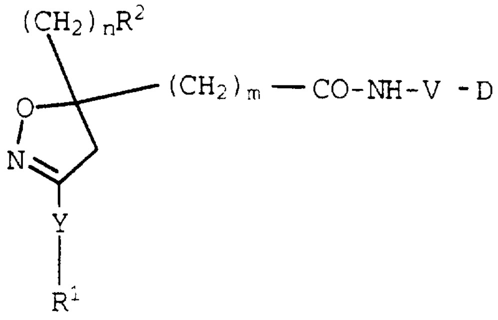
Y is selected from



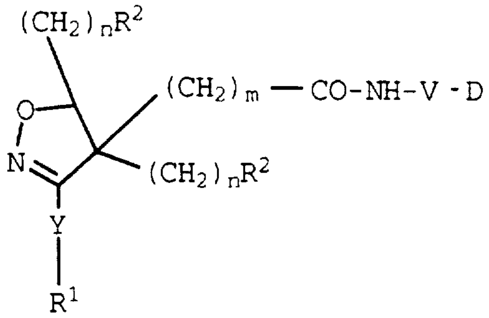
R^1 is $C(NR^{14})NR^5R^6$

Z is absent or is present and is selected from -O- and $-NR^7-$.

4. Compounds of claim 3 having the structures of V and VI:



(V)

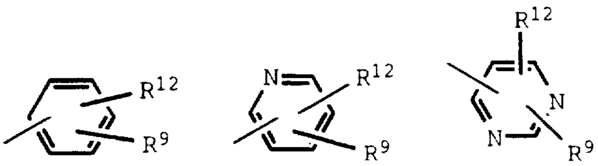


(VI)

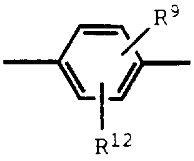
wherein

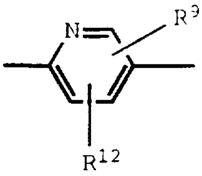
R^1 is $C(NR^{14})NR^5R^6$ and

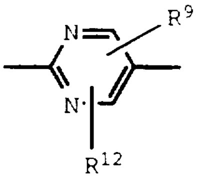
D is selected from



V is selected from the following:







5. A compound of claim 1 selected from the group consisting of the following compounds, including pharmaceutically acceptable salt and prodrug forms thereof, and all stereoisomeric forms thereof and mixtures of such stereoisomeric forms:

3-(3-Amidinophenyl)-5-[(2-naphthylsulfonyl)amino]methyl-isoxazoline

3-(3-amidinophenyl)-5-[[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)-methyl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)methyl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-7-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)methyl[1-oxa-2,7-diazaspiro[4,4]non-2-ene-6,8-diones

3-amidinophenyl 3-(4-amidinophenyl)-5-[(aminocarbonyl)isoxazolin-5-yl]acetamide

4-amidinophenyl 3-(3-amidinophenyl)-5-[(carbometoxy)isoxazolin-5-yl]acetamide

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]-5-[(carbomethoxymethyl)aminocarbonylmethyl]isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(4-amidinophenyl)-5-[(3-amidinophenyl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)methylaminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-benzenesulfonylpiperidin-1-yl)carbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[(4-pyrimidin-5-yl)piperidin-1-yl]carbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-benzenesulfonylphenyl-1-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4-amidinophenyl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[([1,1']-biphenyl-4-yl)aminocarbonyl]-5-(hydroxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3'-n-propyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-t-butylaminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(4'-amino-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-trifluoromethyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl)]-5-(carbomethoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxyethylene)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl)-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethylaminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-[(imidazole-4-yl)ethylaminocarbonylmethyl]isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethylaminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-methyl-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[(2'-aminosulfonyl-3-fluoro-[1,1']-biphenyl-4-yl)aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[2-(2'-aminosulfonylphenyl-1-yl)pyridin-5-yl]aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(aminocarbonylmethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(hydroxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(methoxyethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl]-5-(methyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(carbomethoxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl]-5-(carboxymethyl)isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-carbomethoxymethyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-carbomethoxymethyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylsulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-trifluoromethylsulfonylphenyl-1-yl)pyrimidin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-3-flouro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-3-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethyl-3-flouro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethyl-3-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-aminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-methoxymethyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylaminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[5-(2'-methylaminosulfonylphenyl-1-yl)pyridin-2-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylsulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylsulfonyl-fluoro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-methylsulfonyl-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethylsulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(imidazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethylsulfonyl-3-fluoro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-trifluoromethylsulfonyl-3-chloro-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(tetrazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-5-[2'-aminosulfonyl-[1,1']-biphenyl-4-yl]aminocarbonyl-5-(imidazol-1-yl)methyl-isoxazoline

3-(3-amidinophenyl)-4-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-methoxymethyl-isoxazoline

3-(3-amidinophenyl)-4-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-5-trifluoromethyl-isoxazoline

3-(3-amidinophenyl)-5-(2'-aminosulfonyl-[1,1']-biphenyl-4-yl)aminocarbonyl-4-methoxymethyl-isoxazoline

6. Pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1 through 5 and a pharmaceutically acceptable carrier.

7. A method of treating or preventing a thromboembolic disorder in a mammal which comprises administering to the mammal a therapeutically effective amount of a compound of any of claims 1 through 5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20076

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/42; C07D 261/04
US CL :548/240; 514/378
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)

U.S. : 548/240; 514/378

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

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

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,262,388 A (MUNRO ET AL.) 16 November 1993 (16.11.93), see entire document, especially column 1.	1-7, parts

☐ Further documents are listed in the continuation of Box C. ☐ See patent family 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 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 19 FEBRUARY 1997	Date of mailing of the international search report 07 APR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer R.W. RAMSUER aco Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20076

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

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

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

2. ☒ Claims Nos.: (1-7 parts)
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:

Please See Extra Sheet.

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.

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. U, V, X, Y, Z, R1, R2, R3, u, d, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a N=C-C-C group which does not define a contribution over the prior art. Therefore, the first discernable invention as found in Example 1 (i.e. the compound, the pharmaceutical composition therewith, and the method of treating unstable angina) has been searched.