

BIPHENYL SULFONAMIDES AS
DUAL ANGIOTENSIN ENDOTHELIN RECEPTOR ANTAGONISTS

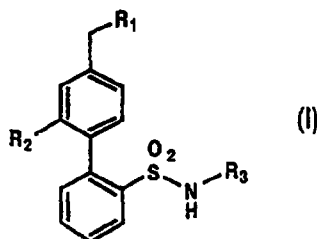
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Field of the Invention

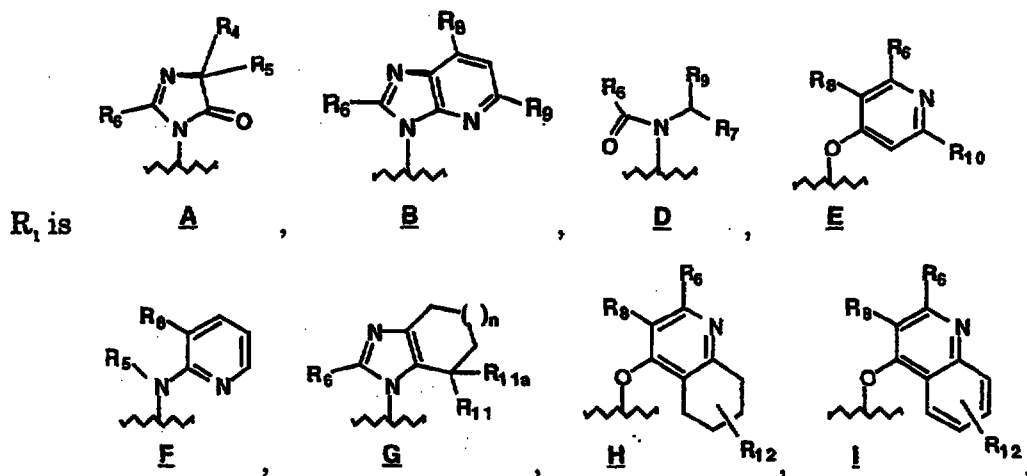
The present invention relates to biphenyl sulfonamide compounds which are combined angiotensin and endothelin receptor antagonists, to methods of using such compounds in the treatment of conditions such as hypertension and other diseases, and to pharmaceutical compositions containing such compounds.

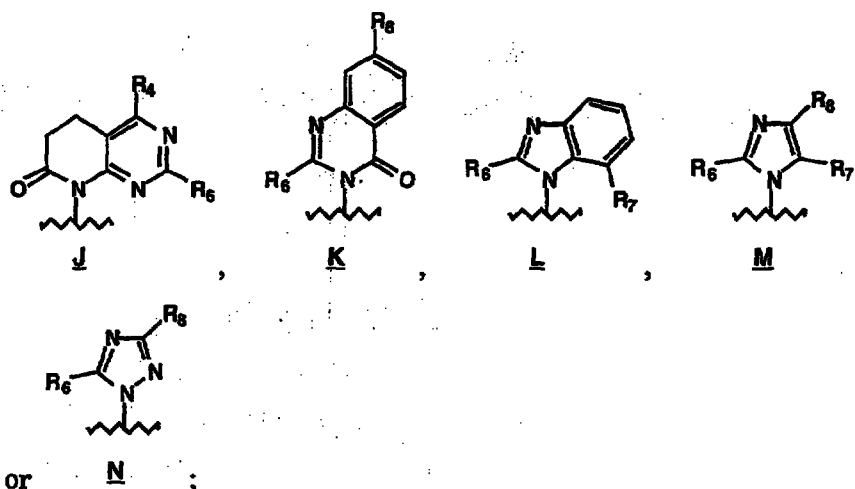
Summary of the Invention

The present invention provides biphenyl sulfonamide compounds of the following formula I and salts thereof:



wherein:





R_2 is hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, $-\text{CH}(\text{OR}_{13})(\text{OR}_{14})$, $-(\text{CH}_2)_w\text{Y}$; with the proviso that when R_1 is B, R_2 is not hydrogen, halogen, alkyl, haloalkyl, alkoxy, hydroxyalkyl, nitro, $-(\text{CH}_2)_w\text{NR}_{19}\text{R}_{20}$ or $\text{NHSO}_2\text{R}_{22}$;

R_3 is heteroaryl;

R_4 and R_5 are each independently alkyl, cycloalkyl or alkoxyalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl or tetrahydropyranyl ring;

R_6 is alkyl, haloalkyl, cycloalkyl, alkoxy or alkoxyalkyl;

R_7 is $-\text{CO}_2\text{R}_{15}$, $-(\text{C}=\text{O})\text{NR}_{16}\text{R}_{17}$, $-\text{CH}_2\text{OH}$, tetrazolyl, oxadiazolyl or triazolyl wherein said tetrazolyl, oxadiazolyl or triazolyl may optionally be substituted with hydrogen, alkyl or halogen;

R_8 , R_9 , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylthioalkyl, alkoxy or alkoxyalkyl;

R_{11} and R_{13} are each independently hydrogen, alkoxy, or together form a carbonyl;

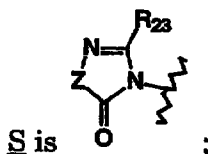
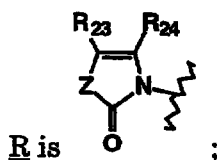
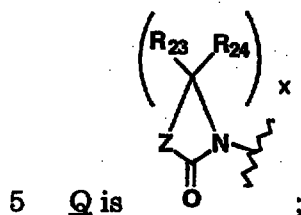
R_{13} and R_{14} are alkyl or together form a five to six-membered ring;

R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, cycloalkyl or aryl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;

n is 1 or 2;

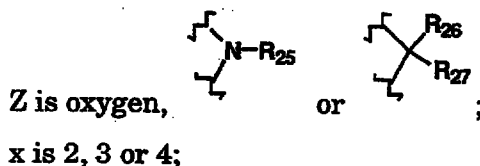
w is 0, 1, or 2;

Y is $-\text{COOH}$, $-\text{COOR}_{18}$, $-\text{NR}_{19}\text{R}_{20}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{R}_{22}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{NR}_{19}\text{R}_{20}$,
 $-\text{NR}_{21}(\text{C}=\text{O})\text{OR}_{18}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{R}_{22}$, Q, R or S;



R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl,
 or R_{19} and R_{20} may together form a four to seven-membered
 10 heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may
 together form a three to seven membered cycloalkyl ring;



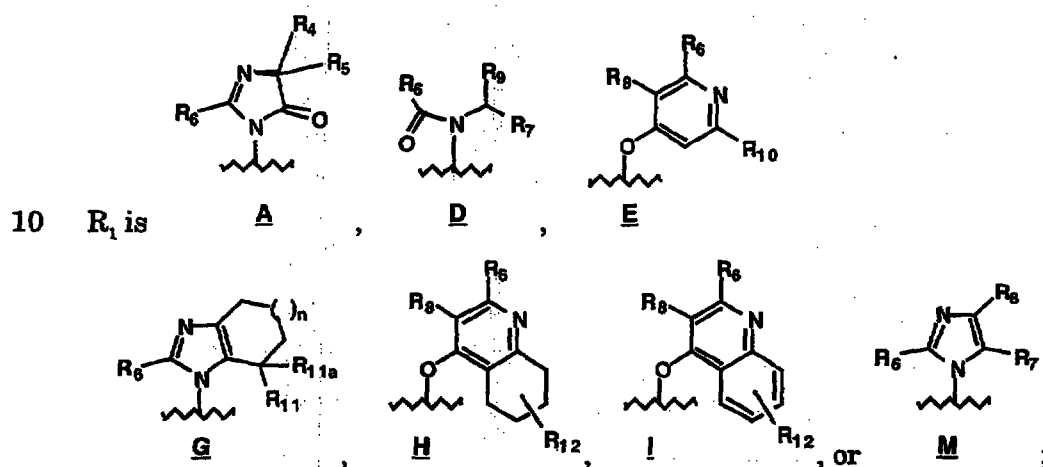
15 R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26}
 and R_{27} may together form a three to seven-membered cycloalkyl
 ring;

wherein said rings; aryl alone or as part of another group; or
 heteroaryl alone or as part of another group may each optionally be
 20 substituted by one or more hydrogen, halogen, cyano, alkyl, alkoxy, nitro
 or trifluoromethyl groups.

The compounds of the formula I and salts thereof may be used as combined endothelin and angiotensin receptor antagonists.

Preferred Compounds

- 5 Compounds of the formula I and salts thereof wherein one or more, and especially all, of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{11a} , R_{12} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , n , w , Y , Q , Z , and x are selected from the following definitions, are preferred compounds of the present invention:



R_2 is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY$;

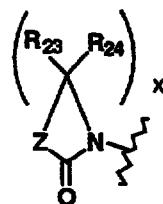
- R_3 is isoxazolyl, pyridizynyl, pyrazinyl or pyrimidinyl, each optionally substituted with one to three of the following substituents:
 15 hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;
 R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;
 R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;
 20 R_7 is $-CO_2R_{16}$, $-(C=O)NR_{16}R_{17}$ or $-CH_2OH$;
 R_8 , R_9 , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;
 R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;

R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl or cycloalkyl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;

n is 1 or 2;

w is 0, 1, or 2;

- 5 Y is $-\text{COOR}_{18}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{R}_{22}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{NR}_{19}\text{R}_{20}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{OR}_{18}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{R}_{22}$ or Q ;

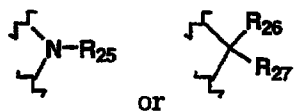


Q is

R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

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R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

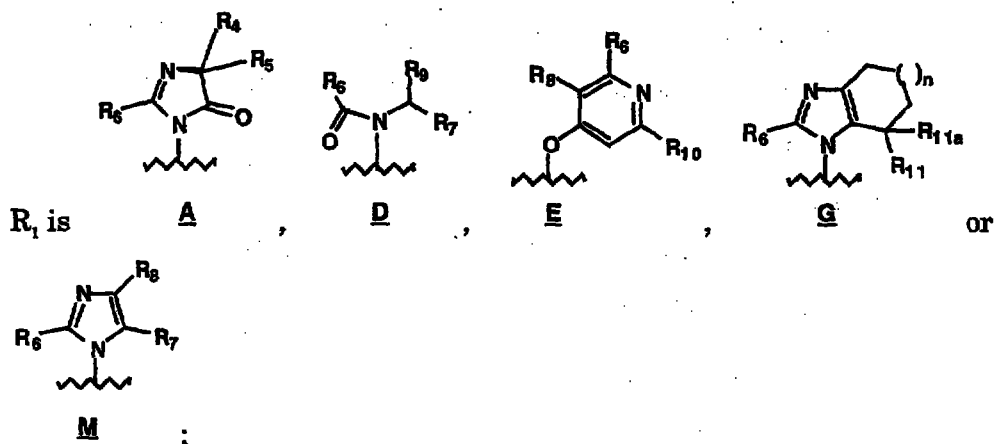


Z is oxygen,

x is 2, 3 or 4;

- 15 R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

Compounds of the formula I and salts thereof wherein one or more, and especially all, of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{11a} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , n , w , Y , Q , Z , and x are selected from the following definitions, are more preferred compounds of the present invention:



R_2 is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, hydroxyalkyl, or $-(CH_2)_wY$;

- 5 R_3 is isoxazolyl, optionally substituted with one or two of the following substituents: hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;

R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;

- 10 R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;

R_7 is $-CO_2R_{15}$ or $-(C=O)NR_{16}R_{17}$;

R_8 , R_9 and R_{10} are each independently hydrogen, halogen, alkyl, cycloalkyl alkoxy or alkoxyalkyl;

R_{11} and R_{11a} together form a carbonyl;

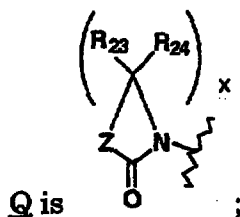
- 15 R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, or cycloalkyl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;

n is 2;

w is 0, 1, or 2;

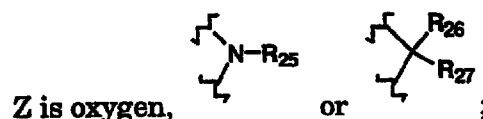
Y is $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$,

- 20 $-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$ or **Q**;



R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may
5 together form a three to seven membered cycloalkyl ring;

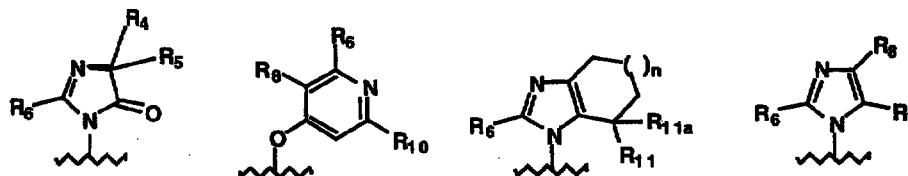


x is 2, 3 or 4;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

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Compounds of the formula I and salts thereof wherein one or more, and especially all, of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_{10} , R_{11} , R_{11a} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{23} , R_{24} , R_{25} , R_{26} , R_{27} , w, Y, Q, Z, and x are selected from the following definitions, are most preferred compounds of the present invention:



15 R_1 is A, E, G, or M ;

R_2 is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY$;

R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two of following substituents: alkyl or halogen;

20 R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;

R_6 is alkyl, halo alkyl, cycloalkyl or alkoxy;

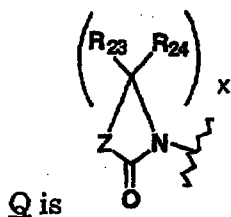
R_7 is $-CO_2R_{15}$ or $-(C=O)NR_{16}R_{17}$;

R_8 and R_{10} are independently H, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

25 n is 2;

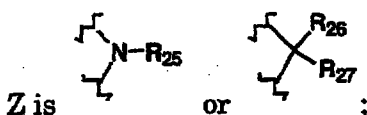
w is 0, 1, or 2;

Y is $-\text{NR}_{21}(\text{C}=\text{O})\text{R}_{22}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{NR}_{19}\text{R}_{20}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{OR}_{18}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$ or $\underline{\text{Q}}$;



R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;



x is 2;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

Detailed Description of the Invention

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred.

The term "alkoxy" refers to an alkyl group bonded through an oxygen (-O-).

The terms "ar" or "aryl" refer to phenyl, naphthyl and biphenyl. Phenyl is a preferred aryl group. Aryl groups may be optionally

substituted with one or more (such as one to three) of the following substituents: hydrogen, halogen, cyano, alkyl, alkoxy, nitro or trifluoromethyl groups.

5 The term "cycloalkyl" refers to fully saturated cyclic hydrocarbon groups having 3 to 8 ring carbon atoms.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine. Haloalkyl refers to an alkyl chain substituted with from one to three halogens.

10 The term "heteroaryl" refers to furyl, thienyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, triazolyl, and tetrazolyl, each of which may optionally be substituted where appropriate by one or more (such as one to three) of the following: hydrogen, halogen, cyano, alkyl, alkoxy, nitro or trifluoromethyl.

15 The terms "heterocyclic" or "heterocyclo" refer to optionally substituted, non-aromatic cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a
20 heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system.

25 Exemplary monocyclic heterocyclic groups include azetidiny, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl,
30 thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like.

The term "ring" encompasses homocyclic (i.e., as used herein, all the ring atoms are carbon) or "heterocyclic" (i.e., as used herein, the ring atoms include carbon and one to four heteroatoms selected from N, O and /or S, also referred to as heterocyclo), where, as used herein, each of which
5 (homocyclic or heterocyclic) may be saturated or partially or completely unsaturated (such as heteroaryl), and each of which (homocyclic or heterocyclic) may optionally be substituted by one or more (such as one to three) hydrogen, halogen, cyano, alkyl, alkoxy, nitro or trifluoromethyl groups.

10 Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise
15 indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety and an acidic moiety, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically
20 acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such
25 as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety may form salts with a variety of organic and inorganic acids. Exemplary acid
addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates,
30 ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates,

butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid),
5 hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates,
10 propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of formula I which contain an acidic moiety may
15 form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with
20 N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g.
25 dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a
30 compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the

formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I are preferably hydrates. Any tautomers which may exist are also contemplated herein as part of the present invention.

All stereoisomers of the present compounds, such as those which
5 may exist due to asymmetric carbons on the R substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may
10 be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

The present invention can be applied to the extensive prior art in
15 the field of angiotensin antagonists to obtain additional novel compounds possessing potent antagonist activity at both endothelin and angiotensin receptors. In particular, a large number of groups (known to be useful within the field of angiotensin receptor antagonists) can be substituted at the R₁ position of Formula I without departing from the scope of the
20 present invention. The table below outlines examples of additional suitable R₁ groups.

Patent No.	Description of R ₁
JP 09291078	Substituted imidazoles
JP 09301956	Substituted imidazoles
JP 09323991	carboxy methyldene cyclohepta imidazoles
WO 97/40040	Pyrimidin-4-ones
US 5674879	tetrahydro-imidazopyridines
WO 97/30036	N-acylaminoacid derivatives

JP 09110691	Imidazotetrahydropyridines
JP 08208640	Benzimidazoles
JP 08165292	purine derivatives
JP 08143552	Cyclohepta imidazoles
JP 08113572	Imidazopyridines
WO 96/10559	Ureas
EP 708103	Imidazolones
WO 96/08476	Pyrimidinones
JP 08041053	Pyrimidines
JP 08034780	Cycloheptimidazoles
WO 96/05195	naphtho-fused lactams
WO 96/04273	Pyrazoles
EP 696583	Benzimidazoles
JP 07316055	Pyrimidines
WO 95/34564	Pyridylimidazoles
JP 07309871	Hydrazotriazoles
WO 95/32198	Pyridylimidazoles
AU 95/16257	Imidazopyridines
WO 95/24902	Imidazoles
DE 4407488	Pyridones
WO 95/22543	Imidazoles
WO 95/21838	Pyridylimidazoles
JP 07157485	fused pyrimidinones
US 5411980	N-arylsubstituted-1,2,4-triazolinones
WO 95/16677	pyrimidine/pyrimidinones
WO 95/16675	Benzazepin-3-yl-ureas
WO 95/16692	Benzazepin-3-yl-ureas
US 5426105	Dihydroimidazopyridines
US 5424450	Imidazolinones
DE 4341453	4-oxo-imidazo-pyridines
JP 07112975	Amino-azoles
DE 4339868	4-oxo-imidazo-pyridazines
WO 95/12598	benzazepinyl urea macrocycles
EP 648763	Imidazoles
WO 95/09632	benzazepin-3-yl-ureas
EP 647627	pyridinones
JP 07048357	aminoacids
WO 95/03290	benzofused lactams
DE 4342724	2-oxo-1,2-dihydro-pyridines
WO 93/17023	pyrazolopyrimidines
US 5385894	6-aminoquinazolines

JP 07002776	N-arylmethylpyridines
JP 06340668	pyrazolotriazoles
US 5380719	quinoxalines and its N-oxides
GB 2280438	carboxymethylidene cycloheptimidazoles
WO/95/00517	imidazoles
US 5378704	benzo- and pyrido-1,2,4-thiadiazines
JP 06287182	alkylglycines
EP 623610	pyridine and pyridones
US 5358947	pyrazolotriazinones
WO 94/22838	pyrazoles
EP 621276	2,3,6-substituted quinazolinone derivatives
WO 94/21629	1-phenyl-imidazol-2-ones
JP 06211814	thioureas
EP 618207	5,8-dihydro-6H-pyrido-pyrimidin-7-ones
DE 4305279	triazolopyrimidines
WO 94/17069	pyrazoles
WO 94/17067	pyrimidones
US 5338736	2,3,6-substituted quinazolinone derivatives
JP 06184086	thioureas
DE 4300912	1-benzyl-1,2,3,4-tetrahydroquinazolin-2-ones or related analogs
US 5330987	pyridopyrimidinones
EP 607077	4-pyrimidinones
WO 94/13675	pyrazolotriazoles
US 5326776	5-membered heterocyclic rings comprising 1-4 N or 2 N and 1 O and comprising 0-2 double bonds
EP 602521	imidazopyridines
WO 94/11379	pyridooxazinones
WO 94/11012	dipeptide analogs
EP 591891	benzimidazoles
US 5315013	pyrazoles
JP 06100541	pyrazolinones
WO 94/04516	5-membered ring heterocycles containing 1-4 heteroatoms
JP 06087833	vinyl imidazoles
EP 594022	2-pyridones
EP 594019	2-pyridones
JP 06073008	alkoxy-pyridines
JP 06072985	ureas and thioureas
DE 4233590	benzimidazoles
JP 06065236	dihydrobenzimidazolones

JP 06056826	quinoxalines
EP 589665	4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxamides
JP 06041122	quinoxalines
DE 4230464	imidazolylbenzimidazoles
US 5296480	2-alkyl-5,6,7,8-tetrahydro-pyrido (4,3-d)-pyrimidine-4-ones
US 5294617	quinazolinones
US 5294611	quinazolinones
US 5292734	quinazolinones
JP 06032782	pyrazoles
US 5290780	quinazolinones
JP 06025250	thieno[3,4-d]imidazoles
JP 06025229	imidazoles
WO 94/03453	pyrazolyl[4,3-c]pyridines
WO 94/03449	imidazoles
WO 94/03435	imidazole-5-carboxylic acids
US 5288720	quinazolinones
JP 06016661	imidazoles
US 5284853	quinazolinones
US 5284852	quinazolinones
JP 06009638	pyrazolopyrimidines
WO 94/02467	imidazoles
US 5281604	quinazolinones
US 5281603	quinazolinones
US 5281602	pyridopyrimidines
DE 4224133	benzimidazoles
US 5276048	imidazoles
GB 2268743	pyridines/pyrazines/pyrimidines
JP 05310696	pyridines
EP 574846	imidazopyridines
DE 4237656	benzimidazoles
FR 2690442	pyrazolopyrimidines
GB 2267089	cycloheptimidazoles
EP 573218	imidazoles
WO 93/23391	indoles, 7-azaindoles
US 5260325	N-linked amides or thioamides
DE 4212748	benzimidazoles
EP 566020	benzimidazoles
DE 4212250	benzimidazoles
US 5250548	aminopyridines

GB 2265900	pyrazoles
EP 562936	imidazolines
WO 93/18035	aza-phthalimides
WO 93/17682	bicyclic heterocycles
WO 93/17681	5-membered ring heterocycles
EP 561252	2-oxoquinolines
JP 05201994	pyridazinones
GB 2264709	imidazopyridines
JP 05194418	2-aminopyrimidines
WO 93/16049	4-oxo-dihydropyridines
JP 05178836	pyridines
EP 556080	pyrazolo[1,5-a]pyridines or imidazo[1.5-a]pyridines
US 5231094	triazolopyrimidines
EP 554107	1,2,4-triazole
EP 554098	imidazo[4,5b]pyridines
WO 93/14086	1-isoquinolones
EP 552765	benzimidazoles
JP 05155884	benzopyrazines or pyridopyrazines
WO 93/13077	hydantoins connected to imidazoles
US 5225408	oxadiazinone
JP 05140152	quinazolinone
EP 550313	pyrazolone and pyrimidinones
US 5219856	imidazoles
EP 547514	imidazopyridines
US 5218125	imidazoles
GB 2262096	4-aminopyrimidines
US 5214153	imidazoles
US 5212195	indoles, azaindoles
EP 543263	benzimidazoles
DE 4221583	pyridones
US 5208234	imidazolephosphonic acids
WO 93/08193	imidazo-tetrahydropyridazines
WO 93/08171	pyrimidocycloalkanes
WO 93/08169	aminopyrimidines
EP 539086	pyrimidinolactams
EP 537937	pyrazinopyrimidinones
DE 4132632	imidazolylpropenoic acids
EP 535465	imidazolylpropenoic acids
EP 535463	imidazolylpropenoic acids
EP 535420	imidazoles
EP 534706	quinazolinone or pyridopyrimidinones

WO 93/05044	pyrazolotriazines
WO 93/05025	pyrazoles
WO 93/04059	imidazoles
WO 93/04045	imidazolinones
JP 05032661	imidazolinones
EP 532410	imidazolinones and larger ring analogs
EP 531876	imidazoindolizines
EP 531874	4,5,6,7-tetrahydroimidazo[4,5-c]pyridine-4-carboxylic acids
EP 530702	1,2-dihydro-2-oxypyridines
WO 93/03040	thienopyrimidin-4-ones
WO 93/03033	imidazo[4,5-d]pyridazines
WO 93/03018	pyrimidines
US 5187168	quinazoline derivatives
JP 05017480	thienoimidazoles
US 5185340	oxypyrimidines
US 5182288	lactams
FR 2677016	acyl amino acid derivatives
WO 93/00341	imidazoles
WO 92/22533	4-aminoquinolines
US 5124335	fused pyrroles
EP 490820	acylamino derivatives
EP 490587	pyrazolo-pyrimidine and imidazopyridazines
EP 495626	oxypyridines, oxyquinolines, and imidazoles
EP 497150	3-quinazolin-4-ones
EP 497121	imidazoles
EP 498721	1,4-dihydroquinolin-4-ones
US 5132216	imidazopyridines
EP 499416	oxypyridines
EP 499415	aminopyridines
EP 499414	Fused oxypyridines
EP 500409	4-pyrimidones
EP 500297	2-pyridones and 2-pyrimidones
EP 502725	fused pyrimidones
EP 502575	1-(2H)-isoquinolinones
EP 502314	benzimidazoles
EP 505098	imidazoles
EP 503785	imidazoles
JP 04230683	7-aza and 4- azabenzimidazoles (i.e., imidazopyridines)
EP 507594	quinolines

JP 04235988	imidazopyridazinediones
EP 505893	imidazopyridines
FR 2672891	pyrazolones
US 5145699	pyridopyrimidines
EP 515265	pyrimidine derivatives
EP 511791	pyrrolopyridines
JP 04257564	benzimidazoles, imidazopyridines, imidazopyrazines
WO 92/16524	benzo-fused lactams
EP 516392	naphyridones and pyrido[c,b]pyrrolidones
WO 92/19211	imidazobenzoquinones
JP 04295478	imidazo[4,5-b]pridines
EP 5212768	triazolo pyrimidines
WO 92/21666	thiazole derivatives
EP 518033	imidazo[4,5-c]pyridine-4-carboxylates and other heterocycles
US 5087702	3H-imidazo-[4,5-b] pyridines
US 5087634	N-substituted imidazol-2-ones
WO 92/00977	imidazoles
EP 475206	various 6-membered heterocycles
WO 92/02508	oxyquinolines
WO 92/04343	tetrahydrobenzazoles
WO 92/04335	1H-1,2,4-triazoles
EP 475898	Azacyclic compounds including imidazolinones
EP 481448	dihydropyrimidines
QO 92/05161	1,3,5-trisubstituted 1,2,4-triazoles
WO 92/07852	xanthine derivatives
JP 04120072	pyrimidine derivatives
EP 487252	quinolines and 1,5-naphthyridine derivatives
EP 483683	thienoimidazoles
EP 470543	fused imidazoles
EP 468470	fused imidazoles
EP 467207	purines
WO 91/19715	imidazo[4,5-d]pyridazines
WO 91/19697	pyridines
EP 465368	imidazoles
EP 465323	pyrimidines
WO 91/18888	triazolones
EP 461039	benzimidazoles
US 5066586	pyridoimidazoles
EP 459136	benzimidazoles

WO 91/17148	triazoles
EP 456510	pyridoimidazoles
EP 456442	quinolines
WO 91/15479	imidazoles, oxazoles, thiazoles
WO 91/15209	pyrimidines
EP 453210	pyridines
WO 91/14679	imidazolinones or pyrimidinones
US 5053329	imidazopyridines
US 5049565	conjugated imidazopyridines
EP 449699	pyrazoles
EP 446062	pyrazoles
EP 445811	pyridin-4-ones and pyrimidin-4-ones
EP 443983	amides, sulfonamides, carbamates
EP 443568	thienopyridin-4-ones, thienopyrimidin-2,4-diones
EP 442473	pyrimidin-2,4-diones
EP 435827	pyrimidinones
EP 434038	fused imidazoles
EP 432737	cycloheptimidazolones
WO 91/07404	azaquinolines
EP 430300	xanthines
EP 426021	fused imidazoles
EP 425921	benzimidazoles
EP 424317	pyrimidines
EP 420237	fused imidazoles
EP 419048	pyrimidinones
EP 415886	fused imidazoles
EP 412848	oxyquinolines
EP 412594	triazolinones
EP 411766	quinazolinones
EP 411507	pyrazole-3-carboxylates
WO 91/00281	imidazoles
WO 91/00277	imidazoles
EP 409332	triazoles
EP 407342	pyrimidinones
EP 407102	fused imidazoles
EP 401030	fused imidazoles
EP 400974	fused imidazoles
EP 400835	benzimidazoles
EP 399732	benzimidazoles
EP 399731	fused imidazoles
EP 392317	benzimidazoles

EP 890719	imidazoles
EP 323841	pyrroles, pyrazoles, and triazoles
EP 291969	biphenyltetrazoles
EP 253310	imidazoles
WO 95/28419	indazoles
EP 638572	fused imidazoles
DE 4320432	aminopyridyl, imidazoles, fused imidazoles
JP 06279437	imidazoles
EP 624583	pyridones
EP 623611	pyridines or 2-pyridones
US 5348955	diacyl piperazines
WO 94/07486	benzo-fused lactams
JP 06128256	imidazopyridines
US 5298517	imidazoles
US 5286729	quinazolinones
DE 4203872	imidazo[1,2-a]pyridines
GB 2263637	fused imidazoles
US 5177097	imidazolones
EP 519831	imidazoles and pyrimidines
US 5153347	phosphonates or phosphinates
DE 4034728	thienoimidazoles
DE 4032522	thienoimidazoles
EP 461040	fused imidazoles
DE 4006693	benzimidazoles
US 4916129	imidazoles
US 4880804	benzimidazoles
WO 97/15556	3-spiroindolin-2-ones
US 5266583	imidazoles
EP 573218	imidazoles
US 5264447	imidazoles
EP 569794	benzopyridones or pyridopyridones
US 5091390	fused imidazoles
US 5256658	morpholines, piperidines, piperazines, thiomorpholines
EP 546358	benzimidazoles

Methods of Preparation

The compounds of the present invention may be prepared by
5 methods such as those illustrated in the following Schemes I to XIII.

Solvents, temperatures, pressures, and other reaction conditions may be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art.

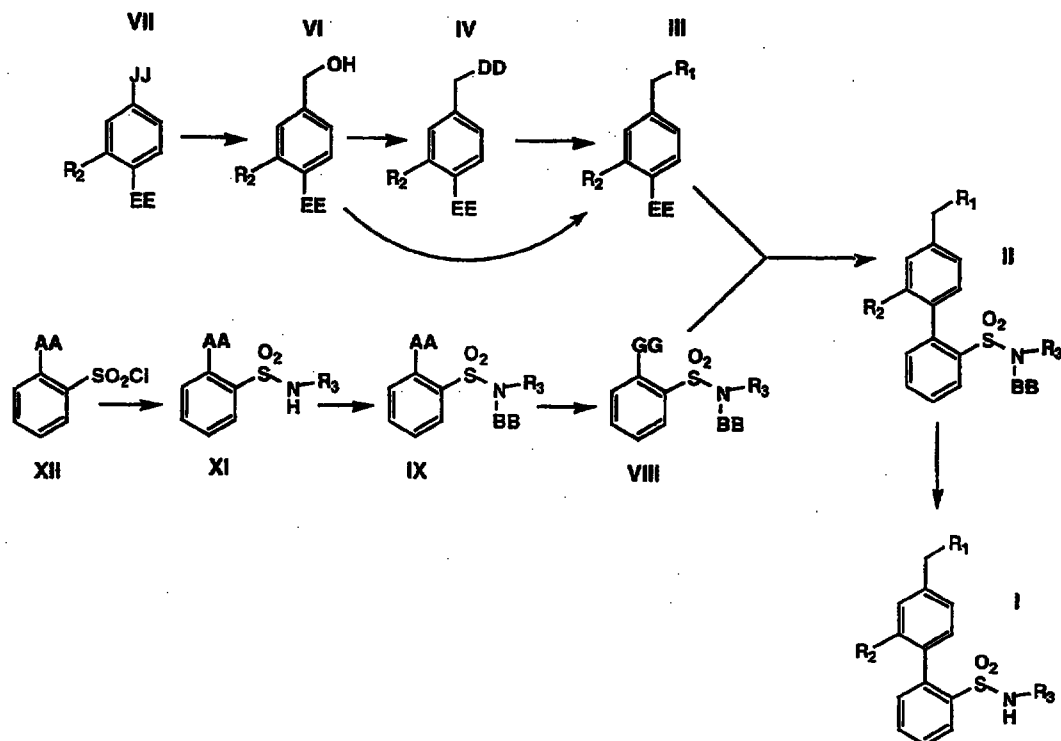
5 The following are the definitions of symbols used throughout Schemes I to XIII:

- AA hydrogen, halogen (chloro, bromo, iodo) or $-\text{OSO}_2\text{CF}_3$;
- BB suitable nitrogen protecting group, exemplified by
methoxymethyl- [MOM], benzyloxymethyl- [BOM], 2-
10 (trimethylsilyl)ethoxymethyl- [SEM], methoxyethoxymethyl-
[MEM], or *t*-butyl groups;
- DD $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ leaving group exemplified by halogen (Cl, Br, I) and
sulfonates ($-\text{OSO}_2$ -aryl (e.g., $-\text{OSO}_2\text{Ph}$ or $-\text{OSO}_2\text{PhCH}_3$), or
 $-\text{OSO}_2$ -alkyl (e.g., $-\text{OSO}_2\text{CH}_3$ or $-\text{OSO}_2\text{CF}_3$));
- 15 EE halogen (chloro, bromo, iodo) or $-\text{OSO}_2\text{CF}_3$;
- GG boronate ester or boronic acid, or trialkylstannane;
- HH metal atom such as tin, zinc, magnesium or lithium as part of an
organometallic compound used as an intermediate for transition
metal mediated aryl-aryl coupling reactions;
- 20 JJ $-\text{CN}$, $-\text{CHO}$, or $-\text{CO}_2\text{R}_{20}$ wherein R_{20} is hydrogen or C_1 to C_3 alkyl.

Exemplary conditions for forming and removing suitable nitrogen protecting groups may be found in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc, New
25 York, 1991, pp. 309-405. One skilled in the art can also recognize that the heteroaryl sulfonamide-NH in compounds of the invention will also have carboxylic acid character, and accordingly, methods used to protect carboxylic acids may be applicable to protecting the nitrogen NH of the sulfonamides in the invention, including intermediates to compounds of
30 formula I. Exemplary conditions for forming and removing suitable carboxylic acid protecting groups may be found in T. W. Greene and P. G.

M. Wuts, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc, New York, 1991, pp. 175-276.

SCHEME I



Compounds of formula I may be prepared from the deprotection of a
 5 compound of formula II wherein BB is a suitable nitrogen protecting
 group. Exemplary conditions for deprotection, and nitrogen protecting
 groups, may be found in T. W. Greene and P. G. M. Wuts, Protecting
Groups in Organic Synthesis, John Wiley & Sons, Inc, New York, 1991,
 pp. 309-405. Preferred nitrogen protecting groups are the methoxymethyl
 10 (MOM), methoxyethoxymethyl (MEM), and 2-(trimethylsilyl)ethoxymethyl
 (SEM) groups.

Compounds of formula II may be prepared from a palladium
 catalyzed coupling of a compound of formula III with a compound of
 formula VIII, in the presence of a suitable base in an inert solvent.
 15 Exemplary palladium catalysts include tetrakis(triphenylphosphine)
 palladium(0), palladium(II) chloride or palladium(II) acetate. The
 preferred palladium catalyst is tetrakis(triphenylphosphine) palladium(0).
 Exemplary bases include tertiary amines, such as, but not limited to,

triethylamine, or aqueous potassium, sodium, or cesium carbonate. The preferred base is aqueous sodium carbonate. Exemplary solvents include tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene, benzene, or straight chain alcohols, or a combination thereof. The preferred solvent is a
5 mixture of toluene and ethanol. Exemplary reaction temperatures are between about 25°C to 125°C, preferably between about 65°C and 110°C.

Compounds of formula III may be prepared from a compound of formula IV via displacement of the leaving group (DD) by the conjugate base of a compound R_1-H , wherein R_1 is as previously defined, using a base
10 in an inert solvent. Exemplary bases include sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, or alkyl lithiums. The preferred base is sodium hydride. Exemplary inert solvents include ethers (tetrahydrofuran, 1,4-dioxane, diethyl ether), or N,N-dimethylformamide. The preferred solvent is N,N-
15 dimethylformamide. Exemplary reaction temperatures are between about 0°C to 154°C, preferably between about 65°C and 110°C.

Compounds of formula III may also be prepared via a Mitsunobu reaction between a compound of formula VI and the conjugate acid R_1-H , preferably using a phosphine and oxidizing agent, in an inert solvent.
20 Exemplary phosphines include trialkylphosphines, triarylphosphines and polymer supported triarylphosphines. The preferred phosphine is triphenylphosphine. Exemplary oxidizing reagents include diethyl azodicarboxylate, diisopropyl azodicarboxylate, or carbon tetrabromide. The preferred oxidizing reagent is diethyl azodicarboxylate. Exemplary
25 inert solvents include ethers (tetrahydrofuran, 1,4-dioxane, diethyl ether), acetonitrile or N,N-dimethylformamide. The preferred solvent is N,N-dimethylformamide. Exemplary reaction temperatures are between about 0°C to 154°C, preferably between about 20°C and 65°C.

Compounds of formula IV (especially, where DD is $-OSO_2Ph$,
30 $-OSO_2PhCH_3$, $-OSO_2CH_3$, $-OSO_2CF_3$) may be prepared from the reaction of

a compound of formula VI with ClSO_2Ph , $\text{ClSO}_2\text{PhCH}_3$, ClSO_2CH_3 or $(\text{CF}_3\text{SO}_2)_2\text{O}$ in the presence of a base in an inert solvent.

Compounds of formula VI may be prepared from reduction of a compound of formula VII using a suitable reducing agent in an inert solvent.

Compounds of formula VII are either commercially available or available by means known to one skilled in the art.

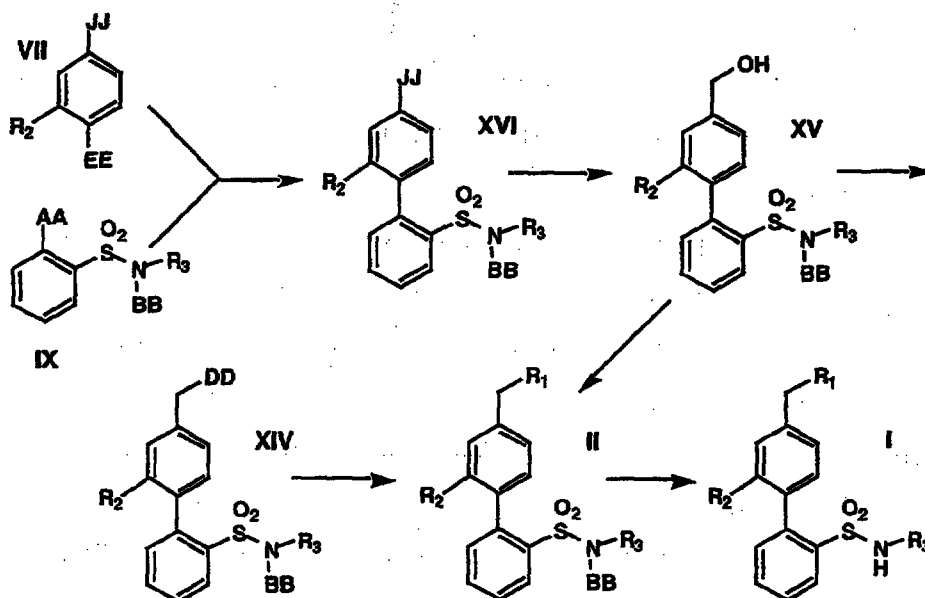
Compounds of formula VIII may be prepared via lithiation of a compound of formula IX wherein AA is hydrogen or a halogen (chloro, bromo, iodo), and reacting the resulting aryl lithium with an appropriate borate derivative.

Compounds of formula IX may be prepared via the protection of the nitrogen in a compound of formula XI. Exemplary nitrogen protecting groups and methods of protecting the nitrogen are similar to those for protecting amines, such as those described in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc, New York, 1991.

Compounds of formula XI may be prepared from the reaction of a compound of formula XII with a compound $\text{R}_3\text{-NH}_2$.

Compounds of the formula XII are either commercially available or available by means known to one skilled in the art.

SCHEME II



Compounds of formula I may be prepared from the deprotection of a
 5 compound of formula II as described in Scheme I.

Compounds of formula II may be prepared from a compound of
 formula XIV via displacement of the leaving group (DD) by the conjugate
 base of a compound $R_1\text{-H}$, wherein R_1 is as previously defined, using a base
 in an inert solvent. Exemplary bases include sodium carbonate,
 10 potassium carbonate, cesium carbonate, sodium hydride, potassium
 hydride, or alkyl lithiums. The preferred base is sodium hydride.
 Exemplary inert solvents include ethers (tetrahydrofuran, 1,4-dioxane,
 diethyl ether), or N,N-dimethylformamide. The preferred solvent is N,N-
 dimethylformamide. Exemplary reaction temperatures are between about
 15 0°C to 154°C , preferably between about 25°C and 110°C .

Compounds of formula II may also be prepared via a Mitsunobu
 reaction between a compound of formula XV and the conjugate acid $R_1\text{-H}$
 using a phosphine and oxidizing agent in an inert solvent. Exemplary
 phosphines include trialkylphosphines, triarylphosphines and polymer
 20 supported triarylphosphines. The preferred phosphine is

triphenylphosphine. Exemplary oxidizing reagents include diethyl azodicarboxylate, diisopropyl azodicarboxylate, or carbon tetrabromide. The preferred oxidizing reagent is diethyl azodicarboxylate. Exemplary inert solvents include ethers (tetrahydrofuran, 1,4-dioxane, diethyl ether), acetonitrile or N,N-dimethylformamide. The preferred solvent is N,N-dimethylformamide. Exemplary reaction temperatures are between about 0°C to 154°C, preferably between about 20°C and 65°C.

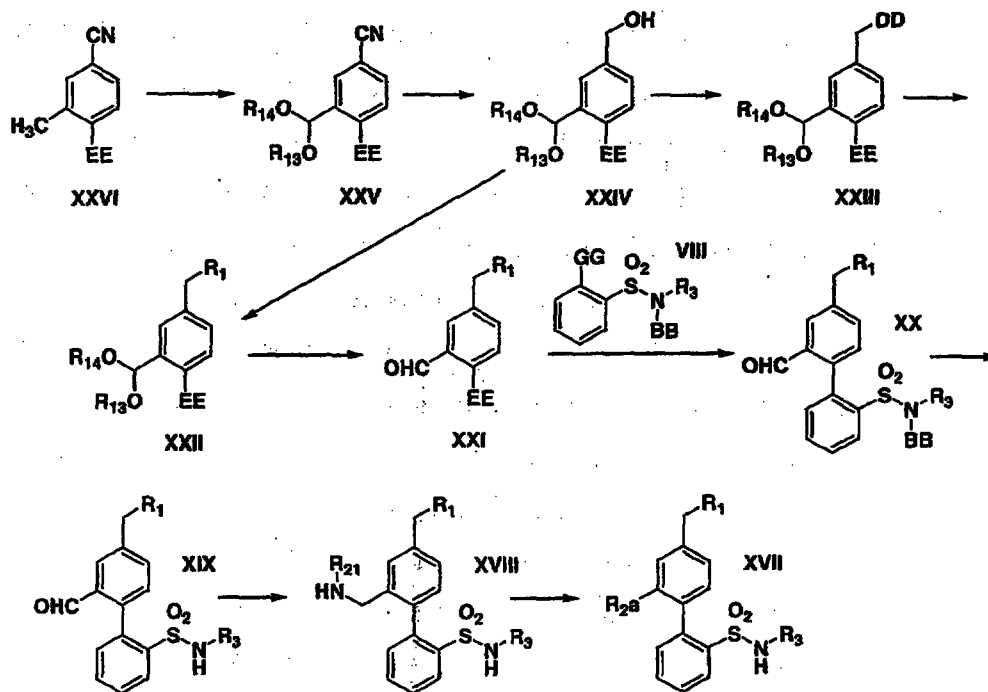
Compounds of formula XIV may be prepared from compounds of formula XV using methods well known in the art. For example, compounds of formula XIV (DD = Br) may be prepared by the treatment of compound XV with carbon tetrabromide and triphenylphosphine in a suitable solvent such as toluene or tetrahydrofuran.

Compounds of formula XV may be prepared from reduction of a compound of formula XVI using a suitable reducing agent in an inert solvent. R₂ is preferably not an amide, an ester, a carboxylic acid or an aldehyde during this operation.

Compounds of formula XVI may be prepared from a palladium catalyzed coupling of a compound of formula VII with a compound of formula IX in the presence of a suitable base and an inert solvent as described in Scheme I.

Compounds of formula VII are available by means known to one skilled in the art.

SCHEME III



- Compounds of formula XVII (which are compounds of formula I
- 5 wherein R_2 is R_{2a} where R_{2a} is $-\text{CH}_2\text{N}(\text{R}_{21})(\text{C}=\text{O})\text{N}(\text{R}_{19})\text{R}_{20}$, $-\text{CH}_2\text{N}(\text{R}_{21})(\text{C}=\text{O})\text{OR}_{18}$ or $-\text{CH}_2\text{N}(\text{R}_{21})(\text{C}=\text{O})\text{R}_{22}$), may be prepared from compounds of formula XVIII (also compounds of formula I, where R_2 is $-\text{CH}_2\text{NHR}_{21}$) by reaction of a compound of formula XVIII with an active ester (i.e., from a carboxylic acid such as R_{22}COOH in the presence of a
- 10 suitable coupling agent such as dicyclohexylcarbodiimide (DCC)), or an acid chloride (i.e., $\text{R}_{22}(\text{C}=\text{O})\text{Cl}$), or an isocyanate (i.e., $\text{R}_{19}\text{N}=\text{C}=\text{O}$), or a chloroformate (i.e., $\text{R}_{18}\text{O}(\text{C}=\text{O})\text{Cl}$) in the presence of a suitable base such as triethylamine and catalyst such as 4-dimethylaminopyridine in an inert solvent. This step may, for example, be conducted combinatorially and a
- 15 library of such compounds created.

Compounds of formula XVIII may be prepared from reductive amination of compounds of formula XIX (compounds of formula I where R_2 is

-CHO) using a primary amine such as R_1NH_2 in the presence of a suitable reducing agent such as sodium triacetoxyborohydride in an inert solvent.

Compounds of formula XIX may be prepared by deprotection of compounds of formula XX wherein BB is a suitable nitrogen protecting group as described in Scheme I.

Compounds of formula XX may be prepared from a palladium catalyzed coupling of a compound of formula XXI with a compound of formula VIII in the presence of a suitable base and an inert solvent as described in Scheme I.

Compounds of formula XXI may be prepared in two steps from a compound of formula XXIII, first by displacement of the leaving group (DD) by the conjugate base of a compound R_1-H , wherein R_1 is as previously defined using a suitable base in an inert solvent as described in Scheme I to provide a compound of formula XXII. Subsequent deprotection of the acetal in a compound of formula XXII using methods known in the art is employed to provide a compound of formula XXI.

Compounds of formula XXII may also be prepared via a Mitsunobu reaction between a compound of formula XXIV and the conjugate acid R_1-H using a phosphine and oxidizing agent in an inert solvent.

Exemplary phosphines include trialkylphosphines, triarylphosphines and polymer supported triarylphosphines. Exemplary oxidizing reagents include diethyl azodicarboxylate, diisopropyl azodicarboxylate, or carbon tetrabromide. Exemplary inert solvents include ethers (tetrahydrofuran, 1,4-dioxane, diethyl ether), acetonitrile or N,N-dimethylformamide.

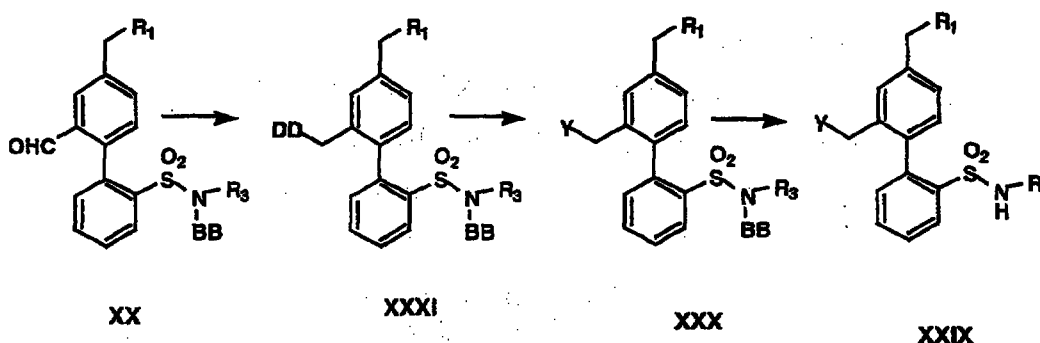
Compounds of formula XXIII may be prepared from compounds of formula XXIV using methods well known in the art. For example, compounds of formula XXIII (DD = Br) may be prepared by the treatment of compound XXIV with carbon tetrabromide and triphenylphosphine in a suitable solvent such as toluene or tetrahydrofuran.

Compounds of formula XXIV may be prepared in two steps from compound XXV via a partial reduction of the nitrile group to the aldehyde

using a suitable reducing agent such as diisobutylaluminum hydride, with subsequent reduction of the aldehyde to hydroxymethyl using an agent such as sodium borohydride.

Methods for the preparation of compounds XXV and XXVI are known in the art [H.-Y. Zhang, et al., *Tetrahedron*, 50, 11339-11362 (1994)].

SCHEME IV



10

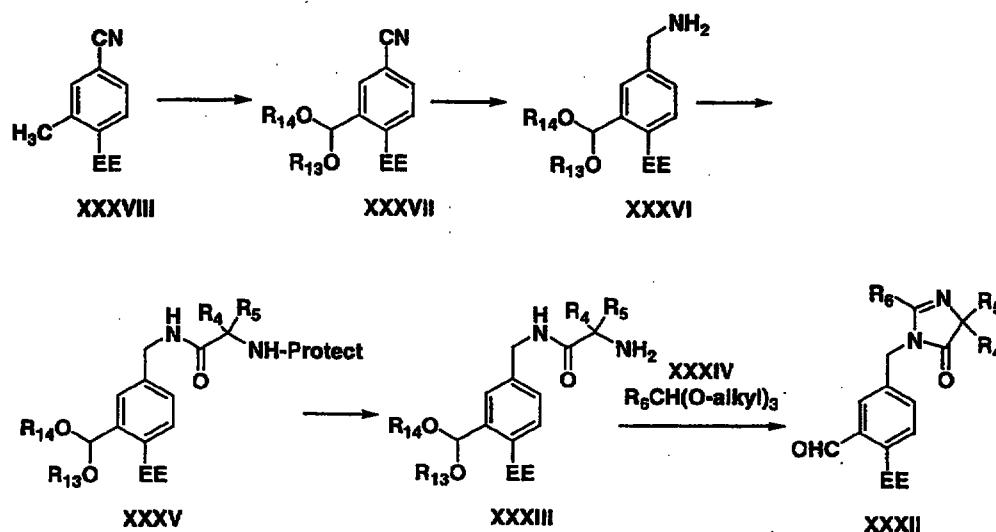
Compounds of formula XXIX (which are compounds of formula I where R_2 is $-\text{CH}_2\text{Y}$) may be prepared from the deprotection of a compound of formula XXX such as is described in Scheme I.

Compounds of formula XXX may be prepared from a compound of formula XXXI via displacement of the leaving group (DD) by the conjugate base of a compound Y-H, wherein Y is as previously defined using a base in an inert solvent. Exemplary bases include sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, or alkyl lithiums. The preferred base is sodium hydride.

Compounds of formula XXXI may be prepared from compounds of formula XX using methods well known in the art. For example, compounds of formula XXXI (DD = Br) may be prepared from compound XX in two steps: first by reducing the aldehyde to a hydroxymethyl group using a suitable reducing agent such as sodium borohydride, and second, conversion of the hydroxymethyl group to the bromomethyl function using

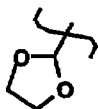
carbon tetrabromide and triphenylphosphine in a suitable solvent such as toluene or tetrahydrofuran.

SCHEME V



Compounds of formula XXXII (which may be employed, for example, in the methods of the preceding Schemes) may be prepared by cyclization of compounds of formula XXXIII in the presence of orthoester XXXIV using a catalytic amount of a weak acid such as acetic acid. Exemplary reaction temperatures are between about 25°C to 154°C, preferably between about 60°C and 110°C.

Compounds of formula XXXIII (e.g., where R_{13} and R_{14} , together with the atoms to which they are bonded, form the five-membered ring



) may be prepared from compounds of formula XXXVI in two steps:

- (1) acylation of compound XXXVI with an N-protected amino acid in the presence of a suitable coupling agent such as dicyclohexylcarbodiimide (DCC) or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) in a suitable solvent such as N,N-dimethylformamide, and (2) removal of the protecting group. Suitable

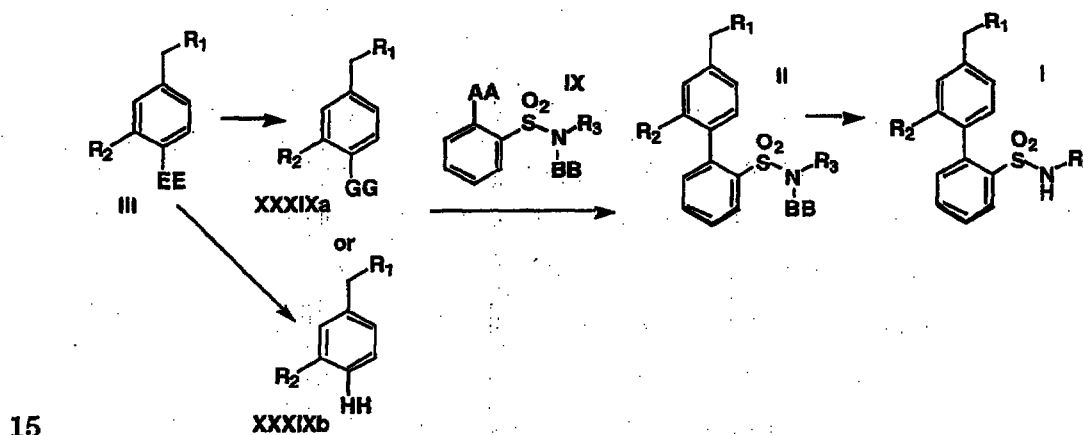
conditions and suitable nitrogen protecting groups and the corresponding deprotection conditions may be found in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc, New York, 1991, pp. 309-405.

- 5 Compounds of formula XXXVI may be prepared via reduction of a compound of formula XXXVII using an appropriate reducing agent such as diborane or lithium aluminum hydride in an appropriate solvent such as tetrahydrofuran.

- 10 Compounds of formula XXXVII may be prepared from compounds of formula XXXVIII as described in Scheme III.

Compounds of formula XXXVIII may be prepared by methods known in the art.

SCHEME VI



Compounds of formula I may be prepared from the deprotection of a compound of formula II as described in Scheme I.

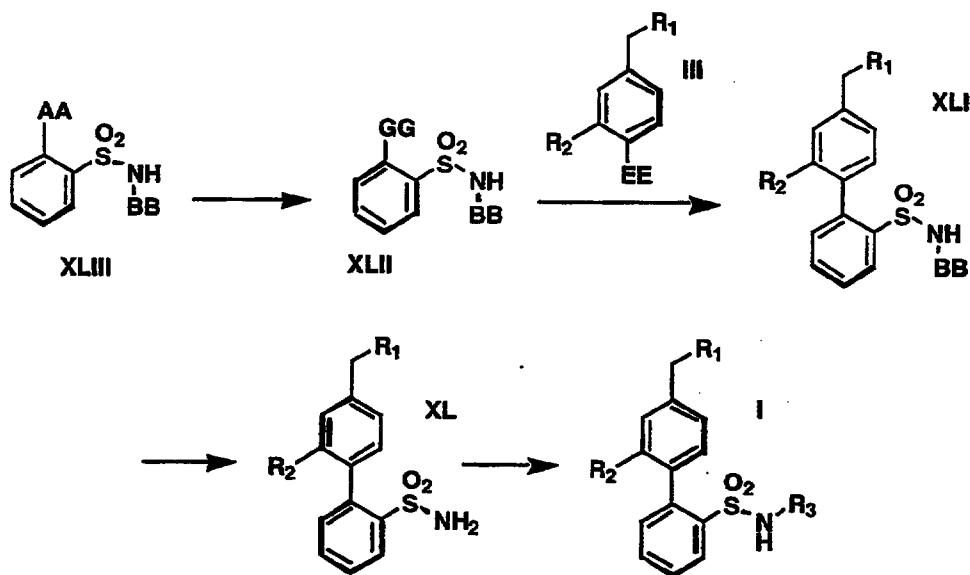
- 20 Compounds of formula II may be prepared by a palladium catalyzed coupling of a compound of formula IX (as described in Scheme I) wherein AA here is -OSO₂CF₃ or a halogen (chlorine, bromine, or iodine; preferably bromine or iodine) with a compound of formula XXXIXa, wherein GG is a boronic acid or ester, in the presence of a base and an inert solvent as described in Scheme I.

Compounds of formula II may also be prepared by a palladium or nickel catalyzed coupling of a compound of formula IX (as described in Scheme I) wherein AA is a halogen (chlorine, bromine, or iodine; preferably bromine or iodine) with a compound of formula XXXIXb wherein HH is a suitable metal atom bearing appropriate ligands. Exemplary metal atoms include tin, zinc, magnesium, and lithium. Exemplary catalysts include tetrakis(triphenylphosphine)palladium(0) and dichlorobis(triphenylphosphine)nickel(II).

Compounds of formula XXXIXa or XXXIXb may be prepared via lithiation of a compound of formula III wherein EE is a halogen (chlorine, bromine, or iodine; preferably bromine or iodine), then reacting the resulting aryl lithium with an appropriate borate derivative or with an appropriate zinc, tin, or magnesium reagent.

Compounds of formula III may be prepared by the methods described in Scheme I.

SCHEME VII



Compounds of formula I may be prepared from the thermal reaction of a compound of formula XL with a heterocyclic compound of formula

R_3-X , wherein X is a halogen (fluorine, chlorine, bromine, or iodine), in the presence of a base and an inert solvent. Exemplary bases include sodium hydride, potassium carbonate, potassium hydride, and potassium bis(trimethylsilyl)amide, preferably sodium hydride. Exemplary solvents
5 include N,N-dimethylformamide and N,N-dimethylacetamide. Exemplary reaction temperatures are between about 80°C and 150°C, preferably between 110°C and 130°C.

Compounds of formula I may also be prepared from the reaction of a compound of formula XL with a heterocyclic compound of formula R_3-X ,
10 wherein X is a halogen (chlorine, bromine, or iodine), in the presence of a palladium catalyst, a phosphine ligand, a base, and an inert solvent. Exemplary palladium catalysts include palladium acetate and tris(dibenzylideneacetone)palladium(0), and the preferred palladium catalyst is palladium acetate. The preferred phosphine ligand is 2,2'-
15 bis(diphenylphosphino)-1,1'-binaphthyl. Exemplary bases include sodium hydride and sodium t-butoxide. The preferred base is sodium hydride. Exemplary reaction temperatures are between about 20°C and 110°C, preferably between 85°C and 110°C.

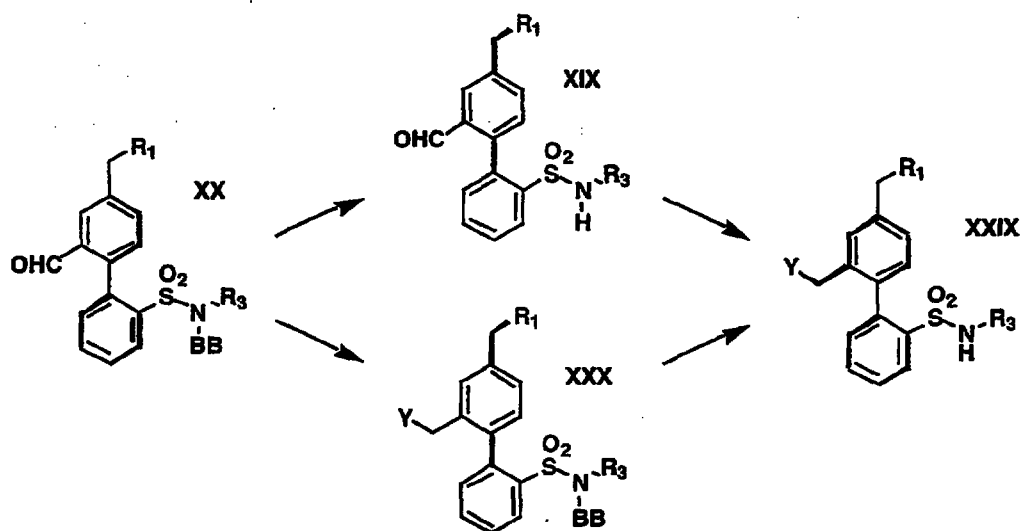
Compounds of formula XL may be prepared by deprotection of a
20 compound of formula XLI, wherein BB is a suitable nitrogen protecting group. Exemplary conditions for protection and deprotection of nitrogen functionalities may be found in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc., New York, 1991, pp. 309-405. The preferred protecting group BB for Scheme
25 VII is *tertiary*-butyl. Exemplary deprotection conditions include the use of acids, such as trifluoroacetic acid.

Compounds of formula XLI may be prepared by a palladium catalyzed coupling of a compound of formula III (as described in Scheme I) wherein EE is a halogen (chlorine, bromine, or iodine; preferably
30 bromine or iodine) with a compound of formula XLII, wherein GG is a

boronic acid or ester, in the presence of a base and an inert solvent as described in Scheme I.

- Compounds of formula XLII may be prepared via the lithiation of a compound of formula XLIII in an inert solvent, followed by reacting the resulting aryl lithium with an appropriate borate derivative. Exemplary reagents for the lithiation reaction include *n*-butyllithium and *t*-butyllithium. Exemplary solvents include ethers such as tetrahydrofuran, either alone or in combination with hydrocarbon solvents such as hexane. The preferred solvent is a mixture of tetrahydrofuran and hexane.
- Compounds of formula XLIII are either commercially available or available by means known to one skilled in the art.

SCHEME VIII



15

- Compounds of formula XXIX (which are certain compounds of formula I where R_2 is $\text{-CH}_2\text{Y}$, as described in Scheme IV) may be prepared from a compound of formula XIX (which is a compound of formula I where R_2 is -CHO , as described in Scheme III) via a two step process: 1) reductive amination of XIX in the presence of a primary amine R_{30}NH_2 ,

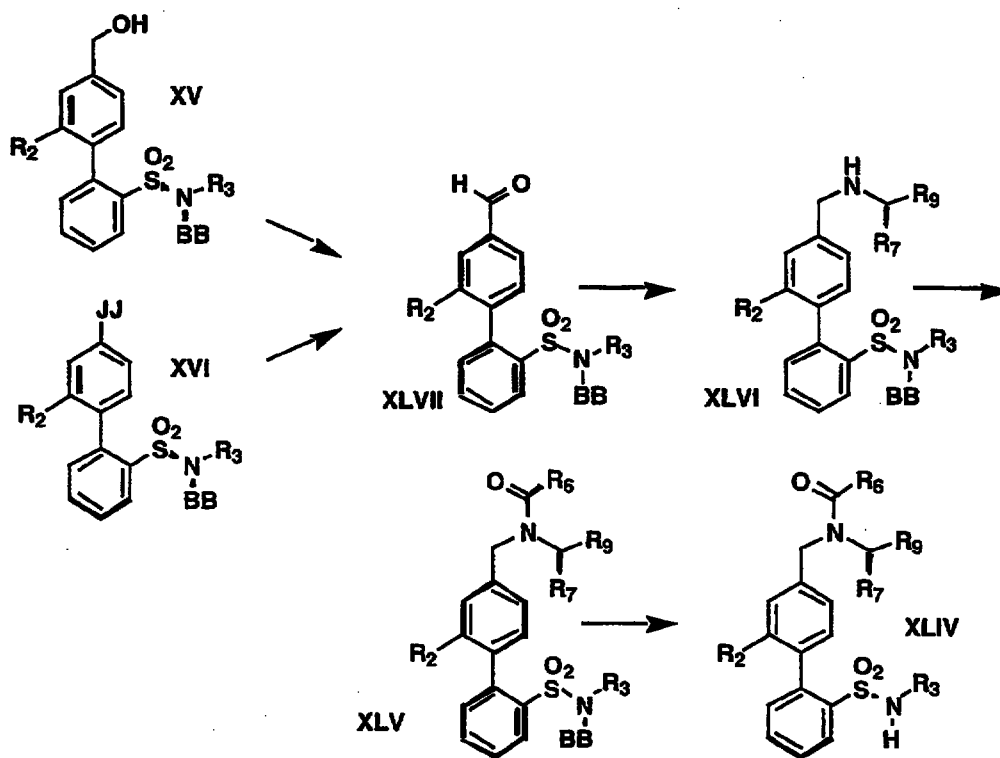
wherein R_{30} is carboxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, or aminoalkyl, using a suitable reducing agent such as sodium triacetoxyborohydride, yields an intermediate amine; 2) subsequent cyclization using an appropriate cyclization reagent yields a compound of formula XXIX. When R_{30} is carboxyalkyl, appropriate cyclization reagents include carbodiimides such as diisopropylcarbodiimide. When R_{30} is hydroxyalkyl or aminoalkyl, appropriate cyclization reagents include phosgene and 1,1'-carbonyldiimidazole. When R_{30} is alkoxycarbonylalkyl, appropriate cyclization reagents include tertiary amine bases such as triethylamine and N,N-diisopropylethylamine.

Compounds of formula XIX may be prepared via deprotection of a compound of formula XX as described in Scheme III.

Compounds of formula XXIX may also be prepared by deprotection of a compound of formula XXX as described in Scheme I.

Compounds of formula XXX may be prepared from a compound of formula XX, using the two step process described above for the formation of compounds of formula XXIX from a compound of formula XIX.

SCHEME IX



5 Compounds of formula XLIV (which are compounds of formula I wherein R₁ is D as defined for formula I) may be prepared from the deprotection of a compound of formula XLV as described in Scheme I.

10 Compounds of formula XLV may be prepared via the acylation of a compound of formula XLVI using either a carboxylic acid such as R₆COOH in the presence of a suitable coupling agent such as dicyclohexylcarbodiimide, or the corresponding acid chloride or acid anhydride in the presence of a suitable base such as triethylamine.

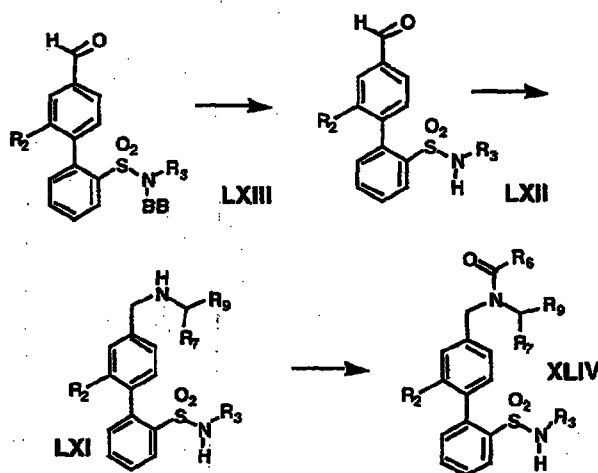
15 Compounds of formula XLVI may be prepared from reduction of a compound of formula XLVII in the presence of a primary amine such as H₂NCHR₇R₉ in the presence of a suitable reducing agent such as sodium triacetoxyborohydride.

Compounds of formula XLVII may be prepared via reduction of a compound of formula XVI, as described in Scheme II, wherein JJ is -CN, or -CO₂R₂₀ wherein R₂₀ is hydrogen or C₁ to C₃ alkyl, using means known to one skilled in the art.

- 5 Compounds of formula XLVII may also be prepared via oxidation of a compound of formula XV, as defined in Scheme II, using means known to one skilled in the art.

SCHEME X

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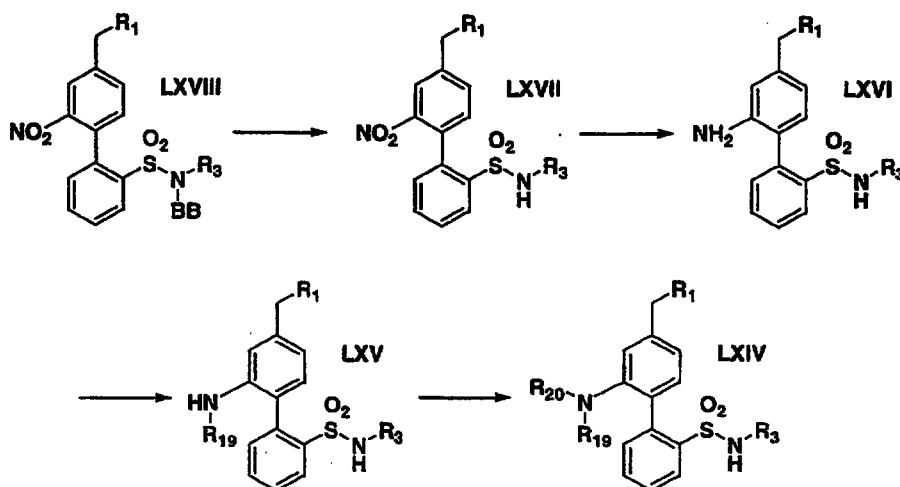


- Compounds of formula XLIV (which are compounds of formula I wherein R₁ is D as defined for formula I) may be prepared by the acylation of a compound of formula LXI using either a carboxylic acid such as R₆COOH in the presence of a suitable coupling agent such as dicyclohexylcarbodiimide, or the corresponding acid chloride or acid anhydride in the presence of a suitable base such as triethylamine.
- 15

- Compounds of formula LXI may be prepared by the reduction of a compound of formula LXII in the presence of a primary amine such as H₂NCHR₇R₉ in the presence of a suitable reducing agent such as sodium triacetoxyborohydride.
- 20

Compounds of formula LXII may be prepared via deprotection of a compound of formula LXIII (which is a compound of formula XVI wherein JJ is CHO), as described in Scheme I.

5

SCHEME XI

Compounds of formula LXIV (which are compounds of formula I wherein R_2 is $-N(R_{19})R_{20}$) may be prepared via reduction of a compound of formula LXV in the presence of an aliphatic, aromatic, or heteroaromatic aldehyde using a suitable reducing agent such as sodium triacetoxyborohydride.

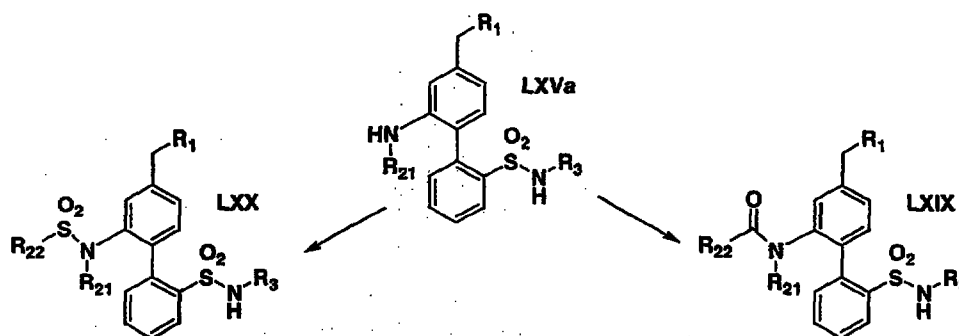
Compounds of formula LXV (which are compounds of formula I wherein R_2 is $-NHR_{19}$) may be similarly prepared via reduction of a compound of formula LXVI in the presence of an aliphatic, aromatic, or heteroaromatic aldehyde using a suitable reducing agent such as sodium triacetoxyborohydride.

Compounds of formula LXVI (which are compounds of formula I wherein R_2 is $-NH_2$) may be prepared by reduction of a compound of formula LXVII using a suitable reducing agent such as tin (II) chloride dihydrate in a suitable solvent such as ethyl acetate.

Compounds of formula LXVII (which are compounds of formula I wherein R_2 is $-\text{NO}_2$) may be prepared by deprotection of a compound of formula LXVIII as described in Scheme I.

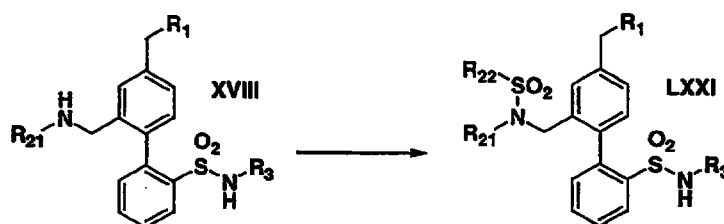
Compounds of formula LXVIII (which are compounds of formula II wherein R_2 is $-\text{NO}_2$) may be prepared by the methods described for the preparation of compounds of formula II in Schemes I and II.

SCHEME XII



Compounds of formula LXIX (which are compounds of formula I wherein R_2 is $-\text{N}(\text{R}_{21})(\text{C}=\text{O})\text{R}_{22}$) may be prepared via acylation of a compound of formula LXVa (prepared as described in Scheme XI for a compound of formula LXV) using either a carboxylic acid such as R_{22}COOH in the presence of a suitable coupling agent such as dicyclohexylcarbodiimide, or the corresponding acid chloride or acid anhydride in the presence of a suitable base such as triethylamine.

Compounds of formula LXX (which are compounds of formula I wherein R_2 is $-\text{N}(\text{R}_{21})\text{SO}_2\text{R}_{22}$) may be prepared via sulfonylation of a compound of formula LXVa using either a sulfonyl chloride such as $\text{R}_{22}\text{SO}_2\text{Cl}$ or the corresponding sulfonic anhydride, in the presence of a suitable base such as triethylamine.

SCHEME XIII

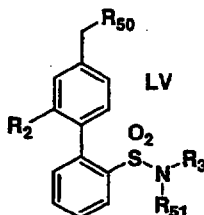
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Compounds of formula LXXI (which are compounds of formula I wherein R_2 is $-\text{CH}_2\text{N}(\text{R}_{21})(\text{SO}_2\text{R}_{22})$) may be prepared via sulfonylation of a compound of formula XVIII (prepared as described in Scheme III) using either a sulfonyl chloride such as $\text{R}_{22}\text{SO}_2\text{Cl}$ or the corresponding sulfonic anhydride in the presence of a suitable base such as triethylamine.

10

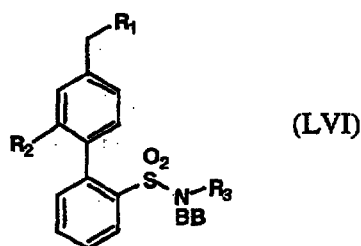
The present invention further provides the following novel compounds, which may be employed as intermediates in the preparation of compounds of the formula I and salts thereof:

15

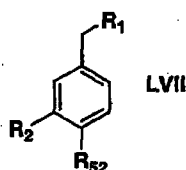


wherein R_2 and R_3 are as defined for a compound of formula I, R_{50} is hydroxy, chloro, bromo, iodo, $-\text{OSO}_2$ -alkyl, or $-\text{OSO}_2$ -aryl, and R_{51} is hydrogen, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2$ -aryl, or other suitable nitrogen protecting group;

20



wherein R_1 , R_2 and R_3 are as defined for a compound of formula I and BB is
 -CH₂OCH₂CH₂OCH₃, -CH₂OCH₂CH₂Si(CH₃)₃, -CH₂OCH₃, -CH₂OCH₂-aryl, or
 5 other suitable nitrogen protecting group; and

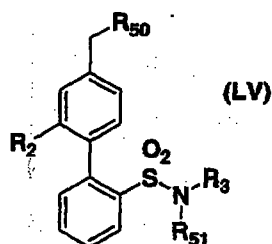


wherein R_1 and R_2 are as defined for a compound of formula I, and R_{52} is
 10 chloro, bromo, iodo, or -OSO₂CF₃.

The present invention also provides the following novel method for
 the preparation of a compound of the formula I or salt thereof, wherein
 said method comprises the steps of:

15

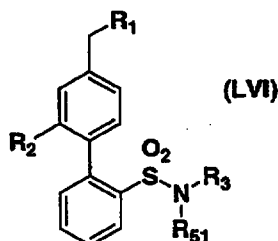
a) displacement of a leaving group R_{50} via the anion of a
 compound R_1 -H from a compound of the formula



wherein R_1 , R_2 and R_3 are as defined for a compound of formula I, R_{50} is
 20 hydroxy, chloro, bromo, iodo, -OSO₂-alkyl or -OSO₂-aryl, and R_{51} is

hydrogen or a suitable nitrogen protecting group, using a Mitsunobu reaction or S_N1 or S_N2 displacement reaction, with removal of said nitrogen protecting group as appropriate;

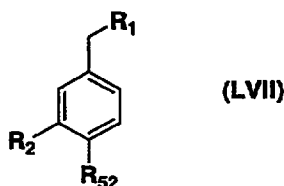
- 5 b) removal of the nitrogen protecting group R_{51} from a compound of formula



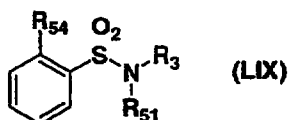
wherein R_1 , R_2 and R_3 are as defined for a compound of formula I, and R_{51} is a suitable nitrogen protecting group;

10

- c) organometallic coupling of a compound of formula



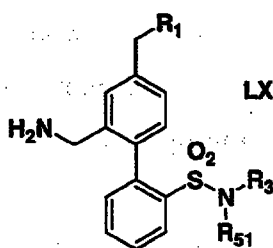
with a compound of formula



- 15 wherein R_1 , R_2 and R_3 are as defined for a compound of formula I and R_{51} is a suitable nitrogen protecting group. When R_{52} is chloro, bromo, iodo or $-OSO_2CF_3$, then R_{54} is a boronic acid, boronic ester or stannane derivative. When R_{52} is a boronic acid, boronic ester or stannane derivative, then R_{54} is chloro, bromo, iodo or $-OSO_2CF_3$.

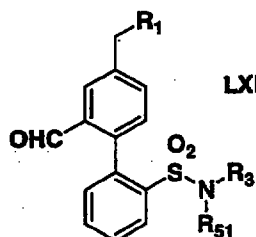
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- d) acylation of a compound of the formula



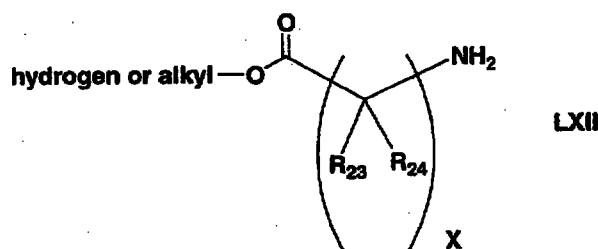
- wherein R_1 and R_3 are as defined for a compound of formula I, and R_{51} is hydrogen or a suitable nitrogen protecting group, with an acylating agent of the formula $R_{55}-(C=O)R_{22}$, $R_{19}N=C=O$, $R_{55}-CO_2R_{18}$, $R_{55}SO_2R_{22}$, wherein R_{18} , R_{19} and R_{22} are as defined for a compound of formula I and R_{55} is an activating group for an acid, or made using an acid activating agent, with removal of said nitrogen protecting group as appropriate; or

e) reductive amination of a compound of formula



10

wherein R_1 and R_3 are as defined for a compound of formula I, and R_{51} is hydrogen or a suitable nitrogen protecting group, with an amine of the formula



15

wherein R_{23} , R_{24} , and x are as defined for a compound of formula I, with removal of said nitrogen protecting group as appropriate.

Utility

The compounds of formula I and salts thereof are antagonists of both endothelin (especially, ET-1) and angiotensin II (especially, subtype AT₁) receptors ("dual angiotensin endothelin receptor antagonists") and
5 are useful in treatment of conditions associated with increased ET levels and/or increased angiotensin II levels and of all endothelin-dependent or angiotensin II-dependent disorders. They are thus useful as antihypertensive agents. By the administration of a composition having one (or a combination) of the compounds of this invention, the blood
10 pressure of a hypertensive mammalian (e.g., human) host is reduced. They are also useful in portal hypertension, hypertension secondary to treatment with erythropoietin and low renin hypertension.

The compounds of the present invention are also useful in the treatment of disorders related to renal, glomerular and mesangial cell
15 function, including acute (such as ischemic, nephrotoxic, or glomerulonephritis) and chronic (such as diabetic, hypertensive or immune-mediated) renal failure, glomerular injury, renal damage secondary to old age or related to dialysis, nephrosclerosis (especially hypertensive nephrosclerosis), nephrotoxicity (including nephrotoxicity
20 related to imaging and contrast agents and to cyclosporine), renal ischemia, primary vesicoureteral reflux, glomerulosclerosis and the like. The compounds of this invention are also useful in the treatment of disorders related to paracrine and endocrine function.

The compounds of the present invention are also useful in the
25 treatment of endotoxemia or endotoxin shock as well as hemorrhagic shock.

The compounds of the present invention are also useful in hypoxic and ischemic disease and as anti-ischemic agents for the treatment of, for example, cardiac, renal and cerebral ischemia and reperfusion (such as
30 that occurring following cardiopulmonary bypass surgery), coronary and cerebral vasospasm, and the like.

In addition, the compounds of this invention are also useful as anti-arrhythmic agents; anti-anginal agents; anti-fibrillatory agents; anti-asthmatic agents; anti-atherosclerotic and anti-arteriosclerotic agents; additives to cardioplegic solutions for cardiopulmonary bypasses; adjuncts
5 to thrombolytic therapy; and anti-diarrheal agents. The compounds of this invention may be useful in therapy for myocardial infarction; therapy for peripheral vascular disease (e.g., Raynaud's disease and Takayasu's disease); treatment of cardiac hypertrophy (e.g., hypertrophic cardiomyopathy); treatment of primary pulmonary hypertension (e.g.,
10 plexogenic, embolic) in adults and in the newborn and pulmonary hypertension secondary to heart failure, radiation and chemotherapeutic injury, or other trauma; treatment of central nervous system vascular disorders, such as stroke, migraine and subarachnoid hemorrhage; treatment of central nervous system behavioral disorders; treatment of
15 gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer and ischemic bowel disease; treatment of gall bladder or bile duct-based diseases such as cholangitis; treatment of pancreatitis; regulation of cell growth; treatment of benign prostatic hypertrophy; restenosis following angioplasty or following any procedures
20 including transplantation; therapy for congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling and dysfunction; and treatment of hepatotoxicity and sudden death. The compounds of this invention are useful in the treatment of sickle cell disease including the initiation and/or evolution of the pain crises of this
25 disease; treatment of the deleterious consequences of ET-producing tumors such as hypertension resulting from hemangiopericytoma; treatment of early and advanced liver disease and injury including attendant complications (e.g., hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder;
30 treatment of hepatorenal syndrome; treatment of immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed

cryoglobulinemia; and treatment of fibrosis associated with renal dysfunction and hepatotoxicity. The compounds of this invention are useful in therapy for metabolic and neurological disorders; cancer; insulin-dependent and non insulin-dependent diabetes mellitus; neuropathy; 5 retinopathy; maternal respiratory distress syndrome; dysmenorrhea; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; and chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis, sarcoidosis and eczematous dermatitis (all types of dermatitis).

10 The compounds of this invention are also useful in the treatment of sexual dysfunction in both men (erectile dysfunction, for example, due to diabetes mellitus, spinal cord injury, radical prostatectomy, psychogenic etiology or any other cause) and women by improving blood flow to the genitalia, especially, the corpus cavernosum.

15 The present invention thus provides methods for the treatment of all endothelin-dependent or angiotensin II-dependent disorders, comprising the step of administering to a subject in need thereof at least one compound of the formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with 20 the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

 The effective amount of a compound of the present invention may 25 be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a human of from about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably from about 0.5 to about 25 mg/kg of body weight (or from about 1 to about 2500 mg, preferably from about 5 to about 500 mg) of active compound per day, 30 which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood

that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general
5 health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to endothelin-dependent or
10 angiotensin II-dependent disorders.

The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating an endothelin-dependent or angiotensin II-dependent disorder in an amount effective therefor, and a pharmaceutically acceptable vehicle or
15 diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives,
20 stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation or called for by accepted pharmaceutical practice.

The compounds of the formula I may be administered by any suitable means, for example, orally, such as in the form of tablets,
25 capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically,
such as in the form of a cream or ointment; or rectally such as in the form
30 of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds

may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally. For example, the active substance can be utilized in a composition such as tablet, capsule, solution or suspension containing about 5 to about 500 mg per unit dosage of a compound or mixture of compounds of formula I or in topical form for wound healing (0.01 to 5% by weight compound of formula I, 1 to 5 treatments per day). They may be compounded in a conventional manner with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., or with a topical carrier. The compounds of formula I can also be formulated in compositions such as sterile solutions or suspensions for parenteral administration. About 0.1 to 500 milligrams of a compound of formula I may be compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is preferably such that a suitable dosage in the range indicated is obtained.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary

compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such
5 formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring
10 agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents
15 such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium
20 chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating
25 excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene). For
30 example, the compounds of the invention may be administered topically to

treat peripheral vascular diseases and as such may be formulated as a cream or ointment.

The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents
5 useful in the treatment of endothelin-dependent or angiotensin II-dependent disorders. For example, the compounds of this invention can be formulated in combination with endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists; potassium channel openers; thrombin inhibitors (e.g., hirudin and the
10 like); growth factor inhibitors such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; renin inhibitors; angiotensin converting enzyme (ACE) inhibitors such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, lisinopril and salts of such compounds; neutral endopeptidase
15 (NEP) inhibitors; dual NEP-ACE inhibitors; HMG CoA reductase inhibitors such as pravastatin and mevacor; squalene synthetase inhibitors; bile acid sequestrants such as questran; calcium channel blockers; potassium channel activators; alpha-adrenergic agents, beta-adrenergic agents; antiarrhythmic agents; diuretics, such as
20 chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide or benzothiazide as well as ethacrynic acid, tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds; thrombolytic
25 agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase and anisoylated plasminogen streptokinase activator complex (APSAC); and PDE V inhibitors such as sildenafil. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described
30 below and the other pharmaceutically active agent within its approved dosage range. The compounds of this invention may also be formulated

with, or useful in conjunction with, antifungal and immunosuppressive agents such as amphotericin B, cyclosporins and the like to counteract the glomerular contraction and nephrotoxicity secondary to such compounds. The compounds of this invention may also be used in conjunction with
5 hemodialysis.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

10 The following assays may be employed in ascertaining the degree of activity of a compound ("drug") as an endothelin and angiotensin II receptor antagonist. Compounds described in the following Examples have been tested in these assays, and have shown activity.

15 ET_{AB} Attached cell binding assay

CHO-K1 cells expressing either the human endothelin A or endothelin B receptor were cultured in Ham's F12 media (Gibco/BRL, Grand Island, NY) with 10% fetal bovine serum (Hyclone), supplemented
20 with 300 µg/mL Geneticin (G-418 Gibco BRL Products, Grand Island, NY) and maintained at 37°C with 5% CO₂ in a humidified incubator. Twenty four hours prior to assay, the cells were treated with 0.25% trypsin-EDTA and were seeded in Falcon, 96 well tissue culture plates at a density of 1.8×10^4 cells/ well (the monolayer should reach 80-90% confluency by the day
25 of assay).

In the attached cell assay, culture media was aspirated from each well and the monolayers were washed with 50 µl of PBS (Mg⁺⁺, Ca⁺⁺ free). The binding assay was performed in a total volume of 125 µl consisting of assay buffer (50 mM Tris, pH 7.4, including 1% BSA, and 2 µM
30 phosphoramidon), and 25 µl of either 500 nM ET-1 (to define nonspecific binding) or competing drug. The reaction was initiated with the addition

of 25 μ L of 0.25 nM [125 I]-ET-1 (New England Nuclear). Incubation was carried out with gentle orbital shaking, at 4°C, reaching equilibrium at 4 hours. The reaction was terminated by aspiration of the reaction buffer and two subsequent washes with cold PBS (Mg^{++} , Ca^{++} free). The cells were
5 dissociated by the addition of 100 μ L of 0.5N NaOH followed by incubation for 40 minutes. Samples were then transferred from the 96 well format into tubes for counting in a Cobra gamma counter (Packard). Data was analyzed with curve fitting software by Sigma plot.

10 RASMC binding assay

Assays were conducted in a total volume of 250 μ L in 96 well microtitre plates. The incubation mixture contained 50 μ L [125 I]-Sar-Ile-Angiotensin II (0.2 nM), 25 μ L of drug dissolved in DMSO, or angiotensin II (1 μ M) to define non-specific binding. Binding to rat aortic smooth
15 muscle cells (RASMCs) was conducted in RPMI media (Gibco BRL Products, Grand Island, NY) containing 0.1% BSA for 2 hours at room temperature with continuous shaking. Unbound radioligand was washed from the wells. The RASMCs with bound radioligand are lysed with 1% Triton X and 0.1% BSA in distilled water for 15 minutes at room
20 temperature with continuous shaking. The solution in each well was transferred to tubes and placed in a gamma counter.

Preferred compounds within the scope of this invention are compounds that have an IC_{50} concentration of less than 5 micromolar
25 versus either or both [125 I]-Sar-Ile-Angiotensin II or [125 I]-ET-1, ideally against both ligands. More preferred compounds within the scope of this invention are compounds that have an IC_{50} concentration of less than 1 micromolar versus either or both [125 I]-Sar-Ile-Angiotensin II or [125 I]-ET-1, ideally against both ligands.

30 All documents cited in the present specification are incorporated herein by reference in their entirety.

The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims. Abbreviations employed herein are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (for example, "1A" denotes the title compound of step A of Example 1), or by the example only where the compound is the title compound of the example (for example, "4" denotes the title compound of Example 4). Compounds prepared for use as synthetic intermediates are identified by the Preparation number and step in which they appear, prefaced by the letter "P." For example, "P1A" denotes the compound generated in step A of Preparation 1, while "P1" denotes the title compound of Preparation 1.

Abbreviations

- 15 Ac = acetyl
(S)-BINAP = (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC = t-butoxycarbonyl
n-Bu = *n*-butyl
- 20 BSA = bovine serum albumin
CDI = 1,1' carbonyldiimidazole
d = days
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H = diisobutylaluminum hydride
- 25 DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
EDCI = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride
EDTA = ethylenediaminetetraacetic acid
eq = equivalents
- 30 Et = ethyl
ET = endothelin

- ET-1 = endothelin-1
EtOAc = ethyl acetate
EtOH = ethanol
h = hours
- 5 Me = methyl
MEM = methoxyethoxymethyl
MeOH = methanol
min = minutes
mp = melting point
- 10 Ms = methanesulfonyl
NBS = N-bromosuccinimide
PBS = phosphate buffered saline
Ph = phenyl
n-Pr = *n*-propyl
- 15 SEM = 2-(trimethylsiloxy)ethoxymethyl
Rochelle's salt = potassium sodium tartrate tetrahydrate
RT = room temperature
TFA = trifluoroacetic acid
THF = tetrahydrofuran

General Methods

The following General Methods were employed in the Preparations and Examples.

5

General Method 1: Suzuki Coupling of Aryl Bromides with Arylboronic Acids



R = H, alkyl

10

A solution of 1.0 eq of an arylboronic acid (or ester) and the appropriate aryl bromide (1.0 eq) in 2:1 toluene:ethanol (0.1 M concentration for each reagent) was sparged with nitrogen for 15 minutes. Tetrakis (triphenylphosphine)palladium (0) (0.05 eq) and 2 M aqueous sodium carbonate (3 eq) were added and the mixture was heated at 85°C for 3 h under a nitrogen atmosphere. The mixture was cooled and ethyl acetate and water were added. The organic layer was washed once with saturated aqueous sodium carbonate, dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate as eluant to yield the biaryl product.

Arylboronic acids used: [2-[[[(3,4-dimethyl-5-isoxazolyl)](2-methoxyethoxy)-methyl]amino]-sulfonyl]phenyl]boronic acid (or the corresponding SEM-protected compound, both of which were prepared as described in U.S. Patent No. 5,612,359); [2-[[[(4,5-dimethyl-3-isoxazolyl)](2-methoxyethoxy)methyl]amino]-sulfonyl]phenyl]boronic acid (prepared as described in U.S. Patent No. 5,612,359 and U.S. Patent Application Serial No. 09/013,952, filed January 27, 1998); [2-(*N*-tert-butylsulfonyl)phenyl]boronic acid (prepared according to Chang, L. L. et al., *J. Med. Chem.*, **38**, 3741-3758 (1995)).

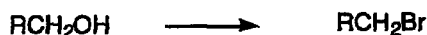
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Arylboronate ester used: N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (prepared as described in WO 97/29747).

5

General Method 2: Conversion of Primary
Alcohols to Alkyl Bromides

10



To a 0.2 M solution of the alcohol in DMF at 0 °C was added carbon tetrabromide (1.5 eq) followed by triphenylphosphine (1.5 eq). The mixture was stirred at 0 °C for 4 h, diluted with 10 parts 2:1 hexanes/ethyl acetate, and washed with water and brine. The solution was dried over sodium sulfate and concentrated, and the residue chromatographed on silica gel using hexanes/ethyl acetate as eluant to yield the alkyl bromide product.

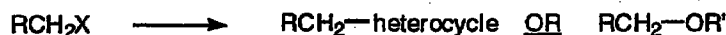
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General Method 3: Conversion of Primary
Alcohols to Alkyl Methanesulfonates

25



To a 0.15 M solution of the alcohol in dichloromethane at 0 °C was added *N,N*-diisopropylethylamine (1.5 eq) followed by methanesulfonyl chloride (1.1 eq). The mixture was stirred at 0 °C for 1 to 3 h, and was then treated with 10% aqueous potassium dihydrogensulfate. The aqueous layer was extracted once with dichloromethane and the combined organic layers were dried over sodium sulfate and concentrated to yield the crude alkyl methanesulfonate.

General Method 4: Alkylation of Heterocycles or Aliphatic Alcohols

X = Br, OMs

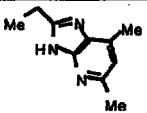
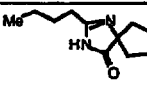
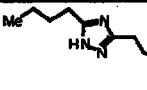
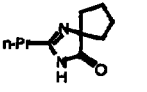
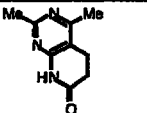
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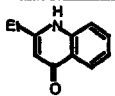
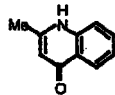
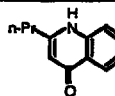
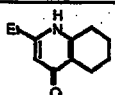
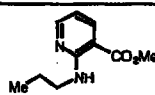
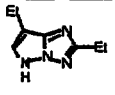
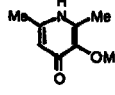
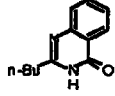
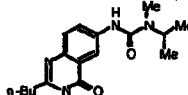
Sodium hydride (60% dispersion in mineral oil, 1.2 eq) was added at 0 °C to a 1.0 M solution or suspension of an appropriate heterocycle or alcohol (1.5 eq) in DMF. The mixture was allowed to warm to RT, was stirred for 20 min, and was then cooled back to 0 °C. To the heterocycle mixture was added a solution of the appropriate alkyl bromide or alkyl methanesulfonate (1.0 eq) in a minimal amount of DMF. The resultant mixture was allowed to warm to RT and was stirred for 16-24 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated, and the residue chromatographed on silica gel with hexanes/ethyl acetate as eluant to yield the alkylation product.

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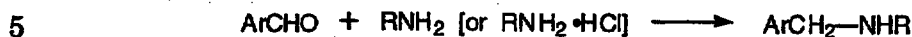
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Heterocycles Used:

	2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine	Senanayake, C. H., et. al. <i>Heterocycles</i> 1996, 42, 821-830.
	2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one	Bernhart, C. A., et. al. <i>J. Med. Chem.</i> , 1993, 36, 3371-3380.
	3,5-di-n-butyl-1,2,4-triazole	Reitz, D.B., et al. <i>Biorganic & Medicinal chemistry Letters</i> , 1994, 4(1), 99-104
	2-propyl-1,3-diazaspiro[4.4]non-1-en-4-one	Bernhart, C. A., et. al. <i>J. Med. Chem.</i> , 1993, 36, 3371-3380.
	7-oxo-2,4-dimethyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine	Hullar, T. L.; French, W. C. <i>J. Med. Chem.</i> , 1969, 12, 424-426.

	2-ethyl-4(1H)-quinolone	Bradbury, R.H.; et. al. <i>J. Med. Chem.</i> 1992, 35, 4027-4038.
	2-methyl-4(1H)-quinolone	commercially available
	2-propyl-4(1H)-quinolone	Bradbury, R.H.; et. al. <i>J. Med. Chem.</i> 1992, 35, 4027-4038.
	2-ethyl-5,6,7,8-tetrahydro-4(1H)-quinolone	Bradbury, R.H.; et. al. <i>J. Med. Chem.</i> 1993, 36, 1245-1254.
	methyl 2-(N-propylamino)pyridine-3-carboxylate	De, B.; et. al. <i>J. Med. Chem.</i> 1992, 35, 3714-3717
	2,7-diethyl-5H-pyrazolo[1,5-b][1,2,4]triazole	U.S. Patent No. 5,475,114
	3-methoxy-2,6-dimethyl-4(4H)-pyridinone	Voss, G.; et. al. <i>Liebigs Ann Chem.</i> 1982, 1466-1477
	2-butyl-4(3H)-quinazolinone	Allen, E. C.; et. al. <i>Biorganic & Medicinal Chemistry Let.</i> 1993, 3(6), 1293-1298
	N-(2-butyl-3,4-dihydro-4-oxo-6-quinazolinonyl)-N'-isopropyl-N-methylurea	Laszlo, S. E.; et al. <i>Biorganic & Medicinal Chemistry Let.</i> 1993, 3(6), 1299-1304

General Method 5: Reductive Amination

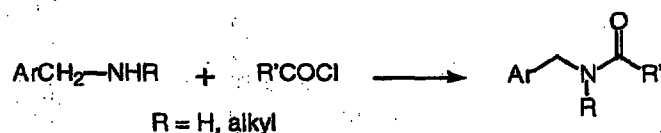


To a mixture of an aromatic aldehyde (1.0 eq) and a primary amine (1.2 eq) in dichloromethane (0.1 M aldehyde concentration) was added 4 Å molecular sieves (5g per mmol aldehyde). [Alternately, a primary amine hydrochloride (1.2 eq) and triethylamine (1.2 eq) could be substituted for
 10 the primary amine free base.] The mixture was stirred vigorously for 1 h,

after which sodium triacetoxyborohydride (1.5 eq) was added. The mixture was stirred vigorously at RT, while the course of the reaction was monitored by HPLC. If the reaction had not reached completion within several hours, additional sodium triacetoxyborohydride (1.0 eq) was added and monitoring was continued. When the reaction was complete the mixture was filtered through celite, aqueous sodium bicarbonate solution was added to the filtrate, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and evaporated. The crude residue was carried on without further purification.

In general, reductive amination with a 4-aminobutanoic acid resulted in a lactam product. In a few cases, cyclization was promoted by treatment of a 0.1 M solution of the crude amino acid product in dichloromethane with 1.0 eq of diisopropylcarbodiimide for 1 h at RT.

General Method 6: Amine Acylation



A 0.15 M solution of a primary or secondary amine (1.0 eq) and *N,N*-diisopropylethylamine (2.0 eq) in dichloromethane was treated at RT with an acyl chloride (1.5 eq). After 1.5 h, methanol (10 eq) was added, followed by aqueous sodium carbonate solution. The aqueous layer was extracted with dichloromethane and the combined organic extracts were combined, dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel with hexanes/ethyl acetate as eluant to provide the product tertiary amide.

**General Method 7: Hydrolysis of SEM or MEM Sulfonamide
Protecting Groups Using Hydrochloric Acid/Ethanol**



R = MEM, SEM

5

To a 0.1 M solution of a SEM- or MEM-protected N-heteroaryl sulfonamide in one volume of 95% EtOH was added an equal volume of 6N aqueous HCl, and the resulting solution was heated at reflux for 1 h. The reaction mixture was concentrated and the pH of the solution was
10 adjusted to pH 8 using aqueous sodium bicarbonate solution. It was then reacidified to pH 5 with glacial acetic acid. The mixture was extracted with three portions of ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by reverse-phase preparative
15 HPLC, or by silica gel chromatography using chloroform/methanol or hexanes/acetone as eluant.

**General Method 8: Hydrolysis of SEM or MEM Sulfonamide
Protecting**

20

Groups Using Hydrogen Chloride in Dioxane/Alcohol

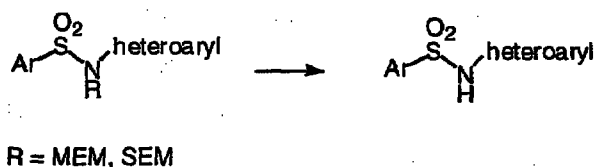


R = MEM, SEM

A solution of a SEM- or MEM-protected N-heteroaryl sulfonamide
25 in one volume of absolute methanol or ethanol was treated with two volumes of 4 N hydrogen chloride/dioxane solution (final substrate

concentration 0.05 M). The resulting solution was heated at 55 °C for 16 h and was then concentrated. The residue was purified by reverse-phase preparative HPLC, or by extraction with ethyl acetate from aqueous potassium phosphate adjusted to pH 5-6, followed by silica gel chromatography.

General Method 9: Cleavage of SEM or MEM Sulfonamide
Protecting
Groups Using Trimethylsilyl Iodide



To a 0.1 M solution of of a SEM- or MEM-protected N-heteroaryl sulfonamide in acetonitrile was added trimethylsilyl chloride (8 eq) followed by sodium iodide (8 eq). The mixture was stirred at RT for 30 min and was then poured onto water and ethyl acetate. The organic layer was washed with saturated sodium sulfite and brine, and was then dried over sodium sulfate and concentrated. The residue was purified by reverse-phase preparative HPLC or by silica gel chromatography.

20
General Method 10: Cleavage of SEM Sulfonamide Protecting
Groups Using Tetrabutylammonium Fluoride



To a 0.05 M solution of a SEM-protected N-heteroaryl sulfonamide in THF was added freshly activated 4Å molecular sieves (20 g per mmol

sulfonamide), followed by tetrabutylammonium fluoride (1.0 M solution in THF, 3 eq). The mixture was heated at 55 °C for 1-2 h, then was cooled and filtered through celite. The filter cake was rinsed with methanol, then aqueous potassium dihydrogen phosphate solution was added to the filtrate and the mixture partially concentrated. The residue was adjusted to pH 4-5 using dilute hydrochloric acid, and the mixture was extracted with two portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by reverse-phase preparative HPLC or by silica gel chromatography.

10

General Method 11: Reduction of Aryl Aldehydes to Benzylic Alcohols Using Sodium Borohydride



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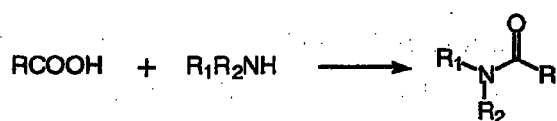
Sodium borohydride (0.5 eq) was added at 0 °C to a 0.2 M solution of an aromatic aldehyde in absolute ethanol or methanol. The mixture was allowed to warm to RT and stirred for 1-2 h. Aqueous potassium dihydrogen phosphate solution (or dilute hydrochloric acid) was added and the mixture was stirred for an additional 15 min. The mixture was partially concentrated and the residue partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the combined organic extracts were dried over sodium sulfate and concentrated. The crude benzylic alcohol was either used directly or was purified by silica gel chromatography using hexanes/ethyl acetate as eluant.

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General Method 12: Amide Formation using 1,1'-Carbonyldiimidazole

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1,1'-Carbonyldiimidazole (2.0 eq) was added to a 0.1 M solution or suspension of an appropriate carboxylic acid (1.0 eq) in THF. The mixture
5 was heated at 50 °C for 1h, and was then cooled to RT. An appropriate amine (5-10 eq) was then added, and the mixture was stirred at RT for 12 h. Ethyl acetate and aqueous sodium bicarbonate solution were added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The
10 residue was purified by reverse-phase preparative HPLC or by silica gel chromatography.

General Method 13: Benzylic Bromination

Using N-Bromosuccinimide

15



To a 0.4 M solution of a methyl-substituted aromatic compound in carbon tetrachloride was added N-bromosuccinimide (1.05 eq) and benzoyl
20 peroxide (0.03 eq), and the mixture was heated at reflux for 8-16 h. The mixture was cooled and filtered and the filtrate concentrated. The residue was purified by trituration with 3:1 hexanes/ethyl acetate, or by silica gel chromatography using hexanes/ethyl acetate as eluant to provide the mono-brominated product.

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General Method 14: Reduction of an Aromatic

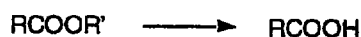
Nitrile to an Aromatic Aldehyde Using DIBAL-H



30

DIBAL-H (1.5 M solution in toluene, 1.5 eq) was added dropwise at 0 °C to a 0.5 M solution of an aromatic nitrile (1.0 eq) in toluene or 9:1 toluene/dichloromethane. The solution was stirred at 0 °C for 1-4 h, and was then treated with excess methanol. After 15 min, 2N hydrochloric acid was added and the mixture was stirred vigorously for an additional 15 min. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to yield the crude aldehyde, which was either carried on crude or purified via silica gel chromatography using hexanes/ethyl acetate as eluant.

General Method 15: Ester Hydrolysis Using Lithium Hydroxide

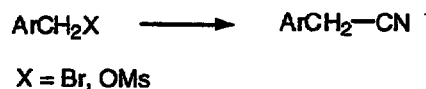


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A 0.25 M solution of an alkyl ester in 1:1 THF/water was treated with lithium hydroxide hydrate (1.5 eq) at RT. The mixture was stirred for 8-16 h and was then acidified with dilute hydrochloric acid. The product was either isolated by direct filtration from the reaction mixture, or by extraction with ethyl acetate, followed by drying of the organic layers with sodium sulfate, concentration, and silica gel chromatography using methanol/chloroform or hexanes/acetone as eluant.

25

General Method 16: Displacement of a Benzylic Bromide or Mesylate with Cyanide



Sodium cyanide (1.2 eq) was added at RT to a 1.0 M solution of a benzylic bromide or mesylate in DMF. The mixture was stirred at RT for

16 h. The reaction mixture was diluted with ethyl acetate and partitioned against aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated, and the residue chromatographed on silica gel with hexanes/ethyl acetate as eluant to yield the nitrile product.

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General Method 17: Swern Oxidation of a Benzylic Alcohol to an Aromatic Aldehyde



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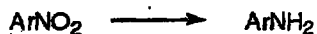
Oxalyl chloride (1.5 eq) was added dropwise to a solution of DMSO (2.0 eq) in dichloromethane at -78°C . After 5 min, a solution of benzylic alcohol substrate (1.0 eq) in dichloromethane was added and the mixture (0.2 M final substrate concentration) was stirred at -78°C for 15 min.

15 Triethylamine (4.0 eq) was added and the mixture was stirred and allowed to warm to RT. Aqueous sodium bicarbonate solution was added, the layers were separated, and the aqueous layer was extracted with one portion of dichloromethane. The combined organic layers were dried over sodium sulfate, concentrated, and the residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluant.

20

General Method 18: Reduction of an Aromatic Nitro Group to an Aromatic Amine Using Tin (II) Chloride Dihydrate

25



Tin (II) chloride dihydrate (4.0 eq) was added to a 0.05 M solution of an aromatic nitro compound in ethyl acetate and the resulting mixture was heated at 70°C for 45 min. The mixture was cooled, half-saturated aqueous sodium carbonate solution was added, and the layers were separated. The aqueous layer was extracted once with ethyl acetate, and

30

the combined organic layers were dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate as eluant to provide the product aromatic amine.

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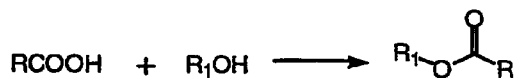
General Method 19: Hydrolysis of a
2-Aryl-1,3-Dioxolane to an Aromatic Aldehyde



- 10 A 0.2 M solution of a 2-aryl-1,3-dioxolane (1.0 eq) in THF was treated with 1N hydrochloric acid (1.5 eq), and the resulting solution was heated at 55 °C for 16 h. The mixture was cooled and neutralized with aqueous sodium bicarbonate solution, then extracted with three portions of ethyl acetate. The combined organic extracts were dried over sodium
- 15 sulfate and concentrated, and the crude aldehyde was used directly with no further purification.

General Method 20: Ester Formation Using
1,1'-Carbonyldiimidazole and DBU

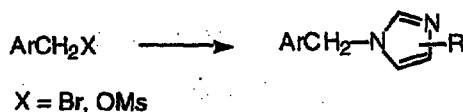
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- 1,1'-Carbonyldiimidazole (2.0 eq) was added to a 0.1 M solution or suspension of an appropriate carboxylic acid (1.0 eq) in THF. The mixture
- 25 was heated at 50 °C for 1h. An appropriate alcohol (3.0 eq) was then added, followed by DBU (3.0 eq). The mixture was heated at 50 °C for 16 h and was then cooled. Ethyl acetate and 35% aqueous citric acid solution were added, and the organic layer was dried over sodium sulfate and

concentrated. The residue was purified by reverse-phase preparative HPLC or by silica gel chromatography.

General Method 21: Phase-Transfer Alkylation of Imidazoles

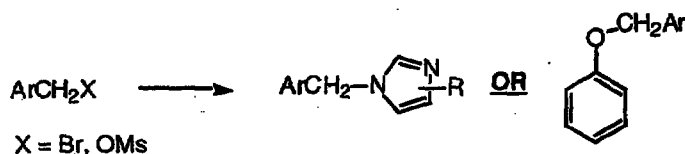


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A solution of an appropriate imidazole (0.1 M) in toluene was treated with 50% aqueous sodium hydroxide solution (0.5 ml per mmol imidazole), tetrabutylammonium hydrogen sulfate (0.05 eq), and an appropriate benzylic alkyl bromide or mesylate (0.95 eq). The mixture was stirred vigorously at 40 °C for 24 h and was then cooled and filtered. Water was added and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated to provide the crude product, which was either purified by silica gel chromatography or was carried on crude. Imidazole used: 2-propyl-4,5,6,7-tetrahydro-8-oxocycloheptimidazole (Yanagisawa, T.; et. al. *Biorg. Med. Chem. Lett.* **1993**, 3, 1559-1564).

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General Method 22: Imidazole or Phenol Alkylation

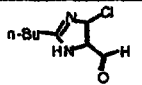
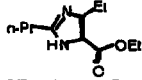
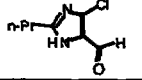


A solution of an appropriate imidazole (0.5 M) in DMF was treated with potassium carbonate (2.0 eq) and a benzylic alkyl bromide or mesylate (1.0 eq) at RT. The mixture was stirred at RT for 16 to 24 h. The solvent was evaporated and the residue was partitioned between

ethyl acetate and water. The ethyl acetate layer was dried over sodium sulfate and concentrated to provide the crude product, which was purified by silica gel chromatography or was carried on crude. When mixtures of N-1 and N-3 alkylation products were obtained, the regiochemistry of the

5 alkylation was determined by NOESY spectroscopy.

Imidazoles Used:

	2-n-butyl-4-chloro-5-formylimidazole	Watson, S.P. <i>Synth. Comm.</i> , 1992, 22, 2971-2977
	ethyl 2-n-propyl-4-ethylimidazole-5-carboxylate	Carini, D. J., WO 92/00977
	2-n-propyl-4-chloro-5-formylimidazole	Watson, S.P. <i>Synth. Comm.</i> , 1992, 22, 2971-2977

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General Method 23: Cleavage of SEM Sulfonamide Protecting Groups Using Cesium Fluoride



15

To a 0.05 M solution of a SEM-protected N-heteroaryl sulfonamide in DMF was added cesium fluoride (5.0 eq), and the resulting mixture was heated at 130 °C for 3 h. The reaction mixture was cooled and the solvent evaporated. Aqueous potassium dihydrogen phosphate solution was added

20 (pH 4-5) and the mixture was extracted with three portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by reverse-phase preparative HPLC or by silica gel chromatography.

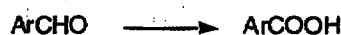
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General Method 24: Sulfonylation of Aromatic Amines

- 5 To a 0.1 M solution of an aromatic amine (1.0 eq.) in dichloromethane at -30 °C was added triethylamine (2.6 eq), followed by a sulfonyl chloride (1.4 eq). The mixture was allowed to warm to RT over 3 hr. Aqueous sodium bisulfate was added (final pH 5) and the aqueous layer was extracted with dichloromethane. The combined organic extracts
10 were washed with water and brine, and were then dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using dichloromethane/methanol as eluant.

General Method 25: Oxidation of Aromatic Aldehydes to Carboxylic

- 15 Acids



- A 0.1 M solution of an aromatic aldehyde in 1:1 THF/water was
20 treated at 0 °C with sulfamic acid (1.5 eq) and sodium chlorite (1.5 eq). After 1 h aqueous potassium bisulfate solution was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to provide the crude carboxylic acid, which was used without further purification.

- 25 General Procedure: Purification by Anion Exchange Chromatography

- Anion exchange chromatography was performed on Varian SAX cartridges (acetate form, 1.5-3 g) or United Chemical Technologies
30 CUQAX13M6-AC cartridges (acetate form, 3 g). Following a methanol rinse, the cartridge was loaded with a dichloromethane solution of crude

product. Elution of impurities with dichloromethane, followed by elution of the desired product with 1-3% TFA in dichloromethane or dichloromethane/methanol, provided the purified product.

5 General Procedure: Purification by Reverse-Phase Preparative HPLC

Reverse-phase preparative HPLC was performed with Shimadzu 8A liquid chromatographs using YMC S5 ODS columns (20 x 100, 20 x 250, or 30 x 250 mm). Gradient elution was performed with methanol/water mixtures in the presence of 0.1% TFA. In some cases a product eluting as a TFA salt was subsequently converted to the corresponding free base by extraction from aqueous sodium bicarbonate or sodium carbonate solution.

Analytical HPLC Methods Employed in Characterization of
Examples

Analytical HPLC was performed on Shimadzu LC10AS liquid chromatographs using the following methods:

- 20 A. Linear gradient of 0 to 100% solvent B over 4 min, with 1 min hold
at 100% B;
UV visualization at 220 nm
Column: YMC S5 ODS Ballistic 4.6 x 50 mm
Flowrate: 4 ml/min
- 25 Solvent A: 0.1% trifluoroacetic acid, 90% water, 10% methanol
Solvent B: 0.1% trifluoroacetic acid, 90% methanol, 10% water
- B. Linear gradient of 0 to 100% solvent B over 30 min, with 5 min hold
at 100% B;
- 30 UV visualization at 254 nm
Column: YMC S3 ODS 6 x 150 mm

Flowrate: 1.5 ml/min

Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol

Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water

- 5 C. Linear gradient of 0 to 100% solvent B over 4 min, with 1 min hold at 100% B
UV visualization at 220 nm
Column: YMC S5 ODS Ballistic 4.6 x 50 mm
Flowrate: 4 ml/min
- 10 Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol
Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water
- D. Linear gradient of 45 to 100% solvent B over 2 min, with 1 min hold at 100% B;
- 15 UV visualization at 220 nm
Column: Phenomenex Primesphere 4.6 x 30 mm
Flowrate: 5 ml/min
Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol
Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water
- 20 E. Same conditions as (B), but with a linear gradient of 40 to 100% solvent B over 30 min, with 5 min hold at 100% B
- F. Same conditions as (B), but with a linear gradient of 70 to 100% solvent B over 30 min, with 5 min hold at 100% B
- 25 G. Same conditions as (D), but with a linear gradient of 40 to 100% solvent B over 2 min, with 1 min hold at 100% B
- 30 H. Linear gradient of 0 to 100% solvent B over 2 min, with 1 min hold at 100% B;

UV visualization at 220 nm

Column: Phenomenex Primesphere 4.6 x 30 mm

Flowrate: 5 ml/min

Solvent A: 0.1% trifluoroacetic acid, 90% water, 10% methanol

5 Solvent B: 0.1% trifluoroacetic acid, 90% methanol, 10% water

I. Same conditions as (B), but with a linear gradient of 50 to 100% solvent B over 30 min, with 5 min hold at 100% B

10 J. Same conditions as (C), but with a linear gradient of 0 to 100% solvent B over 8 min, with 1 min hold at 100% B

K. Same conditions as (D), but with a linear gradient of 0 to 100% solvent B over 2 min, with a 1 minute hold at 100% B.

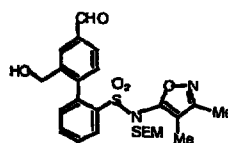
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Preparations

Preparation 1:

N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(hydroxymethyl)-N-[(2-trimethylsiloxy)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

20



A. 4-Bromo-3-(bromomethyl)benzonitrile

25 The product was prepared according to General Method 13 starting from 12.0 g 4-bromo-3-methylbenzonitrile. Partial purification of the crude product was performed by trituration with 3:1 hexanes/ethyl acetate to afford 7.3 g of a slightly yellow solid, which was contaminated with approximately 20 mol% of the starting material.

B. 4-Bromo-3-(acetoxymethyl)benzonitrile

A mixture of P1A (7.3 g), potassium acetate (3.4 g), and DMF (10 ml) was stirred at RT for 16 h. Ethyl acetate was added and the mixture was washed with four portions of water, followed by one portion of brine.

- 5 The ethyl acetate layer was dried over sodium sulfate and concentrated. The solid residue was partially purified by crystallization from ethyl acetate, yielding 4.5 g of a slightly yellow solid.

C. 4-Bromo-3-(hydroxymethyl)benzaldehyde

- 10 P1B (4.4 g) was treated with DIBAL-H according to General Method 14, using 3.5 eq of the reducing agent rather than 1.5 eq. The crude product was an orange oil (4.8 g), judged by ¹H NMR to be approximately 75% pure by weight.

- 15 D. N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(hydroxymethyl)-N-[(2-trimethylsiloxy)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

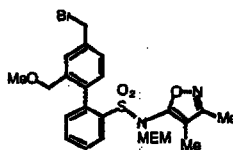
P1C (4.7 g) was subjected to Suzuki coupling according to General Method 1, yielding 7.6 g of the product as an orange oil following silica gel chromatography (2:1 hexanes/ethyl acetate eluant).

20

Preparation 2:

N-(3,4-Dimethyl-5-isoxazolyl)-4'-bromomethyl-2'-(methoxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

25



A. 4-Bromo-3-(bromomethyl)benzonitrile

The product was prepared according to General Method 13 starting from 19.6 g 4-bromo-3-methylbenzonitrile. After cooling the mixture was filtered and the filtrate was washed with H₂O and brine, dried and concentrated. The residue was chromatographed on silica gel using 100:3 and then 100:10 hexane/EtOAc to afford **P2A** (16 g, 58%). R_f=0.15, silica gel, 10:1 hexane/EtOAc.

B. 4-Bromo-3-(Methoxymethyl)benzonitrile

To a solution of **P2A** (6.95 g, 25.28 mmol) in 10 ml DMF, NaOMe (25 wt. % in MeOH, 6.94 ml, 30.3 mmol) was added dropwise. The reaction mixture was stirred at RT for 3 h. Ethyl acetate (100 ml) and hexanes (50 ml) were added, and the mixture was washed twice with water and once with brine. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using 100:6 hexane/EtOAc to afford **P2B** (4.70 g, 82%). R_f=0.5, silica gel, 5:1 hexane/EtOAc.

C. 4-Bromo-3-(methoxymethyl)benzaldehyde

P2B (7.0 g) was treated with DIBAL-H according to General Method 14, using THF instead of toluene as solvent. The crude product was purified by silica gel chromatography using 11:1 hexanes/ethyl acetate as eluant to give 6.2 g **P2C** as a colorless gum. R_f=0.4, silica gel, 5:1 Hexane/EtOAc.

D. N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(methoxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

P2C (6.2 g) was subjected to Suzuki coupling according to General Method 1, giving **P2D** as an oil in 83% yield after silica gel chromatography.

E. N-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-(methoxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

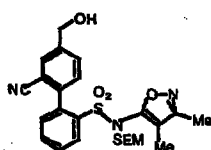
P2D (2.8 g) was reduced with sodium borohydride according to
5 General Method 11, to provide 2.8 g **P2E**.

F. N-(3,4-Dimethyl-5-isoxazolyl)-4'-bromomethyl-2'-(methoxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

P2E (2.8 g) was treated with triphenylphosphine and carbon
10 tetrabromide according to General Method 2, providing the title compound
(2.3 g) in 72% yield.

Preparation 3:

15 2'-Cyano N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-trimethylsiloxy)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide



20 A. 4'-(Acetoxymethyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-formyl-N-[(2-trimethylsiloxy)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide acetoxime

Hydroxylamine hydrochloride (1.13 g) was added to a solution of 7.0
g **P4** in 20 ml pyridine and the mixture was stirred at RT for 2 h. Acetic
anhydride (5.1 ml) was added and the mixture was stirred for 1 h at RT.
25 Ethanol (5 ml) was added and the mixture was concentrated under
reduced pressure. The residue was taken up in ethyl acetate and washed
twice with 0.1 N hydrochloric acid, twice with half-saturated aqueous
sodium carbonate solution, and once with brine. The ethyl acetate layer

was dried over sodium sulfate and concentrated to provide **P3A** as an orange oil.

5 B. 4'-(Acetoxymethyl)-2'-cyano-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-trimethylsiloxy)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

P3A was dissolved in 75 ml acetonitrile, DBU (4.0 ml) was added, and the mixture was stirred at RT for 14 h. The mixture was concentrated, and the residue was taken up in ethyl acetate and washed twice with 0.1 N hydrochloric acid, then once with half-saturated aqueous sodium carbonate solution. The ethyl acetate layer was dried over sodium sulfate and concentrated to give **P3B** as an orange oil.

15 C. 2'-Cyano N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-trimethylsiloxy)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

P3B was dissolved in 150 ml methanol, potassium carbonate (1.5 g) was added, and the mixture was stirred at RT for 2 h. 2N Hydrochloric acid (5.5 ml) was added and the mixture was concentrated. The residue was taken up in ethyl acetate and partitioned against aqueous sodium bicarbonate solution. The ethyl acetate layer was dried over sodium sulfate and concentrated to yield 5.7 g of the crude title compound, which was used without further purification.

Preparations 4 through 22 were performed by application of the General Methods and are listed in the following Table.

25

Preparations by General Methods

No.	Structure	Name	Starting Material	Starting Material Reference	General Methods Applied (yield, %)
P4		N-(3,4-Dimethyl-5-isoxazolyl)-2'-formyl-4'-(hydroxymethyl)-N-[[2-(trimethylsilyl)ethoxy]methyl][1,1'-biphenyl]-2-sulfonamide		Zhang, H.-Y. et al., <i>Tetrahedron</i> , 1994, 50, 11339-11362.	19 (95); 1 (81)
P5		2'-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-4'-formyl-N-[[2-(trimethylsilyl)ethoxy]methyl][1,1'-biphenyl]-2-sulfonamide		Casida, J. E.; Elliott, M.; Pullmann, D. A., EP 294229	1 (83)
P6		N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(trifluoromethyl)-N-[[2-(trimethylsilyl)ethoxy]methyl][1,1'-biphenyl]-2-sulfonamide		DoAmaral, J. R.; French, F. A.; Blanz, E. J. Jr.; French, D. A. <i>J. Med. Chem.</i> 1971, 9, 862-866.	1 (11)
P7		N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-N-[(2-methoxyethoxy)methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide		Pine, S. H.; et. al. <i>J. Org. Chem.</i> 1971, 36, 984-91.	1 (77)
P8		N-(3,4-Dimethyl-5-isoxazolyl)-2'-fluoro-4'-formyl-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide		Palmer, C. J.; Casida, J. E.; Larkin, J. P. US Patent 5,061,726	1 (50)
P9		2'-[[[(3,4-Dimethyl-5-isoxazolyl)[2-(trimethylsilyl)ethoxy]methyl]amino]sulfonyl]-2-(trifluoromethyl)[1,1'-biphenyl]-4-methanol methanesulfonate	P6		11 (90); 3 (75)

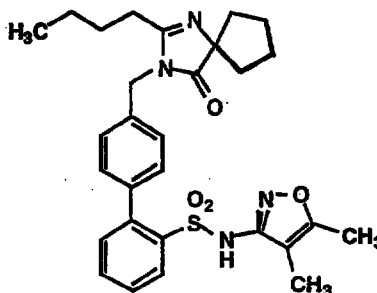
P1 0		2-Chloro-2'-[[[(3,4-dimethyl-5-isoxazolyl)[(2-(trimethylsilyl)ethoxy)methyl]amino]sulfonyl][1,1'-biphenyl]-4-methanol methanesulfonate	P5		11 (90); 3 (83)
P1 1		4'-(Bromomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide	P8		11 (98); 2 (67)
P1 2		2'-[[[(3,4-Dimethyl-5-isoxazolyl)[(2-(trimethylsilyl)ethoxy)methyl]amino]sulfonyl]-4-(hydroxymethyl)[1,1'-biphenyl]-2-methanol methanesulfonate	P1		3 (99); 11 (76)
P1 3		4'-[(Methanesulfonyloxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide	P7		11; 3 (62)
P1 4		2'-[[[(3,4-Dimethyl-5-isoxazolyl)[(2-(trimethylsilyl)ethoxy)methyl]amino]sulfonyl]-2-(hydroxymethyl)[1,1'-biphenyl]-4-methanol methanesulfonate	P4		3 (90); 11 (35)
P1 5		N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-methyl-N-[(2-(trimethylsilyl)ethoxy)methyl][1,1'-biphenyl]-2-sulfonamide		Pine, S. H.; et. al. <i>J. Org. Chem.</i> 1971 , 36, 984-91.	1 (52)
P1 6		N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-N-[(2-(trimethylsilyl)ethoxy)methyl][1,1'-biphenyl]-2-sulfonamide	4-bromo-benz-aldehyde		1 (67)

P1 7		N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-N-([2-methoxyethoxy]methyl)[1,1'-biphenyl]-2-sulfonamide	4-bromo-benzaldehyde		1 (80)
P1 8		4'-Bromomethyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide	P17		11,2 (80)
P1 9		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(methanesulfonyloxy)methyl]-N-([2-(trimethylsilyl)ethoxy]methyl)[1,1'-biphenyl]-2-sulfonamide	P16		11 (83); 3 (90)
P2 0		N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-N-([2-(trimethylsilyl)ethoxy]methyl)[1,1'-biphenyl]-2-sulfonamide	P2C		1 (72)
P2 1		N-(3,4-Dimethyl-5-isoxazolyl)-2'-formyl-4'-(hydroxymethyl)-N-([2-methoxyethoxy]methyl)[1,1'-biphenyl]-2-sulfonamide	 Zhang, H.-Y. et al., <i>Tetrahedron</i> , 1994, 50, 11339-11362.		19 (95); 1 (77)
P2 2		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-([2-methoxyethoxy]methyl)-2'-nitro[1,1'-biphenyl]-2-sulfonamide	4-bromo-3-nitro-toluene		13 (53); 4 (74); 1 (50)

Examples

Example 1

5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-
dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide



- A. N-(4,5-Dimethyl-3-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-
 10 methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide
 4-Bromobenzyl alcohol (750 mg, 4.0 mmol) was coupled with [2-
 [[(4,5-dimethyl-3-isoxazolyl)](2-
 methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid (1.0 g, 2.7
 mmol) according to General Method 1. The crude residue was
 15 chromatographed on silica gel using 3:4 hexane/EtOAc to afford 1A (730
 mg, 66%) as a colorless gum: R_f =0.26, silica gel, 2:3 hexane/EtOAc.
- B. 4'-Bromomethyl-N-(4,5-dimethyl-3-isoxazolyl)-N-[(2-
methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide
 20 1A (730 mg, 1.64 mmol) was converted to the corresponding
 bromide according to General Method 2. The crude residue was
 chromatographed on silica gel using 4:1 hexane/EtOAc to afford 1B (750
 mg, 90%) as a colorless gum: R_f =0.66, silica gel, 1:1 hexane/EtOAc.

C. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

1B (255 mg, 0.5 mmol) was reacted with 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride according to General Method 4. The crude residue was chromatographed on silica gel using 3:4 hexane/EtOAc to afford 1C as a gum: R_f =0.32, silica gel, 1:1 hexane/EtOAc.

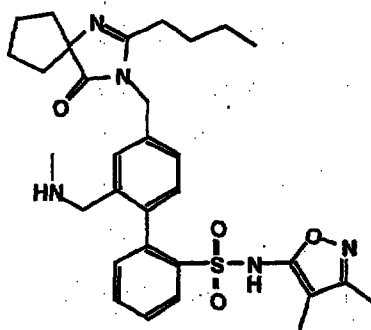
10 D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

1C was subjected to deprotection according to General Method 7. The crude residue was purified by preparative HPLC to provide the title compound as a white solid (130 mg, 49%, for two steps): mp 77-81°C.

15 Analysis calculated for $C_{29}H_{34}N_4O_4S \cdot 1.0H_2O$: Calc'd: C, 63.02; H, 6.57; N, 10.14; S, 5.80. Found: C, 62.75; H, 6.16; N, 9.85; S, 5.54.

Example 2

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(methylamino)methyl][1,1'-biphenyl]-2-sulfonamide



A. 4-Bromo-3-formyl-benzonitrile

To a solution of 4-bromo-3-methyl benzonitrile (14.0 g, 71.4 mmol) in carbon tetrachloride (200 mL), N-bromosuccinimide (13.98 g, 78.55 mmol) and benzoyl peroxide (700 mg) were added, and the mixture was heated at reflux for 8 h while illuminating the solution with a sun lamp. The mixture was cooled and filtered. The filtrate was concentrated to provide a light yellow solid (21 g) which was used in the next step without any further purification.

To a solution of the crude compound (21 g) obtained above in anhydrous DMSO (30 mL) under argon, was added anhydrous trimethylamine N-oxide (6.97 g, prepared as described in Soderquist et al., *Tetrahedron Letters*, 27, 3961 (1986)), and the mixture was stirred at 55°C for 48 h. The mixture was then cooled and added to ice/water (150 mL) and the resulting aqueous mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed once with brine (100 mL), dried and evaporated. The residue was chromatographed on silica gel using 8:1 hexanes/EtOAc to afford **2A** as a white solid (6.1 g, 47% for two steps).

B. 4'-Cyano-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

2A (3.0 g, 14 mmol) was subjected to Suzuki coupling with N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide according to General Method 1. The crude residue was chromatographed on silica gel using 2:1 hexane/EtOAc to afford **3B** (4.5 g, 68%) as a colorless gum.

C. 4'-Cyano-2'-(N-methylaminomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

To **2B** (2.2 g, 4.69 mmol), MeNH₂ (8.03 M in EtOH, 2.33 mL, 18.74 mmol) and 3A molecular sieves in CH₂Cl₂ (47 mL), glacial acetic acid (1.13

g, 18.74 mmol) was added followed by NaB(AcO)₃H (3.98 g, 18.74 mmol). The reaction mixture was stirred at RT overnight, diluted with EtOAc and filtered through celite. The filtrate was washed with H₂O, dried and concentrated. The residue was chromatographed on silica gel using 100:5
5 CH₂Cl₂/MeOH to afford 2C (1.24 g, 55%) as a colorless gum: R_f=0.2, silica gel, 100:5 CH₂Cl₂/MeOH.

10 D. 2'-(N-*t*-Butoxycarbonyl-N-methylaminomethyl)-4'-cyano-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

To 2C (1.3 g, 2.68 mmol), triethylamine (434 mg, 4.3 mmol) and 4-dimethylaminopyridine (33 mg, 0.27 mmol) in THF (10 mL) was added a solution of di-*t*-butyl dicarbonate (703 mg, 3.22 mmol) in THF (10 mL) dropwise. The reaction mixture was stirred at RT for 3 h. 10% aqueous
15 NH₄Cl was added, and the mixture was extracted with EtOAc. The extracts were washed with H₂O and brine, dried and concentrated. The residue was chromatographed on silica gel using 7:4 hexane/EtOAc to afford 2D (1.1 g, 70%) as a colorless gum: R_f=0.57, silica gel, 2:3 hexane/EtOAc.

20

E. 2'-(N-*t*-Butoxycarbonyl-N-methylaminomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-formyl-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

To 2D (1.03 g, 1.76 mmol) in THF (18 mL), diisobutylaluminum
25 hydride (1M in CH₂Cl₂, 5.29 mL, 5.29 mmol) was added dropwise. The reaction mixture was stirred at RT for 4 h. MeOH (20 mL) was added, and the mixture was stirred for 20 min. The mixture was then added into H₂O and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried and concentrated. The residue was chromatographed on
30 silica gel using 5:6 hexane/EtOAc to afford 2E (325 mg, 31%) as a colorless gum: R_f=0.37, silica gel, 1:1 hexane/EtOAc.

F. 2'-(N-*t*-Butoxycarbonyl-N-methylaminomethyl)-4'-Hydroxymethyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

5 **2E** was reduced using sodium borohydride according to General Method 11 to provide **2F**, which was used in the next reaction step without any purification.

G. 4'-Bromomethyl-2'-(N-*t*-butoxycarbonyl-N-methylaminomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

10

2F was treated with carbon tetrabromide and triphenylphosphine according to General Method 2 to provide **2G** in 78% yield.

H. 2'-(N-*t*-Butoxycarbonyl-N-methylaminomethyl)-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

15

2G was treated with 2-*n*-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride according to General Method 4 to provide **2H** in 79% yield.

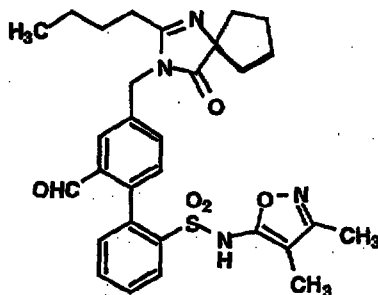
20

I. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(methylamino)methyl][1,1'-biphenyl]-2-sulfonamide

25 **2H** (170 mg, 0.22 mmol) was deprotected according to General Method 7 to provide the title compound in 67% yield: R_f =0.39, silica gel, 10:1 CH₂Cl₂/MeOH; mp: 194-200 °C; LRMS (m/z) 578 (MH⁺).

Example 3

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



5 A. 4'-Cyano-2'-(1,3-dioxolan-2-yl)-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

A mixture of **2B** (1.28 g, 2.73 mmol), ethylene glycol (1.69 g, 27.3 mmol) and *p*-toluenesulfonic acid (38 mg) in toluene (30 mL) was heated at 130°C for 5 h, while a Dean-Stark water separator was used. After cooling, the mixture was diluted with EtOAc. The organic liquid was separated and washed with H₂O and brine, dried and concentrated. The residue was chromatographed on silica gel using 5:4 hexane/EtOAc to afford **3A** (1.1 g, 79%) as a colorless gum: *R_f*=0.57, silica gel, 1:2 hexane/EtOAc.

15 B. 2'-(1,3-Dioxolan-2-yl)-4'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

To **3A** (1.1 g, 2.14 mmol) in THF (21 mL) at 0°C was added DIBAL-H (1M in CH₂Cl₂, 4.28 mL 4.28 mmol) dropwise. The reaction was stirred at RT overnight. MeOH (20 mL) was added and the reaction was stirred for 5 min. The mixture was poured into cold 0.1 N HCl solution (150 mL), shaken for 5 min, and then extracted with 3:1 EtOAc/hexane. The combined organic extracts were washed with H₂O and brine, dried and concentrated. The residue was chromatographed on silica gel using 3:4 hexane/EtOAc to afford **3B** (710 mg, 64%) as a colorless gum: *R_f*=0.45, silica gel, 2:3 hexane/EtOAc.

C. 2'-(1,3-Dioxolan-2-yl)-4'-hydroxymethyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

3B (710 mg, 1.4 mmol) was subjected to sodium borohydride reduction according to General Method 11 to afford 3C, which was used for the next reaction step without further purification.

D. 4'-Bromomethyl-2'-(1,3-dioxolan-2-yl)-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

3C was treated with carbon tetrabromide and triphenylphosphine according to General Method 2. The crude residue was chromatographed on silica gel using 3:2 hexane/EtOAc to afford 3D (750 mg, 94%) as a colorless gum: $R_f=0.74$, silica gel, 1:2 hexane/EtOAc.

E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,3-dioxolan-2-yl)-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl) [1,1'-biphenyl]-2-sulfonamide

3D (750 mg, 1.3 mmol) was treated with 2-*n*-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride (387 mg, 1.68 mmol) according to General Method 4. The crude residue was chromatographed on silica gel using 100:1.7 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to afford 3E as a gum (830 mg, 93%): $R_f=0.40$, silica gel, 100:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

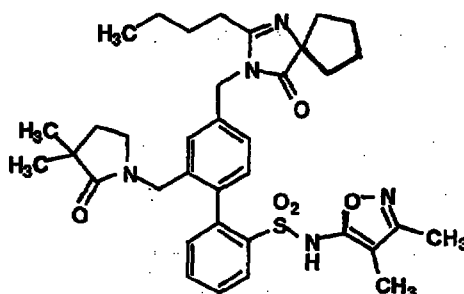
F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

3E (830 mg, 1.20 mmol) was subjected to deprotection according to General Method 7. The crude residue was chromatographed on silica gel using 100:1.5 and then 100:4 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to afford the title compound as a gum (480 mg, 72%): $R_f=0.16$, silica gel, 100:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

Example 4

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-
pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

5



To **3F** (110 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) was added 4-amino-2,2-dimethylbutanoic acid hydrochloride (98 mg, 0.59 mmol) [Scheinmann, et al., *J. Chem. Research (S)*, 414-415 (1993)] and 3Å molecular sieves, followed by glacial acetic acid (35 mg, 0.59 mmol) and then sodium acetate (48 mg, 0.59 mmol). The mixture was stirred for 8 minutes, and $\text{NaB}(\text{AcO})_3\text{H}$ (124 mg, 0.59 mmol) was then added. The reaction mixture was stirred at RT for 2 h, diluted with EtOAc and filtered through celite.

The filtrate was washed with H_2O and brine, dried and concentrated. This material was dissolved in CH_2Cl_2 (6 mL) and 1,3-diisopropylcarbodiimide (32 mg, 0.25 mmol) was added. The reaction mixture was stirred at RT for 2 h and diluted with CH_2Cl_2 , washed with H_2O and brine, dried and concentrated. The residue was purified by preparative HPLC to provide the title compound as a white solid (40 mg, 31%, for two steps): mp 104-110°C. Analysis calculated for $\text{C}_{38}\text{H}_{45}\text{N}_5\text{O}_6\text{S} \cdot 0.8 \text{H}_2\text{O}$: Calc'd: C, 64.13; H, 6.97; N, 10.39; S, 4.75. Found: C, 64.18; H, 6.60; N, 10.23; S, 4.50.

Example 5

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-
(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide (Alternative

Preparation for 3F)

5

A. 2-[(2'-Bromo-5'-formyl)phenyl]-1,3-dioxolane

DIBAL-H (1.0 M solution in toluene, 445 mL, 445 mmol, 1.1 eq) was added over 30 minutes to a solution of 2-[(2'-bromo-5'-cyano)phenyl]-1,3-dioxolane (103 g, 404 mmol, 1.0 eq) [Zhang, H.-Y. et al., *Tetrahedron*, **50**, 11339-11362 (1994)] in toluene (2.0 L) at -78 °C. The solution was allowed to warm to 0 °C. After 1 hour, a solution of Rochelle's salt (125 g) in water (200 mL) was added, and the mixture was allowed to warm to room temperature and was stirred vigorously for 16 h. The organic layer was concentrated and the residue partitioned between ethyl acetate (1 L) and 1 N hydrochloric acid (800 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (800 mL), dried over sodium sulfate, and then concentrated to give 70.5 g of crude **5A** as a yellow solid, which was used without further purification.

20 B. 2-[(2'-Bromo-5'-hydroxymethyl)phenyl]-1,3-dioxolane

Sodium borohydride (3.66 g, 96.7 mmol, 0.5 eq) was added to a solution of crude **5A** (49.7 g, approximately 193 mmol, 1.0 eq) in absolute ethanol (1300 mL) at 0 °C. After 2 hours, a solution of 10% aqueous sodium dihydrogen phosphate (50 mL) was added and the mixture was stirred and allowed to warm to room temperature. The mixture was concentrated, then partitioned between ethyl acetate (800 mL) and saturated aqueous sodium bicarbonate (500 mL). The organic layer was dried over sodium sulfate and concentrated to give 49.0 g of crude **5B** as a yellow oil, which was used without further purification.

30

C. 2-[(2'-Bromo-5'-bromomethyl)phenyl]-1,3-dioxolane

Triphenylphosphine (52.7 g, 199 mmol, 1.05 eq) was added in portions over 15 minutes to a solution of crude **5B** (49.0 g, approximately 189 mmol, 1.0 eq) and carbon tetrabromide (69.0 g, 208 mmol, 1.1 eq) in THF at 0 °C. After 2 hours, saturated aqueous sodium bicarbonate solution (20 mL) was added, and the mixture was allowed to warm to room temperature and was then concentrated. Ether (500 mL) was added, and the resulting mixture was filtered. The filtrate was dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (8:1 hexanes/ethyl acetate as eluant) to give **5C** as a white solid (31.1 g, 51% yield from 2-[(2'-bromo-5'-cyano)phenyl]-1,3-dioxolane).

D. 2-(1,3-Dioxolan-2-yl)-4-[(2-n-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]bromobenzene

Sodium hydride (60% dispersion in mineral oil, 9.65 g, 241 mmol, 2.5 eq) was added in portions over 15 minutes to a mixture of 2-n-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride (18.7 g, 96.5 mmol, 1.0 eq) in DMF (400 mL) at 0°C. The mixture was stirred and allowed to warm to room temperature over 15 minutes. To this mixture was added via canula a solution of **5C** (31.1 g, 96.5 mmol, 1.0 eq) in DMF (100 mL). After 14 hours, the mixture was concentrated *in vacuo* and partitioned between ethyl acetate (500 mL) and 10% aqueous sodium dihydrogen phosphate (300 mL). The organic layer was dried over sodium sulfate and concentrated to give crude **5D** as an orange oil (42.7 g), which was used without further purification.

E. 4-[(2-n-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-formyl-bromobenzene

A solution of crude **5D** (6.0 g, approximately 13.6 mmol, 1.0 eq) in THF (180 mL) and 1N hydrochloric acid (30 mL) was heated at 65°C for 1.5 hours. The mixture was cooled and then treated with saturated

aqueous sodium carbonate solution (75 mL) and ethyl acetate (200 mL). The organic layer was removed and dried over sodium sulfate, concentrated, and then further dried azeotropically with toluene to give **5E** as a crude yellow oil (8.2 g) which contained a small amount of toluene.

5 This material was used without further purification.

F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

10 Palladium catalyzed Suzuki coupling of **5E** and [2-[(3,4-dimethyl-5-isoxazolyl)((2-methoxyethoxy)methyl)amino)sulfonyl]phenyl]boronic acid was performed according to General Method 1 to yield **5F** in 60% yield.

G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

15 Deprotection of **5F** according to General Method 7 provided the title compound (**5G** = **3F**) in 73% yield: R_f = 0.2 (silica gel using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ [100:5]).

20 Example 6

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide (Alternative Preparation for 4)

25

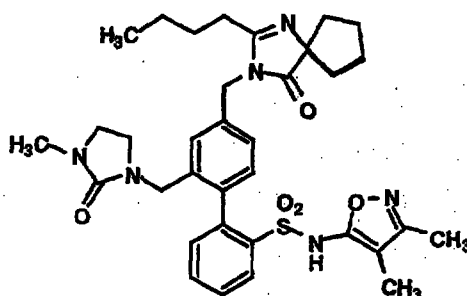
The title compound (**6** = **4**) was obtained as a white solid from **5G** using a procedure similar to that described in Example 4 (945 mg, 35%); mp 104-110°C. Analysis calculated for $\text{C}_{36}\text{H}_{45}\text{N}_5\text{O}_5\text{S} \cdot 0.8 \text{ H}_2\text{O}$: Calc'd: C, 64.13; H, 6.97; N, 10.39; S, 4.75. Found: C, 64.18; H, 6.60; N, 10.23; S, 4.50.

30

Example 7

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
dimethyl-5-isoxazoly)-2'-[(3-methyl-2-oxo-1-
imidazolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

5



- A. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
dimethyl-5-isoxazoly)-N-(2-methoxyethoxymethyl)-2'-[(3-methyl-2-
oxo-1-imidazolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

10

To a solution of 0.3 g (0.46 mmol) of **5F** in CH_2Cl_2 (15 mL) was added 3Å molecular sieves (1 mL), N-methyl ethylenediamine (0.051 g, 0.69 mmol) and glacial acetic acid (0.828 g, 1.38 mmol), and the resulting mixture was stirred under argon for 15 min. Sodium

15 triacetoxyborohydride (0.292 g, 1.38 mmol) was then added to the mixture, and the resulting mixture was stirred at room temperature for 3 h. The solution was then filtered through celite, and the celite was washed with CH_2Cl_2 (25 mL). The combined filtrates were washed with water (2x50 mL), dried and evaporated to afford a colorless gum (0.32 g). This gum

20 was redissolved in CH_2Cl_2 (10 mL), and carbonyldiimidazole was then added (0.112 g, 0.69 mmol). The resulting mixture was stirred at room temperature for 24 h. The mixture was then washed with water (15 mL) and dried and evaporated to provide a colorless gum. Purification on silica gel using 1:1 hexane: EtOAc then provided **7A** (0.17 g, 50%) as a colorless

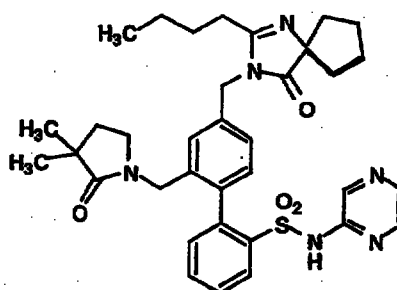
25 gum.

B. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

To a solution of 7A (0.165 g, 0.225 mmol) in 95% EtOH (2 mL) was added 6N aqueous hydrochloric acid (2 mL), and the resulting solution was heated at reflux for 1 h. The mixture was then neutralized with aqueous sodium bicarbonate to pH 7 and then reacidified to pH 6 using aqueous sodium bisulfate. The mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were then washed once with water and dried and evaporated. The residue was purified on silica gel using 5% MeOH in methylene chloride to provide the title compound (0.13 g, 89%) as a light yellow solid: ¹H NMR (CDCl₃) δ 0.89 (t, J=7.0 Hz, 3H), 1.26-1.60 (m, 4H), 1.87 (s, 3H), 1.97 (m, 8H), 2.16 (s, 3H), 2.35 (t, J=7.6 Hz, 2H), 2.72 (s, 3H), 3.29 (br s, 4H), 4.10 (s, 2H), 4.72 (m, 2H), 7.13-7.92 (m, 7H).

Example 8

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide



A. N-tert-Butyl-4'-[(2-n-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl[1,1'-biphenyl]-2-sulfonamide

Crude 5E (8.3 g, approximately 13.6 mmol) was subjected to Suzuki coupling with [2-(*N*-*tert*-butylsulfamoyl)phenyl]boronic acid according to General Method 1. The crude residue was chromatographed on triethylamine-deactivated silica gel (1:1 hexanes/ethyl acetate eluant) to yield 8A (5.03 g, 71% from 5C) as an orange oil.

B. *N*-*tert*-Butyl-4'-[(2-*n*-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

A mixture of 8A (2.0 g, 3.81 mmol, 1.0 eq), 4-amino-2,2-dimethylbutanoic acid hydrochloride (1.28 g, 7.64 mmol, 2.0 eq), freshly-activated 3Å molecular sieves (5.0 g), and methanol (35 mL) was stirred at room temperature. Solid 85% potassium hydroxide (225 mg) was added to adjust the pH to 6.5. After 1.5 hours, sodium cyanoborohydride (120 mg, 1.91 mmol, 1.5 eq) was added, and the mixture was stirred for an additional two hours. Solid 85% potassium hydroxide (640 mg) was added, the mixture was filtered, and the filtrate concentrated. To the residue was added dry dichloromethane (35 mL) and EDCI (1.10 g, 5.72 mmol, 1.5 eq) and the mixture was stirred at room temperature for 17 hours. Saturated aqueous sodium carbonate solution (100 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic extracts were dried over sodium sulfate and concentrated to give 8B (2.50 g) as a crude yellow oil used directly without further purification.

C. 4'-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

Crude 8B (2.50 g) was dissolved in trifluoroacetic acid (16 mL) and the resulting solution was stirred at room temperature for 7 hours. The resulting mixture was concentrated, and saturated aqueous sodium

bicarbonate solution was added to the residue. This mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate and concentrated. Silica gel chromatography of the residue (5% methanol in dichloromethane as eluant) gave 8C (0.98 g, 45% from 8A) as a yellow solid.

D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(2-pyrazinyl) [1,1'-biphenyl]-2-sulfonamide

10 A solution of 8C (110 mg, 0.19 mmol, 1.0 eq) in DMF (2.5 mL) was treated at room temperature with sodium hydride (60% dispersion in mineral oil, 17 mg, 0.43 mmol, 2.2 eq). After 10 minutes, 2-chloropyrazine (68 µl, 0.76 mmol, 4.0 eq) was added via syringe, and the mixture heated at 120 °C for 2 hours and 130 °C for 6 hours. The solvent was evaporated, and the residue partially purified by preparative reverse-phase HPLC.

15 The fractions containing product were evaporated, and the residue partitioned between dichloromethane and 10% aqueous sodium dihydrogen phosphate. The aqueous phase was adjusted to pH 5 and extracted with two additional portions of dichloromethane. The combined organic extracts were dried over sodium sulfate, evaporated, and the residue chromatographed on silica gel (3% methanol in dichloromethane as eluant) to yield still impure product (70 mg). This material was subjected to ion-exchange chromatography to give the pure title compound (8 mg, 6%) as a white powder after lyophilization: ¹H NMR (CDCl₃, 400

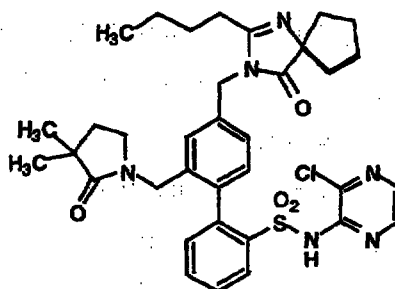
25 MHz) δ 8.52 (s, 1H), 8.29 (dd, *J*=1 and 8 Hz, 1H), 8.16 (d, *J*=3 Hz, 1H), 7.97 (s, 1H), 7.60 (dt, *J*=1 and 7 Hz, 1H), 7.55 (dt, *J*=1 and 7 Hz, 1H), 7.20 (dd, *J*=1 and 7 Hz, 1H), 7.01 (s, 2H), 6.96 (s, 1H), 4.60 (AB quartet, *J*=16 Hz, 2 H), 4.15 (AB quartet, *J*=16 Hz, 2 H), 3.16 (m, 2H), 2.34 (dd, *J*=7 and 8 Hz, 2H), 1.97 (m, 6H), 1.87 (t, *J*=7 Hz, 2H), 1.82 (m, 2H), 1.61 (m, 2H), 1.36 (sextet, *J*=7 Hz, 2 H), 1.17 (s, 3H), 1.16 (s, 3H), 0.90 (t, *J*=7 Hz, 3H); LRMS *m/z* 643 (ESI+ mode).

30

Example 9

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3-chloro-2-pyrazinyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

5

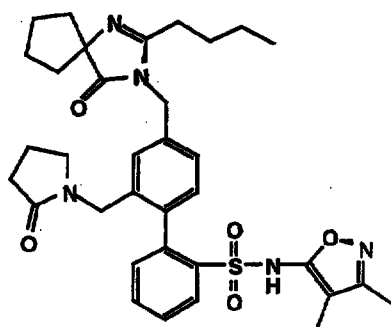


- A solution of 8C (100 mg, 0.18 mmol, 1.0 eq) in DMF (1.8 mL) was treated at room temperature with sodium hydride (60% dispersion in mineral oil, 8.5 mg, 0.21 mmol, 1.2 eq). After 10 minutes, 2,3-dichloropyrazine (79 mg, 0.53 mmol, 3.0 eq) was added via syringe, and the mixture heated at 60°C for 3 hours, then at 85°C for 14 hours, and then at 120°C for 5 hours. Workup and purification as described in
- Example 8 yielded the title compound (7.4 mg, 10%) as a white powder after lyophilization: ¹H NMR (CDCl₃, 400 MHz) δ 8.40 (dd, *J*=1 and 8 Hz, 1H), 8.0 (m, 2H), 7.68 (dt, *J*= 1 and 7 Hz, 1H), 7.61 (dt, *J*=1 and 7 Hz, 1H), 7.22 (dd, *J*=1 and 7 Hz, 1H), 7.16 (s, 1H), 7.05 (d, *J* =8 Hz, 1H), 6.89 (d, *J*=8 Hz, 1H), 6.85 (br s, 2H), 4.87 (AB quartet, *J*=16 Hz, 2 H), 4.31 (d, *J*=16 Hz, 1H), 4.15 (d, *J*=16 Hz, 1H), 3.16 (m, 2H), 2.82 (t, *J*=7 Hz, 2H), 1.90-2.20 (m, 8H), 1.82 (m, 2H), 1.66 (m, 2H), 1.38 (sextet, *J*=7 Hz, 2H), 1.22 (s, 3H), 1.14 (s, 3H), 0.92 (t, *J*=7 Hz, 3H) ppm; LRMS *m/z* 677, 679 (ESI+ mode); *m/z* 675, 677 (ESI- mode).

Example 10

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
dimethyl-5-isoxazolyl)-2'-[(2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-
sulfonamide

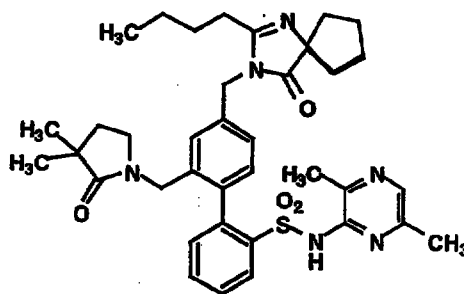
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The title compound was prepared in 51% yield starting from 3F and 4-aminobutyric acid as described in Example 4 as a white solid: mp 95-
 10 100°C; ¹H NMR (CDCl₃) δ 0.90 (t, J=7.3 Hz, 3H), 1.36 (m, 2H), 1.61 (m, 2H), 1.82-2.10 (m, 15H), 2.17 (s, 3H), 2.36 (m, 2H), 3.41 (m, 2H), 4.20 (m, 2H), 4.72 (s, 2H), 7.00-7.90 (m, 7H).

Example 11

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-
dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(3,6-dimethyl-2-pyrazinyl)[1,1'-
biphenyl]-2-sulfonamide



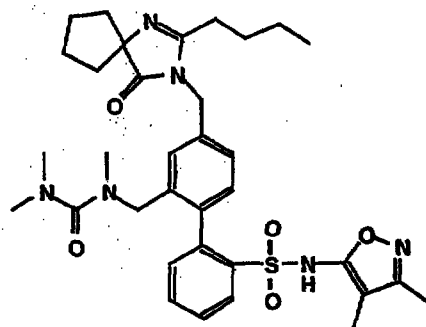
20

A mixture of 8C (200 mg, 0.36 mmol, 1.0 eq), palladium acetate (4 mg, 0.02 mmol, 0.05 eq), (S)-BINAP (2.5 mg, 0.02 mmol, 0.05 eq), and toluene (5 mL) was sparged with nitrogen for 10 minutes. 2-Chloro-3,6-dimethylpyrazine (83 μ l, 0.71 mmol, 2.0 eq) was added via syringe,
 5 followed by sodium hydride (60% dispersion in mineral oil, 28 mg, 0.71 mmol, 2.0 eq). The mixture was heated at 80°C for 15 hours. After cooling, the mixture was diluted with ethyl acetate and partitioned against 10% aqueous sodium phosphate adjusted to pH 5-6, and the aqueous layer was extracted with two additional portions of ethyl acetate.
 10 The combined organic extracts were dried over sodium sulfate, concentrated, and evaporated to a yellow oil, which was chromatographed on silica gel (1:3 hexanes/ethyl acetate eluant) to yield the title compound (50 mg, 21%) as an off-white solid: ^1H NMR (CD_3OD , 400 MHz) δ 8.14 (d, $J=7$ Hz, 1H), 7.75 (br s, 1H), 7.49 (m, 2H), 7.11 (dd, $J=1$ and 7 Hz, 1H),
 15 6.87 (s, 2H), 6.70 (s, 1H), 4.65 (br s, 2 H), 4.11 (s, 2H), 3.95 (m, 2H), 2.92 (m, 2H), 2.29 (br s, 2H), 2.17 (s, 3H), 2.06 (s, 3H), 1.79 (m, 6H), 1.68 (m, 2H), 1.65 (m, 2H), 1.41 (m, 2H), 1.17 (m, 2H), 1.03 (s, 3H), 1.00 (s, 3H), 0.72 (t, $J=7$ Hz, 3H); LRMS m/z 671 (ESI+ mode); m/z 669 (ESI- mode).

20

Example 12

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,N',N'-trimethylurea

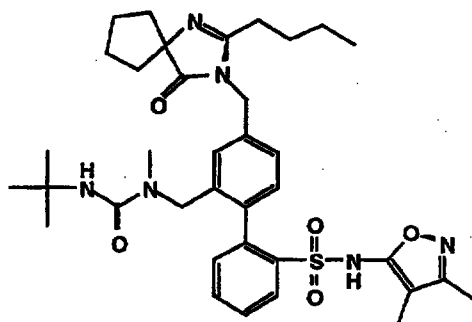


25

To **2I** (34.7 mg, 0.06 mmol) in CH_2Cl_2 (0.6 mL) and DMF (0.15 mL) was added dimethylcarbamyl chloride (6.5 mg, 0.06 mmol) followed by triethyl amine (6.7 mg, 0.066 mmol). The resulting mixture was stirred at RT for two days. The mixture was purified by anion-exchange chromatography to provide the title compound (90%). Characterization recorded with Example 73.

Example 13

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N'-(1,1-dimethylethyl)-N-methylurea



15

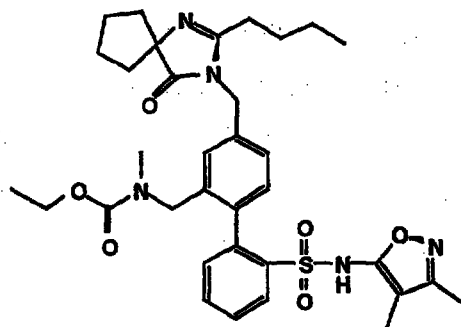
To **2I** (34.7 mg, 0.06 mmol) in CH_2Cl_2 (0.6 mL) and DMF (0.15 mL), *t*-butylisocyanate (6.0 mg, 0.06 mmol) was added, and the resulting mixture was stirred at RT for two days. The mixture was purified by anion-exchange chromatography to provide the title compound (90%).

20 Characterization recorded with Example 74.

Example 14

[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]methylcarbamic acid ethyl ester

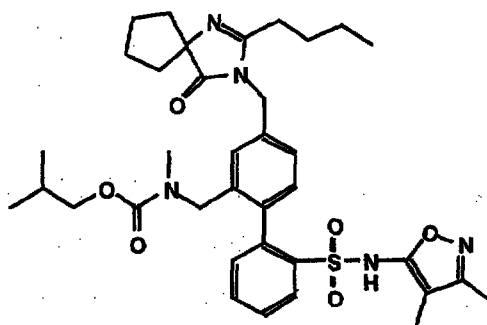
25



The title compound was prepared from **2I** and ethyl chloroformate
 5 using a procedure similar to the one described in Example 12 (90%).
 Characterization recorded with Example 75.

Example 15

10 [[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-
dimethyl-5-isoxazolyl)aminosulfonyl][1,1'-biphenyl]-2-
yl)methyl]methylcarbamic acid 2-methylpropyl ester

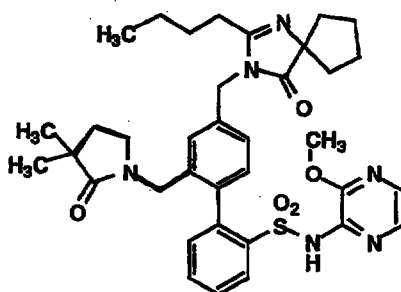


15 The title compound was prepared from **2I** and isobutyl
 chloroformate using a procedure similar to the one described in Example
 12 (90%). Characterization recorded with Example 76.

Example 16

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(3-methoxy-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide

5

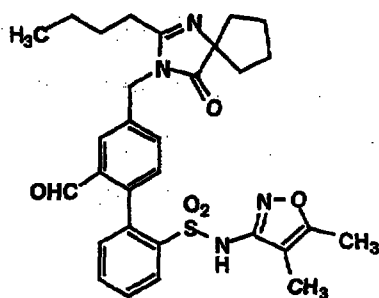


The title compound was prepared from **8C** (486 mg, 0.86 mmol) and 2-chloro-3-methoxypyrazine (250 mg, 1.72 mmol) [Uchimaru, F. et al., *Chem. Pharm. Bull.*, **20**, 2204-2208 (1972)] using a procedure similar to the one used in Example 9. Preparative reverse-phase HPLC of the crude product after extractive workup gave the title compound (24 mg, 4%) as an off-white solid after lyophilization: ¹H NMR (CDCl₃, 400 MHz) δ 10.8 (br s, 2H), 8.36 (dd, *J*=1 and 8 Hz, 1H), 7.50-7.65 (m, 4H), 7.19 (dd, *J*=1 and 7 Hz, 1H), 7.15 (s, 1H), 7.01 (s, 2H), 4.92 (AB quartet, *J*=16 Hz, 2H), 4.20 (AB quartet, *J*=16 Hz, 2H), 3.99 (s, 3H), 3.18 (m, 2H), 2.82 (m, 2H), 2.18 (m, 4H), 1.96 (m, 4H), 1.82 (m, 2H), 1.63 (m, 2H), 1.32 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H), 0.87 (t, 3H, *J*=7 Hz, 3H); LRMS *m/z* 673 (ESI+ mode); *m/z* 671 (ESI- mode); HPLC retention time 25.52 minutes (Method B).

20

Example 17

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



- A. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(4,5-dimethyl-3-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

5

Palladium catalyzed Suzuki coupling of **5E** and [2-[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid was performed according to General Method 1 to afford **17A** (81%) following silica-gel chromatography.

10

- B. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

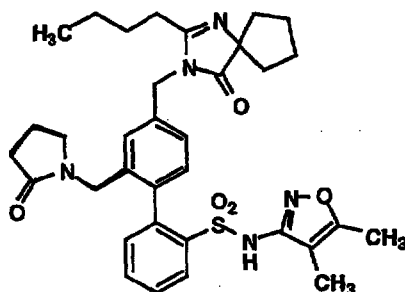
Treatment of **17A** with 6N aqueous hydrochloric acid according to General Method 7 provided the title compound (85%): $R_f = 0.38$, 5% MeOH in methylene chloride.

15

Example 18

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

5

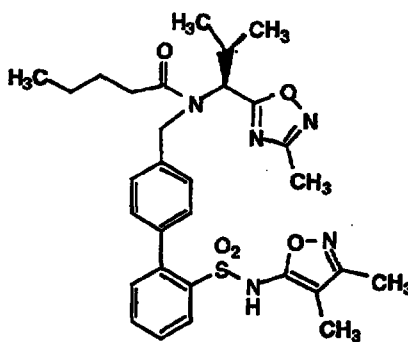


The title compound was obtained as a white solid using **17B** and 4-aminobutyric acid as described in Example 4 (25%); mp 97-103°C; ¹H NMR (CDCl₃) δ 0.90 (t, J=7 Hz, 3H), 1.36 (m, 2H), 1.62 (m, 2H), 1.80-2.10 (m, 13H), 2.26 (s, 3H), 2.39 (m, 4H), 3.31 (m, 2H), 4.20 (s, 2H), 4.73 (s, 2H), 7.05-8.10 (m, 7H).

Example 19

(S)-N-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pentanamide

20



A. (S)-5-(1-amino-2-methylpropyl)-3-methyl-1,2,4-oxadiazole

A solution of BOC-L-valine (4.34 g, 20.0 mmol) in dichloromethane (20 mL) was cooled to 0°C and treated dropwise with a solution of dicyclohexylcarbodiimide (2.06 g, 10.0 mmol) in dichloromethane (5 mL).

- 5 After 1 hour the white solid which had formed was removed by filtration and the filtrate concentrated under reduced pressure. The residue was dissolved in pyridine (15 mL) and treated with acetamidoxime (488 mg, 6.6 mmol) in pyridine (5 mL) and the mixture heated at reflux for 1 hour. The pyridine was evaporated under reduced pressure and the residue
- 10 partitioned between ethyl acetate and water. The organic phase was washed several times with water, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 10% ethyl acetate in hexanes to elute the product (0.62 g, 25%) as a white solid.

- A solution of the above product in 3 M hydrochloric acid (10 mL)
- 15 was stirred at room temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure and then azeotroped with toluene. This gave **19A** as a white solid (100%).

B. 2'-[[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-carboxaldehyde

P17 (0.35 g, 0.79 mmol) was subjected to deprotection according to General Method 7. Extraction and concentration gave 200 mg (71%) of **19B** as a yellow solid which was used without purification.

C. (S)-[[1-[2'-[[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-ylmethylamino]-2-methylpropyl]-3-methyl-1,2,4-oxadiazole

- A mixture of **19B** (100 mg, 0.28 mmol) and **19A** (53 mg, 0.28 mmol) in dichloroethane (8 mL) was treated with sodium triacetoxyborohydride (74 mg, 0.35 mmol) in one portion and the mixture stirred under argon at
- 30 room temperature. After 1 hour more sodium triacetoxyborohydride (32 mg, 0.15 mmol) was added to the mixture which stirred for 45 minutes

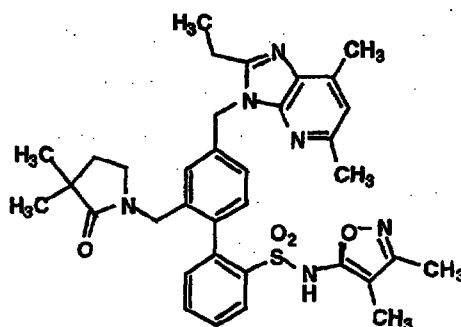
more and the mixture was adjusted to pH 6 with saturated sodium bicarbonate solution. The mixture was diluted with 50 mL dichloromethane and the organic phase washed with water, dried over magnesium sulfate and concentrated to give crude **19C** (110 mg, 79%) which was used without purification in the next step.

D. (S)-N-[[2'-[(3,4-Dimethyl-5-isoxazolyl)aminosulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pentanamide

A mixture of **19C** (100 mg, 0.20 mmol), dichloromethane (5 mL) and triethylamine (70 mL, 0.5 mmol) was treated with valeryl chloride (60 mg, 0.5 mmol) and the mixture stirred under argon for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue treated with 2 M sodium hydroxide (1 mL) and 2-propanol (2 mL) and stirred at room temperature for 1.5 hours. Citric acid was added to adjust the pH to 5 - 6 and the mixture extracted with dichloromethane. The residue obtained after drying the extract over magnesium sulfate and concentrating under reduced pressure was chromatographed on silica gel using 30 to 50% ethyl acetate in hexanes to elute the title product (73 mg, 63%) as a white foam: ESIMS (NH_3) m/z 580 (MH^+ 100), 597 ($\text{M} + \text{NH}_4^+$, 20), 1176 ($2\text{M} + \text{NH}_4^+$, 10); HRMS calcd for $\text{C}_{30}\text{H}_{37}\text{N}_5\text{O}_5\text{S}$ (MH^+) 580.2593, found 580.2619.

Example 20

N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide



A. N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-hydroxymethyl-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

Preparation P21 (4.25 g, 9.0 mmol) was reacted with ethyl 4-amino-2,2-dimethylbutanoate hydrochloride (2.13 g, 10.9 mmol) according to General Method 5. The crude residue was chromatographed on silica gel (5% methanol in dichloromethane eluant) to yield 3.05 g of **20A** (59%) as an orange oil.

B. N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

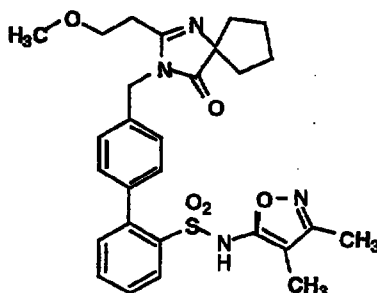
A solution of **20A** (500 mg, 0.87 mmol, 1.0 eq), triphenylphosphine (344 mg, 1.3 mmol, 1.5 eq), and 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (184 mg, 1.1 mmol, 1.2 eq) in tetrahydrofuran (5 mL) was treated at 0°C with diethylazodicarboxylate (206 µl, 1.3 mmol, 1.5 eq). The mixture was allowed to warm to room temperature, was stirred for 16 hr, and then concentrated. The residue was chromatographed on silica gel (3:2 hexanes/acetone as eluant) to give 320 mg of a mixture containing **20B** and 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine (approximately 3:1 ratio by weight).

C. N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide

20B (320 mg) was deprotected according to General Method 8 (ethanol). The crude residue was purified by reverse-phase preparative HPLC followed by extraction (3x50 mL ethyl acetate) of the product from brine adjusted to pH 4 with hydrochloric acid, to provide 135 mg of the title compound (24% from 20A) as a white solid after lyophilization; mp 95-104 °C; MS m/e 641 (ESI+ mode); MS m/e 639 (ESI- mode); HPLC retention time 3.43 minutes (Method C).

Example 21

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[2-(2-methoxyethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide



A. Methyl 1-[(3-methoxy-1-oxopropyl)aminocyclopentane-1-carboxylate

20 3-Methoxypropanoic acid (1.65 mL, 17.6 mmol, 2.1 eq) was added to a mixture of EDCI (1.77 g, 9.24 mmol, 1.1 eq), triethylamine (3.5 mL, 25.2 mmol, 3.0 eq), 4-dimethylaminopyridine (20 mg, 0.18 mmol, 0.02 eq), and dichloromethane (100 mL) at room temperature. After 5 minutes, methyl 1-aminocyclopentane-1-carboxylate hydrochloride (1.50 g, 8.4 mmol, 1.0 eq) was added and the mixture was stirred at room temperature for 18 hours. The reaction mixture was partitioned against 1N hydrochloric acid

and the aqueous phase was extracted once with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Silica gel chromatography of the residue (1:3 hexanes/ethyl acetate as eluant) yielded 1.30 g of **21A** (67%) as a colorless oil.

5

B. 1-[(3-Methoxy-1-oxopropyl)amino]cyclopentane-1-carboxylic acid

A mixture of **21A** (1.25 g, 5.5 mmol, 1.0 eq), lithium hydroxide hydrate (300 mg, 7.1 mmol, 1.3 eq), THF (10 mL), and water (10 mL) was stirred at room temperature for 5.5 hours. 1N hydrochloric acid (10 mL) was added and the mixture was saturated with solid sodium chloride, then extracted with ethyl acetate (3x30 mL). The combined organic extracts were dried over sodium sulfate and concentrated to provide 0.95 g of **21B** (80%) as a white solid.

15 C. 1-[(3-Methoxy-1-oxopropyl)amino]cyclopentane-1-carboxamide

A suspension of **21B** (0.95 g, 4.4 mmol, 1.0 eq) in THF (20 mL) was treated with 1,1'-carbonyldiimidazole (930 mg, 5.7 mmol, 1.3 eq) at room temperature. After 30 minutes, the mixture was cooled to -78 °C and ammonia gas was introduced. The resulting heterogeneous mixture was allowed to warm to room temperature and was stirred for 16 hours. The solvent was evaporated and 1N hydrochloric acid saturated with sodium chloride was added to the residue. The aqueous mixture was extracted with ethyl acetate (6x50 mL), and the combined organic layers were dried over sodium sulfate and concentrated to yield 500 mg of **21C** (53%) as a white solid.

25 D. 2-(2-Methoxyethyl)-1.3-diazaspiro[4.4]non-1-en-4-one

A solution of **21C** (460 mg, 2.15 mmol, 1.0 eq), potassium hydroxide (288 mg, 4.30 mmol, 2.0 eq) and methanol (15 mL) was heated at reflux for 20 hours. The mixture was cooled, solid ammonium chloride was added, and the solvent was evaporated. Water was added and the mixture was

extracted with ethyl acetate (3x30 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and the residue chromatographed on silica gel (4% methanol in dichloromethane as eluant) to yield 162 mg of **21D** (38%) as an amber oil.

5

E. N-(3,4-Dimethyl-5-isoxazolyl)-4'-[2-(2-methoxyethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide

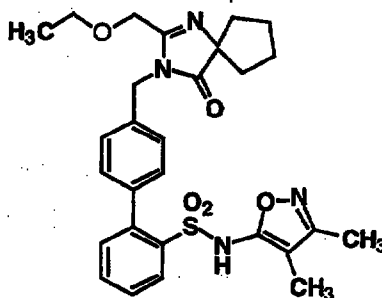
21D (75 mg, 0.38 mmol, 1.0 eq) was alkylated with **P18** (195 mg, 0.38 mmol, 1.0 eq) according to General Method 4. The resulting crude orange oil was dissolved in methanol (7 mL). Concentrated hydrochloric acid (7 mL) was added and the solution was heated at 55°C for 14 hours. The reaction mixture was concentrated and then partitioned between ethyl acetate and pH 5 sodium phosphate buffer. The organic layer was dried over sodium sulfate and concentrated to provide a crude residue.

15 The title compound (7 mg, 3% yield) was obtained as a white powder following silica gel chromatography (4% methanol in chloroform as eluant), preparative reverse-phase HPLC, and lyophilization: MS m/e 537 (ESI+ mode); MS m/e 535 (ESI- mode); HPLC retention time 3.35 minutes (Method A).

20

Example 22

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[2-(2-ethoxymethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide



25

A. Methyl 1-[(2-ethoxyethanoyl)aminocyclopentane-1-carboxylate

2-Ethoxyacetic acid (3.3 mL, 35 mmol, 2.1 eq) was added to a mixture of EDCI (3.38 g, 18 mmol, 1.1 eq), triethylamine (7.0 mL, 50 mmol, 3.0 eq), 4-dimethylaminopyridine (20 mg, 0.18 mmol, 0.01 eq), and
5 dichloromethane (100 mL) at room temperature. After 5 minutes, methyl 1-aminocyclopentane-1-carboxylate hydrochloride (3.0 g, 17 mmol, 1.0 eq) was added and the mixture was stirred at room temperature for 18 hours. The solvent was evaporated and the residue partitioned between ether and 1N hydrochloric acid. The organic layer was washed once with 1N
10 hydrochloric acid, then twice with saturated aqueous sodium bicarbonate, and once with brine. The organic layer was dried over magnesium sulfate and concentrated to give 2.0 g of **22A** (52%) as a pink oil.

B. 2-(2-Ethoxymethyl)-1,3-diazaspiro[4.4]non-1-en-4-one

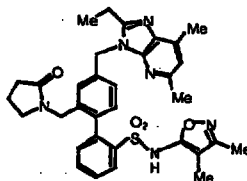
15 A mixture of **22A** (2.0 g, 8.7 mmol, 1.0 eq), lithium hydroxide hydrate (440 mg, 10.5 mmol, 1.2 eq), THF (10 mL), and water (3 mL) was stirred at room temperature for 16 hours. 2N hydrochloric acid (6 mL) was added and the solvents were evaporated. The residue was dried azeotropically with toluene, then dissolved in THF (15 mL) and treated
20 with 1,1'-carbonyldiimidazole (2.8 g, 17.3 mmol, 2.1 eq) at room temperature. After 2 hours, the mixture was cooled to -78 °C and ammonia gas was introduced. The resulting mixture was allowed to warm to room temperature and was stirred for 16 hours, after which the solvent was evaporated. The residue was suspended in methanol (15 mL), solid
25 potassium hydroxide (2.9 g, 43 mmol, 5 eq) was added, and the mixture was heated at reflux for 72 hours. After cooling, the mixture was treated with solid ammonium chloride and the solvent was evaporated. Water was added and the mixture was extracted with ethyl acetate (3x30 mL). The combined organic extracts were dried over sodium sulfate,
30 concentrated, and the residue chromatographed on silica gel (4% methanol in chloroform as eluant) to yield 370 mg of **22B** (22%) as an orange oil.

C. N-(3,4-Dimethyl-5-isoxazolyl)-4'-[2-(2-ethoxymethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide

The title compound was prepared from **22B** (80 mg, 0.41 mmol) and **P18** (209 mg, 0.41 mmol) according to the procedure described in Example 61, Step E, substituting ethanol for methanol in the deprotection reaction. The crude residue was chromatographed twice on silica gel (4% methanol in chloroform as eluant, followed by 25:75:1 hexanes/ethyl acetate/ acetic acid as eluant), then was further purified by reverse-phase preparative HPLC to provide 42 mg of the title compound (19%) as a white solid after lyophilization; MS m/e 537 (ESI+ mode); MS m/e 535 (ESI- mode); HPLC retention time 3.51 minutes (Method A).

Example 23

15 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(2-oxo-1-pyrrolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide



20

A. 2'-Formyl-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(methanesulfonyl)oxyl]-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

25

P21 (2.4 g) was converted to the corresponding mesylate according to General Method 3. The crude product (2.7 g) was carried on without further purification.

B. 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

5 **23A** (2.7 g) was used to alkylate 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine according to General Method 4. The crude product was chromatographed on silica gel using 1:3 hexanes/ethyl acetate as eluant to provide 1.8 g **23B** as a colorless oil.

10 C. 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(2-oxo-1-pyrrolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

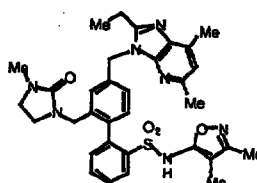
23B (1.5 g) was subjected to reductive amination with ethyl 4-aminobutanoate hydrochloride according to General Method 5. The
15 reaction mixture was allowed to stir for 24 h to allow time for cyclization of the amino ester to the corresponding lactam. The crude product after workup was purified by silica gel chromatography (1:1 hexanes/acetone eluant) to provide **23C** (0.50 g) as a yellow oil.

20 D. 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(2-oxo-1-pyrrolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

23C (0.50 g) was subjected to sulfonamide deprotection using HCl/dioxane/ethanol according to General Method 8. The crude product
25 was purified by silica gel chromatography (90:9:1 dichloromethane/methanol/ammonium hydroxide eluant), and the purified product was partitioned between ethyl acetate and pH 5 potassium phosphate buffer. The ethyl acetate layer was dried over sodium sulfate and concentrated to provide 310 mg of the title compound as a white solid;
30 mp 98-102 °C; MS m/e 613 (ESI+ mode); HPLC retention time 3.09 min (Method A); HPLC purity 97%.

Example 24

4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide



A. 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

23B (2.0 g) was subjected to reductive amination with *N*-methylethylenediamine according to General Method 5. The crude product following extractive workup was dissolved in dichloromethane (25 ml) and treated with CDI (0.77 g). The mixture was stirred at RT for 24 h, and was then washed once with water and once with brine. The dichloromethane layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using 95:5 chloroform/methanol as eluant to give **24A** (0.53 g) as a slightly yellow oil.

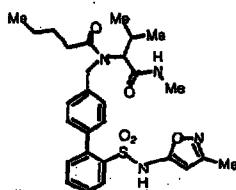
B. 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

24A (0.50 g) was subjected to sulfonamide deprotection according to General Method 8. The crude product was purified by reverse-phase preparative HPLC to yield 140 mg of the title compound as a white solid following lyophilization; MS m/e 628 (ESI+ mode); HPLC retention time
 5 3.03 min (Method A); HPLC purity 97%.

Example 25

(S)-2-[N-[2'-[N-(3-Methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide

10



15 A. N-(3-Methyl-5-isoxazolyl)-2-bromobenzenesulfonamide

5-Amino-3-methylisoxazole (3.84 g) was added at RT in portions to a solution of 2-bromobenzenesulfonyl chloride (10.0 g) in pyridine (40 ml). The mixture was heated at 60 °C for 16 h, then the solvent was evaporated. The residue was taken up in ethyl acetate and washed three
 20 times with 1 N hydrochloric acid. The ethyl acetate layer was dried over sodium sulfate and concentrated to give 25A (8.8 g).

B. N-[(2-Trimethylsilyl)ethoxymethyl]-N-(3-methyl-5-isoxazolyl)-2-bromobenzenesulfonamide

25 2-(Trimethylsilyl)ethoxymethyl chloride (5.2 ml) was added to a mixture of 25A (8.8 g), potassium carbonate (7.7 g), and DMF (40 ml) at 0 °C. The mixture was allowed to warm to RT and was then stirred for 16 h. The solvent was evaporated, and the residue was taken up in ethyl acetate

and washed with water and brine. The ethyl acetate layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography using 3:2 hexanes/ethyl acetate as eluant to provide **25B** (6.6 g) as an oil.

5

C. 4'-Formyl-N-(3-methyl-5-isoxazolyl)-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

25B (2.0 g) and 4-formylphenylboronic acid (1.5 g) were subjected to Suzuki coupling according to General Method 1. The crude product was chromatographed on silica gel using 9:1 hexanes/ethyl acetate as eluant to yield 0.75 g **25C** as a colorless oil.

10

D. (S)-2-[N-[2'-[[N-(3-Methyl-5-isoxazolyl)-N-[(2-trimethylsilyl)ethoxymethyl]aminosulfonyl][1,1'-biphenyl]-4-yl]methyl]-aminol-3,N-dimethylbutanamide

15

25C (0.75 g) was subjected to reductive amination with L-valine N-methyl amide hydrochloride according to General Method 5. Crude **25D** (0.93 g) was obtained as an orange oil.

E. (S)-2-[N-[2'-[[N-(3-Methyl-5-isoxazolyl)-N-[(2-trimethylsilyl)ethoxymethyl]amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-oxopentyl)aminol-3,N-dimethylbutanamide

20

25D (0.93 g) was subjected to acylation with valeryl chloride according to General Method 6. The crude product was chromatographed on silica gel using 2:3 hexanes/ethyl acetate as eluant to yield 0.78 g **25E** as a colorless oil.

25

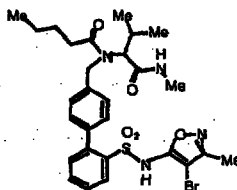
F. (S)-2-[N-[2'-[[N-(3-Methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-oxopentyl)aminol-3,N-dimethylbutanamide

30

25E (0.78 g) was deprotected with HCl/methanol according to General Method 8. The crude product was purified by silica gel chromatography using 3:7 hexanes/ethyl acetate as eluant, providing the title compound (210 mg) as a white solid; MS m/e 541 (ESI+ mode); HPLC retention time 31.32 min (Method B); HPLC purity >98%.

Example 26

(S)-2-[N-[2'-[[N-(4-Bromo-3-methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide



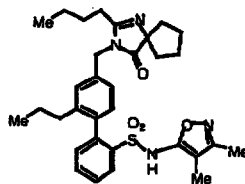
15

A solution of 25 (75 mg) in chloroform (1.5 ml) was treated with NBS (25 mg) at RT. After 1h, the mixture was diluted with dichloromethane and partitioned against water. The organic layer was dried over sodium sulfate and concentrated, and the residue was chromatographed on silica gel using 3:7 hexanes/ethyl acetate as eluant to provide the title compound (25 mg) as a white solid; MS m/e 619, 621 (ESI+ mode); HPLC retention time 31.83 min (Method B); HPLC purity >99%.

25

Example 27

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide



5 A. 4-Bromo-3-(1-propen-1-yl)benzonitrile

n-Butyllithium (2.5M solution in hexane, 7.6 ml, 19 mmol) was added dropwise to a solution of ethyltriphenylphosphonium bromide (6.42 g, 17.3 mmol) in 100 ml of 1:1 THF/ether at -15 °C. The mixture was stirred for 3h at RT and then was cooled to -50 °C. 2A (4.0 g, 19.0 mmol) in THF (10 ml) was added and the mixture was allowed to warm to RT and was stirred for 16 h. The mixture was added to water and extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with water, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel using 95:5 hexane/EtOAc to afford 27A as an E/Z mixture (3.5 g, 83%).

B. 4-Bromo-3-propylbenzonitrile

A mixture of 27A (1.5 g) and 150 mg of PtO₂ in 40 ml EtOH was hydrogenated at 35 PSI for 40 min. Filtration and concentration gave 1.44 g of 27B (85%).

C. 4-Bromo-3-propylbenzaldehyde

27B (1.44 g) was treated with DIBAL-H according to General Method 14 to provide crude 27C (1.4 g, 97%) as an oil.

D. N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-propyl-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

27C (1.4 g) was subjected to Suzuki coupling according to General Method 1 to provide **27D** (27%) as an oil.

5 E. **N**-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-propyl-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

27D (810 mg) was reduced with sodium borohydride in methanol according to General Method 11 to provide **27E** (32%) as an oil.

10 F. **N**-(3,4-Dimethyl-5-isoxazolyl)-4'-(methanesulfonyl)oxymethyl-2'-propyl-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

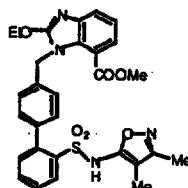
27E (250 mg) was converted to the corresponding methanesulfonate ester according to General Method 3 to provide **27F** (68%) as an oil.

15 G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-propyl-N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

20 **27F** (100 mg) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. **27G** (100 mg, 85%) was produced as an oil.

H. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-propyl-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

25 **27G** (100 mg) was deprotected according to General Method 7. The crude product was purified by preparative HPLC to provide the title compound (57 mg, 66%) as a solid; MS m/e 577 (ESI+ mode); HPLC retention time 29.11 min (Method B); HPLC purity >98%.

Example 284'-[(7-Methoxycarbonyl-2-ethoxybenzimidazol-1-yl)methyl]-
N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

5

A. N-(2-Methoxycarbonyl-6-nitrophenyl)-4-bromobenzylamine

Triethylamine (5.2 ml, 37 mmol) was added to a mixture of methyl
 10 2-chloro-3-nitrobenzoate (3.2 g, 15 mmol) and 4-bromobenzylamine
 hydrochloride (3.4 g, 15 mmol) in acetonitrile (75 ml). The mixture was
 heated at reflux for 48 hr, then was cooled and concentrated. 10%
 Aqueous sodium dihydrogen phosphate solution was added and the
 mixture was extracted with 2 portions of ethyl acetate. The combined
 15 organic extracts were dried over sodium sulfate and concentrated, and the
 residue was crystallized from ethyl acetate to give 28A (3.2 g) as a yellow
 solid.

B. 4'-[(2-Methoxycarbonyl-6-nitrophenyl)aminomethyl]-N-(3,4-
 20 dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxyethyl)-[1,1'-biphenyl]-2-
 sulfonamide

28A (3.5 g, 9.6 mmol) was subjected to Suzuki coupling according to
 General Method 1, providing 28B as a yellow oil (3.1 g) following silica gel
 chromatography using 5:1 hexanes/ethyl acetate as eluant.

25

C. 4'-[(2-Methoxycarbonyl-6-aminophenyl)aminomethyl]-N-(3,4-
 dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxyethyl)-[1,1'-biphenyl]-2-
 sulfonamide

28B (2.4 g, 3.6 mmol) was treated with tin (II) chloride dihydrate (3.3 g) in ethyl acetate (80 ml) according to General Method 18. The crude product was purified by silica gel chromatography using 2:1 hexanes/ethyl acetate as eluant to provide 28C (1.3 g) as a pale yellow oil.

5

D. 4'-[(7-Methoxycarbonyl-2-ethoxybenzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxyethyl)-[1,1'-biphenyl]-2-sulfonamide

10 28C (1.3 g), tetraethylorthocarbonate (6 ml), and acetic acid (0.2 ml) was heated under a nitrogen atmosphere at 70 °C for 2 h. The mixture was cooled and concentrated, and the residue was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide 28D (1.1 g) as a brown oil.

15

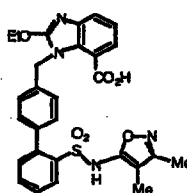
E. 4'-[(7-Methoxycarbonyl-2-ethoxybenzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

20 28D (1.1 g) was subjected to sulfonamide deprotection using TBAF in THF according to General Method 10. The crude product was purified by silica gel chromatography using 2:1 hexanes/acetone as eluant to provide 0.75 g of the title compound as a white solid; mp 105-110 °C; MS m/e 561 (ESI+ mode); HPLC retention time 3.96 min (Method A); HPLC purity 96%.

25

Example 29

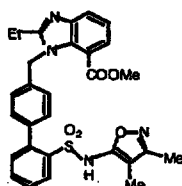
4'-[(7-Carboxy-2-ethoxybenzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



28 (0.70 g) was subjected to ester hydrolysis according to General
 5 Method 15 to provide the crude product (0.66 g). Purification of a portion
 by reverse-phase preparative HPLC provided the title compound (9 mg,
 white solid); MS m/e 547 (ESI+ mode); HPLC retention time 3.79 min
 (Method A); HPLC purity 91%.

Example 30

4'-[(7-Methoxycarbonyl-2-ethylbenzimidazol-1-yl)methyl]-N-
(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



A solution of 28C (3.8 g, 5.9 mmol) and triethylamine (1.7 ml, 12
 mmol) in dichloromethane (25 ml) was treated at 0 °C with propionyl
 chloride (0.67 ml, 10 mmol), and the mixture was allowed to come to RT.
 20 After 2.5 h, aqueous sodium bicarbonate solution was added to the
 mixture and the aqueous layer was extracted with two portions of
 dichloromethane. The combined organic extracts were dried over sodium
 sulfate and concentrated to provide an orange oil.

To this residue was added methanolic hydrogen chloride (prepared
 25 from 100 ml methanol and 11 ml (200 mmol) acetyl chloride), and the

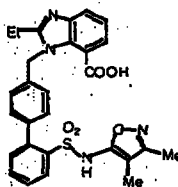
resulting solution was heated at 50 °C for 16 h. The mixture was cooled and concentrated, and the residue was extracted with two portions of ethyl acetate from sodium phosphate buffer adjusted to pH 4. The combined ethyl acetate extracts were dried over sodium sulfate and concentrated.

- 5 The residue was chromatographed on silica gel using 1:2 hexanes/acetone as eluant to provide the title compound (2.6 g) as a slightly orange solid; MS m/e 545 (ESI+ mode); HPLC retention time 3.32 min (Method C); HPLC purity 95%.

10

Example 31

4'-[(7-Carboxy-2-ethylbenzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



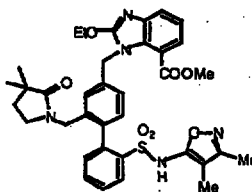
15

- 30 (2.6 g, 4.8 mmol) was subjected to ester hydrolysis according to General Method 15. The THF was evaporated and the residue was treated with 6 ml of 2N hydrochloric acid, resulting in the precipitation of a white solid. The solid was collected on a filter, rinsed with water, and dried to provide 2.4 g of the title compound; MS m/e 531 (ESI+ mode); HPLC retention time 2.94 min (Method A); HPLC purity 95%.
- 20

25

Example 32

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(methoxycarbonyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



A. 2-[(5'-Aminomethyl-2'-bromo)phenyl]-1,3-dioxolane

5 Borane•THF (100 ml of a 1.0 M solution in THF, 100 mmol) was added at 0 °C to a solution of 2-[(2'-Bromo-5'-cyano)phenyl]-1,3-dioxolane [Zhang, H.-Y. et al., *Tetrahedron*, **50**, 11339-11362 (1994)] (10.8 g, 43 mmol) in 25 ml THF. The mixture was allowed to warm to RT and was stirred for 18 h. After cooling to 0 °C, the mixture was treated carefully
10 with 10 ml methanol and was then evaporated. The residue was taken up in 150 ml ethyl acetate and was washed with 1N aqueous sodium hydroxide, followed by water and brine. The organic layer was dried over magnesium sulfate and concentrated to give crude **32A** (11.0 g) as an amber oil, which was estimated (HPLC) to be 80% pure.

15

B. N-(2-Methoxycarbonyl-6-nitrophenyl)-4-bromo-3-(1,3-dioxolan-2-yl)benzylamine

Triethylamine (4.8 ml, 34 mmol) was added to a mixture of methyl
20 2-chloro-3-nitrobenzoate (4.9 g, 23 mmol) and **32A** (5.9 g of a 65% pure mixture, 15 mmol) in acetonitrile (150 ml). The mixture was heated at reflux for 24 h and was then cooled and concentrated. Ethyl acetate was added and the solution was washed twice with 10% aqueous potassium dihydrogen phosphate solution and once with aqueous sodium bicarbonate
25 solution. The organic layer was concentrated and the residue purified by silica gel column chromatography using 3:1 hexanes/ethyl acetate as eluant, followed by trituration with 3:1 hexanes/ethyl acetate. **32B** was a yellow solid (6.6 g).

C. N-(2-Methoxycarbonyl-6-nitrophenyl)-4-bromo-3-(formyl)benzylamine

5 **32B** (6.6 g, 15 mmol) was subjected to acetal hydrolysis according to General Method 19, providing **32C** as a crude yellow solid following extractive workup.

10 D. 2'-Formyl-4'-[(2-methoxycarbonyl-6-nitrophenyl)aminomethyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxymethyl)[1,1'-biphenyl]-2-sulfonamide

15 Crude **32C** was subjected to Suzuki coupling according to General Method 1, providing **32D** (5.9 g) as a yellow oil following silica gel chromatography using 2:1 hexanes/ethyl acetate as eluant.

20 E. 2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-methoxycarbonyl-6-nitrophenyl)aminomethyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxymethyl)[1,1'-biphenyl]-2-sulfonamide

25 **32D** (4.3 g) was subjected to reductive amination with ethyl 4-amino-2, 2-dimethylbutanoate hydrochloride according to General Method 5. The reaction mixture was allowed to stir for 60 h at RT to allow time for cyclization of the amino ester to the corresponding lactam. The crude product after workup was purified by silica gel chromatography, using 3:2 hexanes/ethyl acetate as eluant, to provide **32E** (2.8 g) as a yellow oil.

30 F. 2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-methoxycarbonyl-6-aminophenyl)aminomethyl]-N-(3,4-dimethyl-5-

isoxazolyl)-N-(2-trimethylsiloxyethyl)[1,1'-biphenyl]-2-sulfonamide

5 **32E** (2.8 g, 3.6 mmol) was treated with tin (II) chloride dihydrate (3.2 g) in ethyl acetate (200 ml) according to General Method 18. The crude product (3.5 g) was used without further purification.

G. 2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(7-methoxycarbonyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxyethyl)[1,1'-biphenyl]-2-sulfonamide

10

A mixture of **32F** (1.5 g, 2.0 mmol), tetraethylorthocarbonate (6 ml), and acetic acid (0.15 ml) was heated under a nitrogen atmosphere at 70 °C for 2 h. The mixture was cooled and concentrated, and the residue chromatographed on silica using 1:2 hexanes/ethyl acetate as eluant to provide **32G** (0.80 g) as a yellow oil.

15

H. 2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(methoxycarbonyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

20

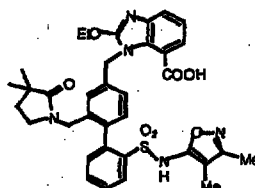
32G (0.80 g) was subjected to sulfonamide deprotection using TBAF in THF according to General Method 10. The crude product was purified by silica gel chromatography using 3:2 hexanes/acetone as eluant to provide 0.55 g of the title compound as a white solid; mp 101-103 °C (decomp); MS m/e 686 (ESI+ mode); HPLC retention time 3.91 min (Method A); HPLC purity >98%.

25

Example 33

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(carboxy)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

5



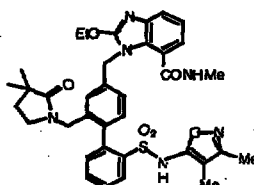
32 (0.31 g) was subjected to ester hydrolysis according to General Method 15. Purification by reverse-phase preparative HPLC provided the title compound (14 mg) as a white solid; MS m/e 672 (ESI+ mode); HPLC retention time 3.61 min (Method A); HPLC purity 82%.

10

Example 34

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(N-methylcarbamoyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

15



20

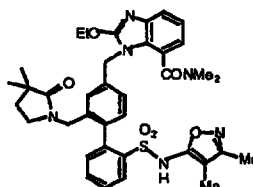
33 (80 mg) was subjected to amide formation according to General Method 12 using methylamine as the amine component. The product was purified by reverse-phase preparative HPLC: white solid (7 mg); MS m/e 685 (ESI+ mode); HPLC retention time 3.39 min (Method A); HPLC purity 81%.

25

Example 35

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(N,N-dimethylcarbamoyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

5

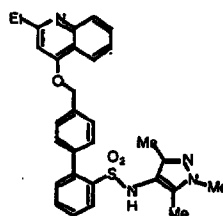


- 10 **33** (80 mg) was subjected to amide formation according to General Method 12 using dimethylamine as the amine component. The crude product was subjected to reverse-phase preparative HPLC to give the title compound as a white solid (6 mg); MS m/e 699 (ESI+ mode); HPLC retention time 3.46 min (Method A); HPLC purity 66% [contaminant
- 15 (34%) is the corresponding imidazolin-2-one].

Example 36

4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(1,3,5-trimethylpyrazol-4-yl)-[1,1'-biphenyl]-2-sulfonamide

20



A. **4'-[(4-Bromophenyl)methoxy]-2-ethylquinoline**

A mixture of 2-ethyl-4-quinolone (1.0 g, 5.8 mmol), 4-bromobenzyl bromide (1.7 g, 6.9 mmol), potassium carbonate (1.6 g, 11.6 mmol), and DMF (10 ml) was stirred at RT for 16 h. Ethyl acetate (100 ml) was added and the mixture was washed four times with water, then once with brine. The organic layer was dried over sodium sulfate and evaporated, and the residue was triturated with 1:1 hexanes/ethyl acetate to provide 1.6 g **36A** as a white solid.

10 B. 4-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(tert-butyl)-[1,1'-biphenyl]-2-sulfonamide

A mixture of **36A** (1.5 g, 4.4 mmol) and [2-(*N*-tert-butylsulfamoyl)phenyl]boronic acid (2.3 g, 8.7 mmol) was subjected to Suzuki coupling according to General Method 1. The crude product was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide the **36B** (1.8 g) as a yellow solid.

20 C. 4'-[(2-Ethylquinolin-4-yl)oxymethyl]-[1,1'-biphenyl]-2-sulfonamide

A solution of **36B** (1.8 g, 3.8 mmol) in 4 ml dichloromethane and 8 ml TFA was stirred at RT for 14 h, then was heated at reflux for 8 h. The solvent was evaporated and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. A small amount of a solid precipitate was retained with the organic layer. The organic layer was washed twice with water, then was concentrated. The crude product was crystallized from 1:1 toluene/ethyl acetate to provide **36C** (1.2 g) as a yellow solid.

25

D. 4'-[(2-Ethylquinolin-4-yl)oxymethyl] [1,1'-biphenyl]-2-sulfonic acid

A suspension of **36C** (1.1 g, 2.7 mmol) in 25 ml acetonitrile was treated at 0 °C with nitrosonium tetrafluoroborate (370 mg, 3.2 mmol). After 30 min the mixture was allowed to warm to RT and was stirred at RT for 4 h. The mixture was concentrated to provide **36D** (1.2 g) as a crude white solid.

30

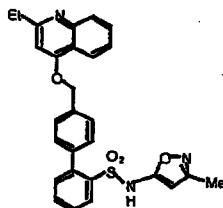
E. 4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(1,3,5-trimethylpyrazol-4-yl)[1,1'-biphenyl]-2-sulfonamide

A suspension of **36D** (100 mg, 0.24 mmol) in thionyl chloride (4 ml) was treated with DMF (10 µl). The resulting mixture was refluxed for 45 min, then the solvent was evaporated. The residue was twice taken up in toluene and evaporated to dryness. Pyridine (2.5 ml) and 4-amino-1,3,5-trimethylpyrazole (90 mg, 0.72 mmol) were added and the mixture was stirred at RT for 14 h, then the solvent was evaporated. The residue was purified by silica gel chromatography (100:1 chloroform/methanol eluant), followed by silica gel thin-layer chromatography (1:1 hexanes/acetone eluant) to provide the title compound (24 mg) as an amorphous white solid: mp 212-215 °C (decomp); MS m/e 527 (ESI+ mode); HPLC retention time 3.18 min (Method C); HPLC purity 94%.

15

Example 37

4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(3-methylisoxazol-5-yl)[1,1'-biphenyl]-2-sulfonamide

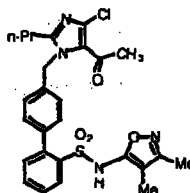


20

A suspension of the product of **36D** (370 mg, 0.88 mmol) was subjected to the procedure used for Example 36, Step E, substituting 5-amino-3-methylisoxazole as the amine component. The crude product was purified by reverse-phase preparative HPLC to provide the title compound (8 mg) as an amorphous tan solid: MS m/e 500 (ESI+ mode); HPLC retention time 3.32 min (Method A); HPLC purity >98%.

Example 38

4'-[(5-Acetyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



5

A. 5-(1-Hydroxyethyl)-2-n-propyl-4-chloroimidazole

A solution of 2-n-propyl-4-chloroimidazole-5-carboxaldehyde
 10 (Watson, S.P. *Synth. Comm.*, 1992, 22, 2971-2977) (1.5 g, 8.7 mmol) in THF (50 ml) was treated dropwise at 0 °C with methylmagnesium bromide (8.7 ml of a 3.0 M solution in ether). Upon completion of the addition, the mixture was allowed to warm to RT and was stirred for 2h. The mixture was cooled again to 0 °C and was quenched with the addition
 15 of 1N hydrochloric acid. The mixture was adjusted to pH 8-9 by the addition of aqueous dipotassium hydrogen phosphate solution, then was partitioned against ethyl acetate. The ethyl acetate layer and an accompanying precipitate were collected and the solvent was evaporated to provide 38A (1.6 g) as a slightly yellow solid.

20

B. 5-Acetyl-4-chloro-2-n-propyl-imidazole

A mixture of 38A (1.6 g), activated manganese dioxide (5.7 g), and dioxane (20 ml) was heated at 55 °C for 48 h. The mixture was cooled and filtered through celite, and the filter cake was rinsed with
 25 dichloromethane. The combined filtrates were evaporated and the residue was chromatographed on silica gel using 3:1 hexanes/ethyl acetate as eluant. The product was further purified by trituration with 9:1 hexanes/ethyl acetate, providing 0.6 g 38B as an orange solid.

C. 4'-[(5-Acetyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxyethyl)[1,1'-biphenyl]-2-sulfonamide

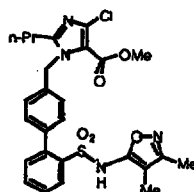
5 **38B** (148 mg, 0.79 mmol) was alkylated with **P19** (300 mg, 0.53 mmol) according to General Method 22. The crude product was purified by silica gel chromatography using 2:1 hexanes/ethyl acetate as eluent to provide **38C** (89 mg) as a yellow oil.

10 D. 4'-[(5-Acetyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

Deprotection of **38C** (60 mg) according to General Method 8, followed by preparative thin-layer chromatography using 1:1 hexanes/acetone as eluant, provided the title compound (24 mg) as a
 15 white solid: MS m/e 528 (ESI+ mode); HPLC retention time 3.75 min (Method A); HPLC purity 98%.

Example 39

20 4'-[(5-Methoxycarbonyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide



25 A. 4'-[(5-Formyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxyethyl)[1,1'-biphenyl]-2-sulfonamide

P19 (300 mg) was used to alkylate 2-n-propyl-4-chloroimidazole-5-carboxaldehyde according to General Method 22. The crude product was chromatographed on silica gel using 4:1 hexanes/ethyl acetate as eluant to provide 39A (200 mg) as a yellow oil.

5

B. 4'-[(5-Carboxy-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-trimethylsiloxymethyl)[1,1'-biphenyl]-2-sulfonamide

Sodium chlorite (19 mg, 0.21 mmol) was added to a mixture of 39A (90 mg, 0.14 mmol) and sulfamic acid (20 mg, 0.21 mmol) in 1:1 THF/water (8 ml) at 0 °C. The mixture was stirred at 0 °C for 1h, then saturated potassium bisulfate solution was added. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed once with brine, then were dried over sodium sulfate and concentrated to provide 39B (62 mg) as a yellow oil.

C. 4'-[(5-Carboxy-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl) 1,1'-biphenyl]-2-sulfonamide

39B (62 mg) was deprotected according to General Method 8, using water in place of an alcohol as co-solvent. Crude 39C (54 mg) was a yellow oil.

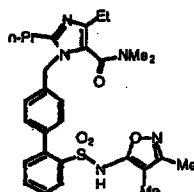
D. 4'-[(5-Methoxycarbonyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl) 1,1'-biphenyl]-2-sulfonamide

39C (54 mg) was subjected to ester formation according to General Method 20. Reverse-phase preparative HPLC provided the title compound (9 mg) as a white solid: MS m/e 544 (ESI+ mode); HPLC retention time 3.94 min (Method A); HPLC purity >98%

Example 40

4'-[(5-(N,N-dimethylcarbamoyl)-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

5



- A. 4'-[(5-Ethoxycarbonyl-2-n-propyl-4-ethylimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-(2-methoxyethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

10

Ethyl 2-n-propyl-4-ethylimidazole-5-carboxylate (94 mg, 0.45 mmol) was alkylated with **P18** (380 mg, 0.37 mmol), according to General Method 22 to provide crude **40A** as a 3:1 mixture of N-1 and N-3 regioisomeric alkylation products.

15

- B. 4'-[(5-Carboxy-2-n-propyl-4-ethylimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

A solution of **40A** (0.45 g) in dioxane (3 ml) and 6N hydrochloric acid (3 ml) was heated at 70 °C for 2 h. The mixture was cooled to RT and made basic (pH > 14) with the addition of 45% aqueous potassium hydroxide solution. Additional dioxane and water were added to obtain a clear solution and the mixture was stirred at RT for 16 h, followed by heating at 70 °C for 3 h. The pH was adjusted to 2-3 with the addition of 6N hydrochloric acid and solid trisodium phosphate, and the mixture was extracted with three portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and evaporated to give **40B** (0.33 g) as a crude oil.

20

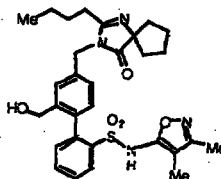
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C. 4'-[(5-(N,N-dimethylcarbamoyl)-2-n-propyl-4-ethylimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide

- 5 40B (110 mg) was subjected to amide formation according to General Method 12 using dimethylamine as the amine component. The crude material was subjected to reverse-phase preparative HPLC to provide the title compound (19 mg) as a white solid: MS m/e 550 (ESI+ mode); HPLC retention time 19.54 min (Method B); HPLC purity 74%.
- 10 The contaminant (24%) is the isomeric product arising from N-3 alkylation of the imidazole in Step A (HPLC retention time 19.77 min).

Example 41

- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-hydroxymethyl[1,1'-biphenyl]-2-sulfonamide



- 20 A. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-trimethylsilylethoxy)methyl]-2'-hydroxymethyl[1,1'-biphenyl]-2-sulfonamide

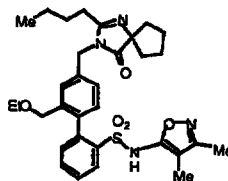
- P14 (243 mg, 0.41 mmol) was used to alkylate 2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-ene hydrochloride according to General Method 4.
- 25 41A (100 mg, 35% yield) was isolated as a slightly yellow oil after silica gel chromatography using 1:1 hexanes/ethyl acetate as eluant.

B. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-hydroxymethyl[1,1'-biphenyl]-2-sulfonamide

Deprotection of **41A** (100 mg, 0.14 mmol) according to General Method 8 (ethanol) gave the title compound as white solid in 46% yield following silica gel chromatography (96:4 methanol/chloroform eluant): MS m/e 565 (ESI+ mode); HPLC retention time 3.21 min (Method A); HPLC purity >98%.

Example 42

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide



A. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-2'-hydroxymethyl[1,1'-biphenyl]-2-sulfonamide

Triethylsilane (6 ml) and TFA (6 ml) were added to a solution of **5F** (960 mg, 1.5 mmol) in 15 ml dichloromethane at RT. The mixture was stirred at RT for 2 h and was then concentrated. The residue was taken up in ethyl acetate and was washed successively with aqueous sodium bicarbonate, water, and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using 100:2 dichloromethane/methanol to afford **42A** (740 mg, 77%) as a colorless gum. Rf=0.13, silica gel, 100:5 dichloromethane/methanol.

B. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide

A mixture of **42A** (100 mg, 0.15 mmol), iodoethane (960 mg, 6.1 mmol) and silver (I) oxide (180 mg, 0.77 mmol) in 0.7 ml DMF was heated at 40 °C for 16 h. Additional iodoethane (190 mg, 1.2 mmol) and silver (I) oxide (71 mg, 0.31 mmol) were added and the reaction mixture was heated at 40 °C for an additional 4 h. The mixture was diluted with 1:4 hexanes/ethylacetate and was then washed with water and brine. The organic layer was dried over sodium sulfate and was then concentrated. The residue was chromatographed on silica gel using 200:3 dichloromethane/methanol as eluant to afford **42B** (51mg, 49%) as a colorless gum. Rf=0.35, silica gel, 100:5 dichloromethane/methanol.

C. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide

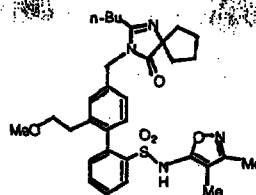
42B (51 mg) was deprotected according to General Method 7 to afford the title compound in 80% yield following preparative reverse-phase HPLC purification: white solid; m.p. 74-80 °C (amorphous); ¹H NMR (CDCl₃) δ 0.87(tr, J=7Hz, 3H), 0.99(tr, J=7Hz, 3H), 1.32(m, 2H), 1.59(m, 2H), 1.75-2.02(m, 11H), 2.16(s, 3H), 2.35(m, 2H), 3.38 (m, 2H), 4.23(m, 2H), 4.73(s, 2H), 7.11-7.85 (m, 7H); MS m/e 593 (ESI+ mode); HPLC retention time 18.22 min. (Method E); HPLC purity >97%.

25

Example 43

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide

30



- A. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(2-methoxyvinyl)[1,1'-biphenyl]-2-sulfonamide

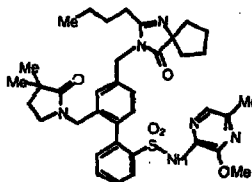
5 **5F** was treated with methoxymethyltriphenylphosphonium bromide according to the procedure used in Example 27, Step A. The product (34%) was generated as a mixture of E and Z isomers.

- 10 B. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-methoxyethyl[1,1'-biphenyl]-2-sulfonamide

43A (18 mg) was treated with triethylsilane and TFA according to the procedure of Example 42, Step B, to provide the title compound (6 mg, 45%) as an oil: MS m/e 593 (ESI+ mode); HPLC retention time 24.74 min. (Method B); HPLC purity >98%.

Example 44

- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(3-methoxy-5-methyl-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide



- A. N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-bromobenzenesulfonamide

2-amino-3-methoxy-5-methylpyrazine (1.50 g, 10.8 mmol;
synthesized according to Bradbury, R. H., et. al. *J. Med. Chem.* **1997**, *40*,
996-1004) and 2-bromobenzenesulfonyl chloride (2.80 g, 11.0 mmol) were
reacted according to the procedure of Example 25, Step A. **44A** was a pink
5 solid, 2.0 g (52%).

B. N-(3-Methoxy-5-methyl-2-pyrazinyl)-N-[2-(trimethylsilyl)ethoxymethyl]-2-bromobenzenesulfonamide
44A (2.0 g) was reacted with 2-(trimethylsilyl)ethoxymethyl
10 chloride (1.15 ml) according to the procedure of Example 25, Step B. The
crude residue was chromatographed on silica gel using 4:1 hexanes/ethyl
acetate to give **44B** (2.37 g, 86%) as a yellow oil.

C. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,3-dioxolan-2-yl)-N-[2-(trimethylsilyl)ethoxymethyl]-N-(3-methoxy-5-methyl-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide
15
A solution of **5E** (2.0 g, 4.6 mmol) in ether (45 ml) was treated at -78
°C with t-butyllithium (1.7 M in pentane, 5.9 ml, 10.1 mmol). After
stirring at -78 °C for 10 min, the mixture was treated with
20 trimethylborate (1.3 ml, 11.5 mmol) and was then allowed to warm to RT.
The mixture was concentrated and the residue azeotroped twice with
methanol to produce a pale yellow solid (3.5 g).

The crude solid was subjected to Suzuki coupling with **44B** (2.37 g)
according to General Method 1. Silica gel chromatography using 1:1
25 hexanes/ethyl acetate as eluant provide 1.45 g **44C** (39%) as a yellow oil.

D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3-methoxy-5-methyl-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide
30
44C (1.45 g, 1.9 mmol) was treated with 2M sulfuric acid (11 ml)
and ethanol (11 ml) at RT for 6 h. Aqueous sodium bicarbonate was added

(final pH 7) and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated to provide crude **44D** (0.91 g) as an off-white solid.

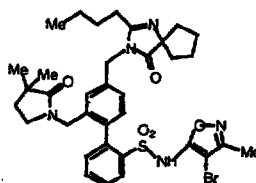
- 5 E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(3-methoxy-5-methyl-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide

44D (0.91 g) was reacted with ethyl 4-amino-2,2-dimethylbutanoate hydrochloride according to General Method 5. The crude residue was
 10 purified by silica gel column chromatography using 1:3 hexanes/ethyl acetate as eluant to provide the title compound (230 mg, 18% over two steps) as a yellow solid: MS m/e 687 (ESI+ mode); HPLC retention time 3.58 min (Method A); HPLC purity 95%.

15

Example 45

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-bromo-3-methyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide



20

- A. N-(2-methoxyethoxymethyl)-N-(3-methyl-5-isoxazolyl)-2-bromobenzenesulfonamide

25 **25A** (10.0 g, 31.5 mmol) was reacted with MEM chloride according to the procedure of Example 25, Step B. The crude residue was chromatographed on silica gel using 2:1 hexanes/ethyl acetate to give 4.8 g **45A** (38%) as a yellow oil.

B. 2-[[[(3-methyl-5-isoxazolyl)](2-methoxyethoxy)-methyl]aminol
sulfonyl]phenyl]boronic acid

n-Butyllithium (1.35 M solution in hexanes, 9.7 ml, 13 mmol) was
5 added dropwise over 5 min to a 0.2 M solution of the 45A (4.8 g, 12 mmol)
in THF at -90 °C. After 10 min, trimethylborate (1.6 ml, 14 mmol) was
added and the mixture was allowed to warm to RT and stirred for 30 min.
The mixture was cooled to 0 °C and treated with 21 ml of 3N hydrochloric
acid, after which it was allowed to warm to RT over 30 min. Brine was
10 added and the mixture was extracted with dichloromethane. The
combined extracts were dried over sodium sulfate and concentrated to give
45B (5.3 g) as a yellow oil.

C. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(2-
15 methoxyethoxymethyl)-N-(3-methyl-5-isoxazolyl)-2'-formyl[1,1'-
biphenyl]-2-sulfonamide

45B (4.5 g) was subjected to Suzuki coupling with 5E according to
General Method 1. Silica gel chromatography using 1:2 hexanes/ethyl
acetate as eluant provide 45C (1.30 g, 17%) as a yellow oil.

20

D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3-
methyl-5-isoxazolyl)-N-[2-methoxyethoxy)methyl]-2'-[(3,3-dimethyl-
2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

45C (420 mg, 0.66 mmol) was reacted with ethyl 4-amino-2,2-
25 dimethylbutanoate hydrochloride and sodium cyanoborohydride using a
procedure similar to that of Example 8, Step B. The crude residue was
chromatographed on silica gel using 1:3 hexanes/ethyl acetate as eluant to
provide 45D (150 mg) as a yellow oil.

E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3-methyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

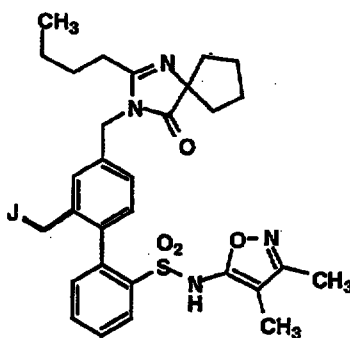
45D (110 mg) was deprotected according to General Method 7. The crude residue was chromatographed on silica gel using 95:5 chloroform/methanol as eluant to provide 45E (50 mg) as a white solid.

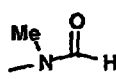
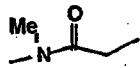
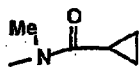
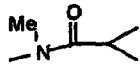
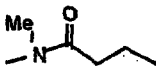
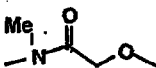
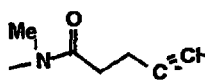
F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-bromo-3-methyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide

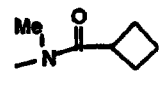
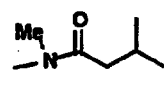
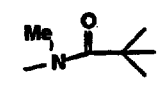
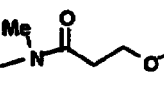
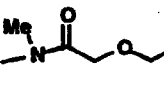
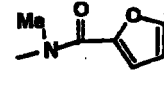
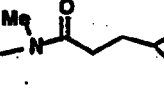
45E (33 mg) was brominated using NBS according to the procedure used for Example 26. Preparative TLC purification of the crude residue provided the title compound (4 mg) as a white powder: MS m/e 724, 726 (ESI+ mode); HPLC retention time 3.53 min (Method A); HPLC purity 98%.

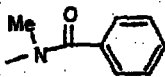
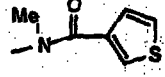
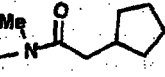
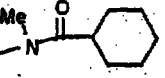
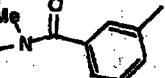
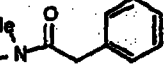
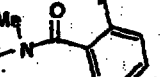
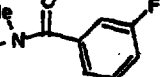
Examples 46 to 97

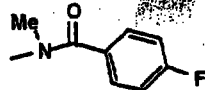
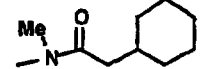
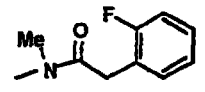
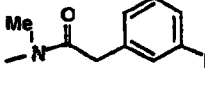
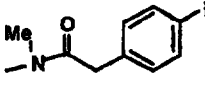
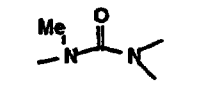
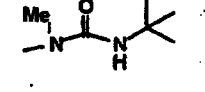
The following compounds 46 to 97 were prepared by a solution phase combinatorial chemistry method using 2I and the corresponding carboxylic acid in the presence of diisopropylcarbodiimide. The products were purified by ion-exchange chromatography according to the General Method. HPLC retention times were determined using HPLC Method C.

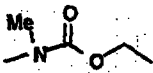
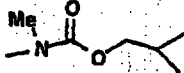
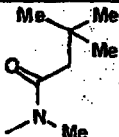
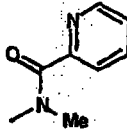
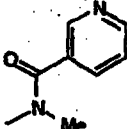
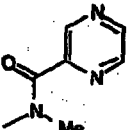
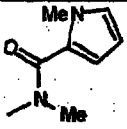
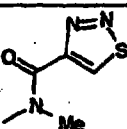


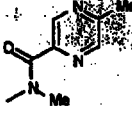
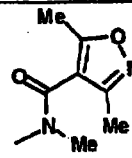
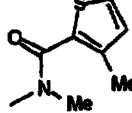
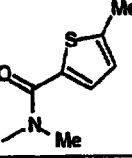
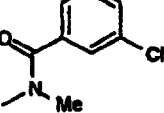
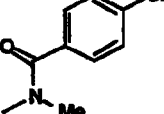
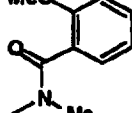
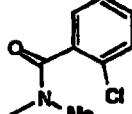
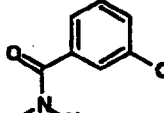
Ex. No.	Compound Name	J	HPLC Retention Time (min)	LRMS m/z [MH ⁺]
46	4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(formylmethylamino)methyl][1,1'-biphenyl]-2-sulfonamide		3.23	606
47	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylpropanamide		3.28	634
48	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclopropanecarbox-amide		3.33	646
49	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,2-dimethylpropanamide		3.41	648
50	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbutanamide		3.45	648
51	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-methoxy-N-methylacetamide		3.29	650
52	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-4-pentynamide		3.32	658

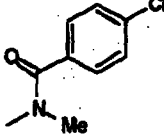
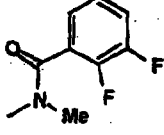
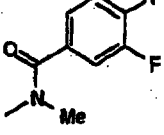
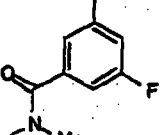
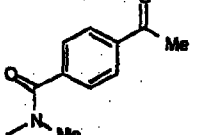
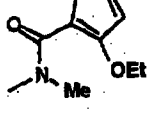
53	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclobutanecarbox-amide		3.50	660
54	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3-dimethylbutanamide		3.57	662
55	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,2,2-trimethylpropanamide		3.80	662
56	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-methoxy-N-methylpropanamide		3.38	664
57	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-ethoxy-N-methylacetamide		3.25	664
58	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-2-furancarboxamide		3.30	672
59	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,4-dimethylpentanamide		3.95	676

60	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbenzamide		3.66	682
61	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-3-thiophenecarboxamide		3.59	688
62	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclopentaneacetamide		3.82	688
63	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclohexanecarboxamide		3.76	688
64	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3-dimethylbenzamide		3.82	696
65	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbenzeneacetamide		3.78	696
66	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-fluoro-N-methylbenzamide		3.46	700
67	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-fluoro-N-methylbenzamide		3.53	700

68	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-fluoro-N-methylbenzamide		3.72	700
69	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclohexaneacetamide		3.96	702
70	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-fluoro-N-methylbenzeneacetamide		3.79	714
71	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-fluoro-N-methylbenzeneacetamide		3.82	714
72	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-fluoro-N-methylbenzeneacetamide		3.82	714
73	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,N,N'-trimethylurea		3.44	649
74	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N'-(1,1-dimethylethyl)-N-methylurea		3.74	677

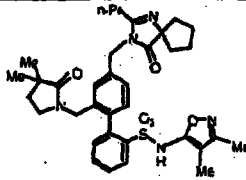
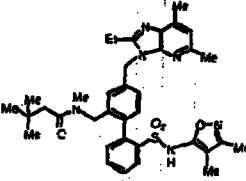
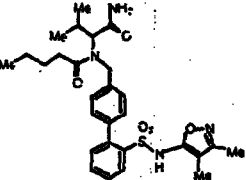
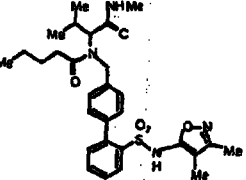
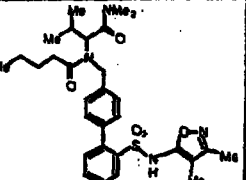
75	[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl)methylcarbamic acid ethyl ester		3.69	650
76	[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl)methylcarbamic acid 2-methylpropyl ester		4.01	678
77	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide		3.85	676
78	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-2-pyridinecarboxamide		3.33	683
79	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-3-pyridinecarboxamide		3.16	683
80	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-3-pyridinecarboxamide		3.27	684
81	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,1-dimethyl-1H-pyrrole-2-carboxamide		3.64	685
82	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-1,2,3-thiadiazole-4-carboxamide		3.36	690

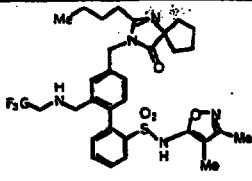
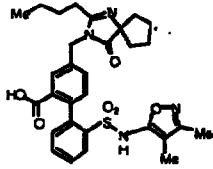
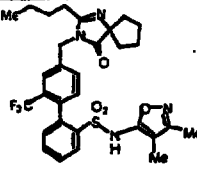
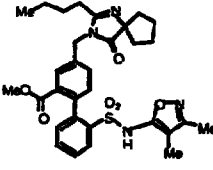
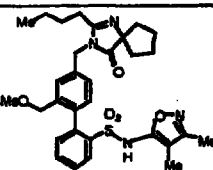
83	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,5-dimethyl-2-pyrazinecarboxamide		3.37	698
84	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3,5-trimethyl-4-isoxazolecarboxamide		3.42	701
85	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3-dimethyl-2-thiophenecarboxamide		3.66	702
86	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,5-dimethyl-2-thiophenecarboxamide		3.72	702
87	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-cyano-N-methylbenzamide		3.45	707
88	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-cyano-N-methylbenzamide		3.49	707
89	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-methoxy-N-methylbenzamide		3.63	712
90	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-chloro-N-methylbenzamide		3.77	717
91	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-chloro-N-methylbenzamide		3.84	717

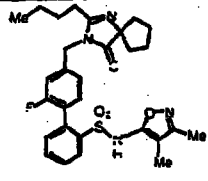
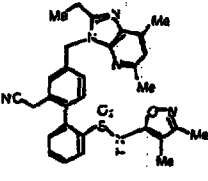
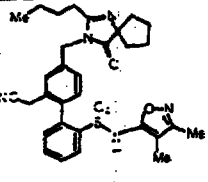
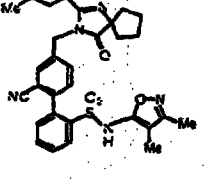
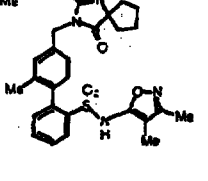
92	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-chloro-N-methylbenzamide		3.87	717
93	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2,3-difluoro-N-methylbenzamide		3.66	718
94	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3,4-difluoro-N-methylbenzamide		3.76	718
95	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3,5-difluoro-N-methylbenzamide		3.76	718
96	4-Acetyl-N-[[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbenzamide		3.48	724
97	N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-ethoxy-N-methyl-2-thiophenecarboxamide		3.63	732

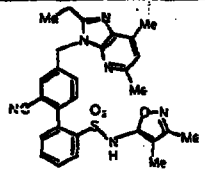
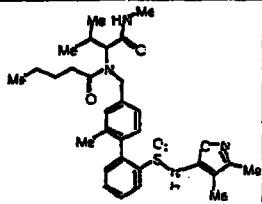
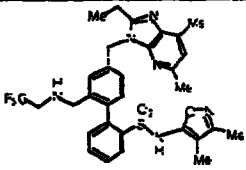
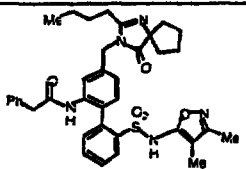
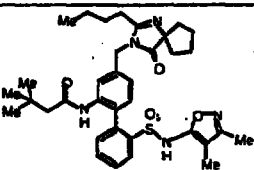
The following examples were synthesized by combinations of the General Methods.

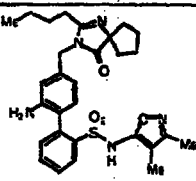
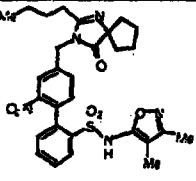
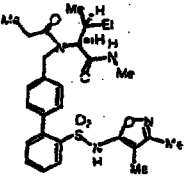
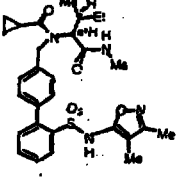
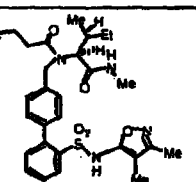
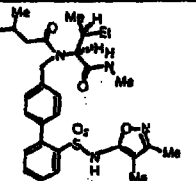
EXAMPLE	STRUCTURE	NAME	STARTING MATERIAL	General Methods Applied (yield, %)	M/z (MH) ⁺	HPLC % Purity	HPLC ret time, min (method)
98		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide	P18	4, 7 (32)	535	>98	15.00 (I)
99		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-((propylsulfonyl)amino)[1,1'-biphenyl]-2-sulfonamide	123	24 (67)	656	98	14.58 (E)
100		N-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-(1-oxopentyl)-L-valine methyl ester	P17	5,6 (16); 9 (60)	556	>98	16.27 (F)
101		N-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-(1-oxopentyl)-L-valine methyl ester	100	15 (40)	542	>98	13.55 (F)

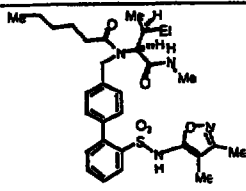
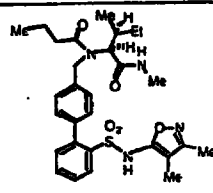
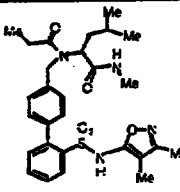
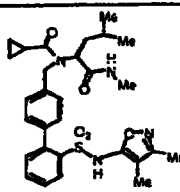
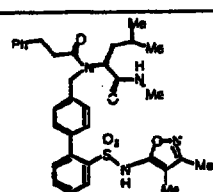
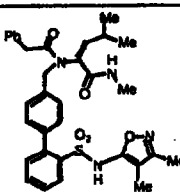
102		N-(3,4-Dimethyl-5-isoxazolyl)-2'-((3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl)-4'-((2-propyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)[1,1'-biphenyl]-2-sulfonamide	5C	4 (65); 19, 1 (70); 5 (36); 9 (50)	646	97	7.92 (E)
103		N-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl]-4-(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)[1,1'-biphenyl]-2-yl)methyl)-N,3,3-trimethylbutanamide	2G	4 (32); 7, 6 (80)	657	>98	25.45 (B)
104		N'-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl)-N'-(1-oxopentyl)-L-valinamide	101	12. NH ₂ (70)	541	98	11.39 (B)
105		N'-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl)-N-methyl-N'-(1-oxopentyl)-L-valinamide	101	12, MeNH ₂ (67)	555	98	11.27 (F)
106		N'-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl)-N,N-dimethyl-N'-(1-oxopentyl)-L-valinamide	101	12, Me ₂ NH (12)	569	94	12.28 (F)

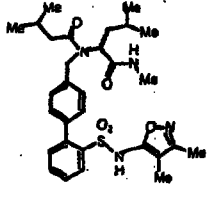
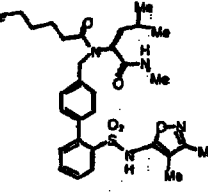
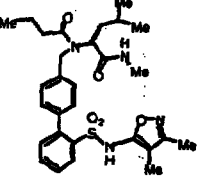
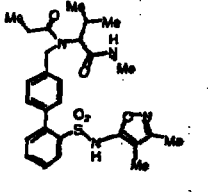
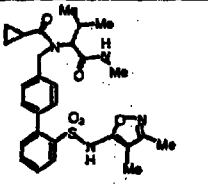
107		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(2,2,2-trifluoroethyl)amino)methyl][1,1'-biphenyl]-2-sulfonamide	P4	3 (90); 4 (37); 5 (56); 8, EtOH (91)	646	>99	3.46 (A)
108		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-carboxylic acid	110	15 (62)	578	95	3.16 (A)
109		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-sulfonamide	P9	4 (60); 10 (90)	603	94	2.33 (D)
110		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-carboxylic acid methyl ester	methyl 2-bro- mo-6- methyl- benzo- ate	13, 4 (61); 1 (50); 8, MeOH (34)	593	96	3.42 (A)
111		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide	P2	4 (53); 7 (58)	579	>98	16.26 (E)

112		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide	P11	4 (82); 7 (85)	553	>99	25.90 (B)
113		2'-(Cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-1,1'-biphenyl-2-sulfonamide	P12	16, 3, 4 (35); 8, EtOH (81)	555	97	3.16 (A)
114		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-1,1'-biphenyl-2-sulfonamide	P12	16, 3, 4 (35); 8, EtOH (52)	574	96	3.36 (A)
115		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-1,1'-biphenyl-2-sulfonamide	P3	3 (88); 4 (45); 10 (40)	560	>97	3.31 (C)
116		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide	P7	11 (83); 2 (87); 4 (70); 1 (35); 7 (20)	549	98	27.21 (B)

117		2'-Cyano-N-(3,4-dimethyl-5-isoxazolyl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)[1,1'-biphenyl]-2-sulfonamide	P3	3 (88); 4 (45); 10 (38)	541	98	3.10 (A)
118		N²-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)-2-methyl[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxopentyl)-L-valinamide	P15	5 (39); 6 (92); 10 (30)	569	>99	2.15 (H)
119		N-(3,4-Dimethyl-5-isoxazolyl)-4'-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-2'-[[[(2,2,2-trifluoroethyl)amino]methyl][1,1'-biphenyl]-2-sulfonamide	P4	3 (90); 4 (49); 5 (83); 10 (15)	627	89	3.10 (A)
120		N-[4-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2'-((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl]benzeneacetamide	122	6 (27)	668	97	14.97 (I)
121		N-[4-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2'-((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl]-3,3-dimethylbutanamide	122	6 (36)	648	>98	16.38 (I)

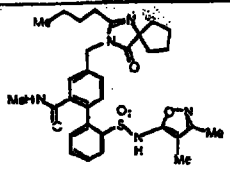
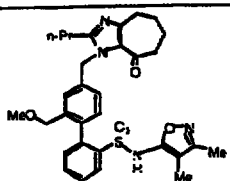
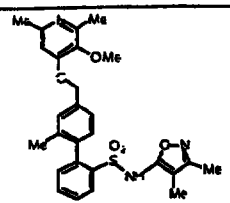
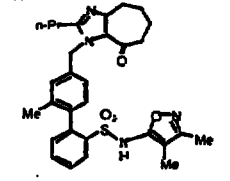
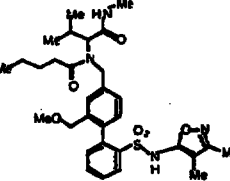
122		2'-Amino-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide	123	18 (75)	550	>98	8.39 (I)
123		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-nitro[1,1'-biphenyl]-2-sulfonamide	P22	7 (93)	580	>98	11.17 (I)
124		N ² -[[2'-[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N ² -(1-oxopropyl)-L-isoleucinamide	P16	5 (85); 6, 10 (62)	541	96	1.00 (G)
125		N ² -(Cyclopropylcarbo-nyl)-N ² -[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-isoleucinamide	P16	5 (85); 6, 10 (62)	553	96	1.09 (G)
126		N ² -[[2'-[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N ² -(1-oxo-3-phenylpropyl)-L-isoleucinamide	P16	5 (85); 6, 10 (64)	617	95	1.63 (G)
127		N ² -[[2'-[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N ² -(3-methyl-1-oxobutyl)-L-isoleucinamide	P16	5 (85); 6, 10 (58)	569	98	1.47 (G)

128		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxohexyl)-L-isoleucinamide	P16	5 (85); 6, 10 (75)	583	98	1.74 (G)
129		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxobutyl)-L-isoleucinamide	P16	5 (85); 6, 10 (62)	555	95	1.31 (G)
130		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxopropyl)-L-leucinamide	P16	5 (83); 6, 10 (75)	541	90	1.01 (G)
131		N²-((Cyclopropylcarbonyl)-N²-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-leucinamide	P16	5 (83); 6, 10 (79)	553	95	1.11 (G)
132		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxo-3-phenylpropyl)-L-leucinamide	P16	5 (83); 6, 10 (20)	617	95	1.08 (G)
133		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(phenylacetyl)-L-leucinamide	P16	5 (83); 6, 10 (20)	603	95	1.68 (G)

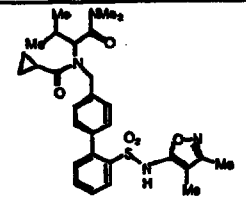
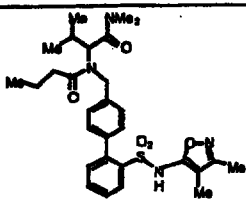
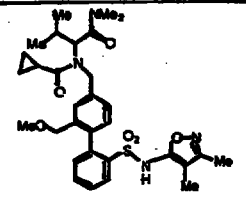
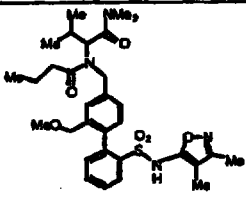
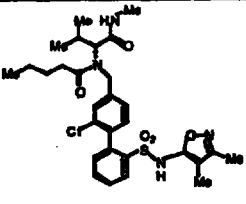
134		N²-[(2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(3-methyl-1-oxobutyl)-L-leucinamide	P16	5 (83); 6, 10 (62)	569	90	1.51 (G)
135		N²-[(2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxohexyl)-L-leucinamide	P16	5 (83); 6, 10 (47)	583	97	1.76 (G)
136		N²-[(2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxobutyl)-L-leucinamide	P16	5 (83); 6, 10 (64)	555	94	1.29 (G)
137		N²-[(2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxopropyl)-L-valinamide	P16	5 (89); 6, 10 (39)	527	90	0.73 (G)
138		N²-(Cyclopropylcarbonyl)-N²-[(2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-valinamide	P16	5 (89); 6, 10 (66)	539	98	0.89 (G)

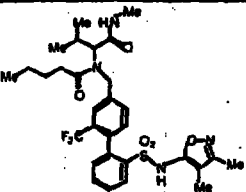
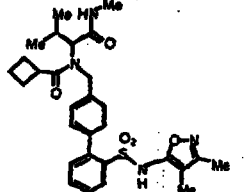
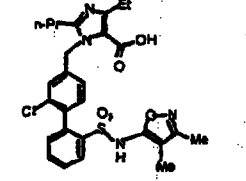
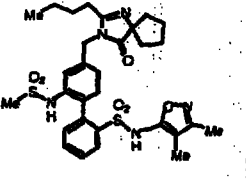
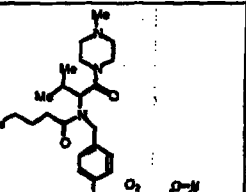
139		N²-([2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-methyl-N²-(1-oxo-3-phenylpropyl)-L-valinamide	P16	5 (89); 6, 10 (6)	603	95	1.63 (G)
140		N²-([2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-methyl-N²-(phenylacetyl)-L-valinamide	P16	5 (89); 6, 10 (54)	589	93	1.53 (G)
141		N²-([2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-methyl-N²-(3-methyl-1-oxobutyl)-L-valinamide	P16	5 (89); 6, 10 (45)	555	98	1.37 (G)
142		N²-([2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-methyl-N²-(1-oxohexyl)-L-valinamide	P16	5 (89); 6, 10 (61)	569	98	1.58 (G)
143		N²-([2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-methyl-N²-(1-oxobutyl)-L-valinamide	P16	5 (89); 6, 10 (43)	541	98	1.65 (G)
144		N²-([2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-ethyl-N²-(1-oxopentyl)-L-valinamide	P17	5 (87); 6 (88); 9 (65); 15 (85); 12 (65)	569	>97	12.94 (F)

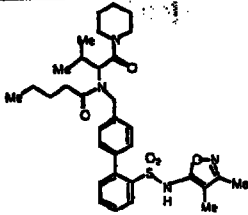
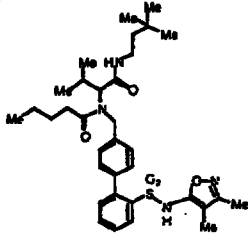
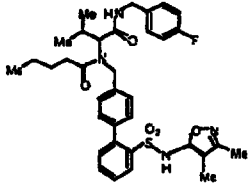
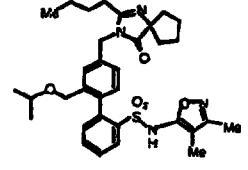
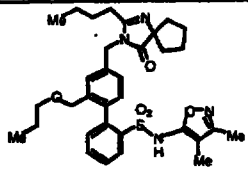
145		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-hexyl-N²-(1-oxopentyl)-L-valinamide	P17	5 (87); 6 (93); 9 (65); 15 (85); 12 (65)	625	>98	22.19 (F)
146		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-cyano[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxopentyl)-L-valinamide	P3	17 (58); 5, 6 (49); 10 (14)	580	>98	3.78 (C)
147		N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-hydroxymethyl[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(1-oxopentyl)-L-valinamide	P1	5 (77); 6 (92); 10 (17)	585	94	3.82, 3.90 (A) (two diastereomers)
148		4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide	108	12 (33)	578	99	3.16 (A)
149		N,N-Dimethyl-4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide	108	12 (61)	606	99	3.22 (A)

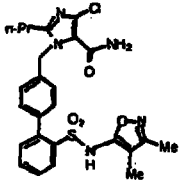
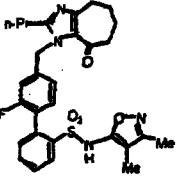
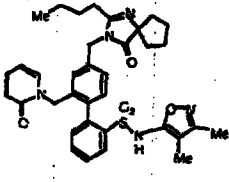
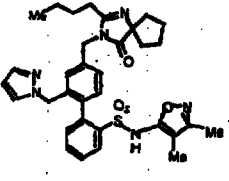
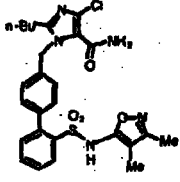
150		N-Methyl-4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazoyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide	108	12 (93)	592	99	3.17 (A)
151		N-(3,4-Dimethyl-5-isoxazoyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazoyl)methyl]-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide	P2	11 (87); 8 (38); 8 (42)	577	>98	11.58 (E)
152		N-(3,4-Dimethyl-5-isoxazoyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide	P13	4 (20); 7 (27)	508	>98	22.83 (B)
153		N-(3,4-Dimethyl-5-isoxazoyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazoyl)methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide	P13	21 (60); 7 (20)	547	>98	23.29 (B)
154		N'-[[2'-[[[(3,4-Dimethyl-5-isoxazoyl)amino]sulfonyl]-2-(methoxymethyl)][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N'-(1-oxopentyl)-L-valinamide	P20	5 (90); 6 (90); 7 (42)	599	>98	12.71, 12.95 (F), migrates as diastereomers

155		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide	P14	21 (29); 8, EtOH (32)	563	>98	2.99 (A)
156		2'-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(5,6,7,8-tetrahydro-2-ethyl-4-quinolinyl)oxymethyl][1,1'-biphenyl]-2-sulfonamide	P10	4, 8 (33)	553	97	1.69 (D)
157		N'-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-fluoro[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N'-(1-oxopentyl)-L-valinamide	P8	5 (30); 6 (34); 7 (45)	573	>98	30.02 (B)
158		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(phenoxy)methyl[1,1'-biphenyl]-2-sulfonamide	42A	3 (70); 22 (68); 7 (76)	641	94	19.91 (I)
159		N'-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(1H-pyrazol-1-yl)methyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N'-(1-oxopentyl)-L-valinamide	P1	5 (77); 6 (92); 3 (99); 4 (69); 23 (18)	635	95	4.08 (A)

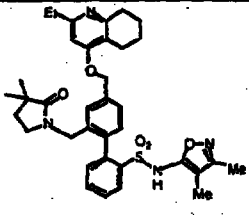
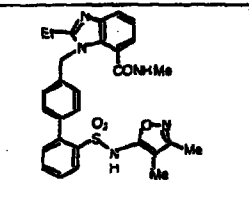
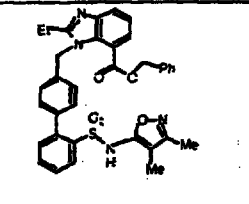
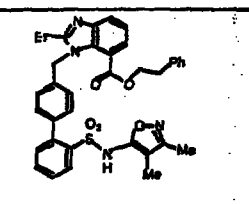
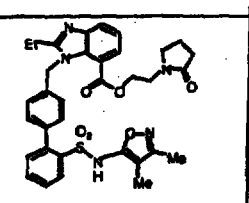
160		N ² - (Cyclopropylcarbo nyl)-N ² -[[2'-[[[(3,4- dimethyl-5- isoxazolyl)amino]s ulfonyl][1,1'- biphenyl]-4- yl)methyl]-N,N- dimethyl-L- valinamide	P16	5 (85); 6, 10 (28)	553	88	2.58 (D)
161		N ² -[[2'-[[[(3,4- Dimethyl-5- isoxazolyl)amino]s ulfonyl][1,1'- biphenyl]-4- yl)methyl]-N,N- dimethyl-N ² -(1- oxobutyl)-L- valinamide	P16	5 (85); 6, 10 (33)	555	93	2.82 (D)
162		N ² - (Cyclopropylcarbo nyl)-N ² -[[2'-[[[(3,4- dimethyl-5- isoxazolyl)amino]s ulfonyl]-2- (methoxymethyl)][1 ,1'-biphenyl]-4- yl)methyl]-N,N- dimethyl-L- valinamide	P2	5 (50); 6, 8, EtOH (56)	597	>98	2.50, 2.63 (D) (migrates as diastere- omers)
163		N ² -[[2'-[[[(3,4- Dimethyl-5- isoxazolyl)amino]s ulfonyl]-2- (methoxymethyl)][1 ,1'-biphenyl]-4- yl)methyl]-N,N- dimethyl-N ² -(1- oxobutyl)-L- valinamide	P2	5 (50); 6, 8, EtOH (59)	599	96	2.92, 3.02 (D) (migrates as diastere- omers)
164		N ² -[[2-Chloro-2'- [[[(3,4-dimethyl-5- isoxazolyl)amino]s ulfonyl][1,1'- biphenyl]-4- yl)methyl]-N- methyl-N ² -(1- oxopentyl)-L- valinamide	P5	5 (69); 6, 10 (50)	590	96	3.03 (D)

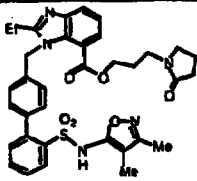
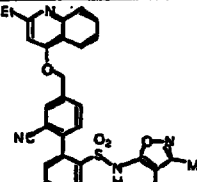
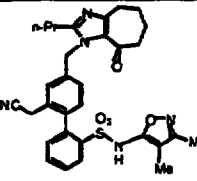
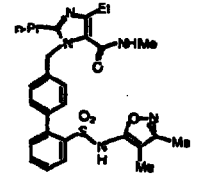
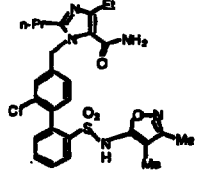
165		N ² -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(trifluoromethyl)][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N ² -(1-oxopentyl)-L-valinamide	P6	5 (80); 6, 10 (83)	623	95	2.93, 3.05 (D) (migrates as diastere- omers)
166		N ² -(Cyclobutylcarbonyl)-N ² -[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide	P16	5 (85); 6, 10 (35)	553	98	2.82 (D)
167		1-[[2-Chloro-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxylic acid	P10	22 (60); 8, EtOH (90); 15 (99)	558	>98	3.04 (A)
168		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(methylsulfonyl)amino][1,1'-biphenyl]-2-sulfonamide	122	24 (25)	628	>98	11.48 (E)
169		(S)-N-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-(4-methyl-1-piperazinyl)carbonyl]propyl]pentanamide	101	12 (43)	624	>98	28.26 (B)

170		(S)-N-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-(2-methyl-1-((4-methyl-1-piperazinyl)carbon-yl)propyl)pentanamide	101	12 (30)	609	>98	34.45 (B)
171		N-(3,3-Dimethylbutyl)-N'-([2'-((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl-N'-(1-oxopentyl)-L-valinamide	101	12 (38)	625	>98	33.97 (B)
172		N'-([2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl-N-((4-fluorophenyl)methyl)-N'-(1-oxopentyl)-L-valinamide	101	12 (38)	649	>98	32.90 (B)
173		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-((methylethoxy)methyl)[1,1'-biphenyl]-2-sulfonamide	42A	2 (67); 4 (51); 7 (62)	607	97	13.59 (E)
174		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-((propoxymethyl)[1,1'-biphenyl]-2-sulfonamide	42A	2 (67); 4 (49); 7 (68)	607	>97	20.61 (E)

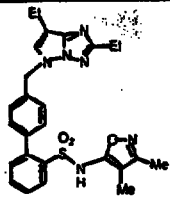
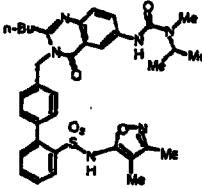
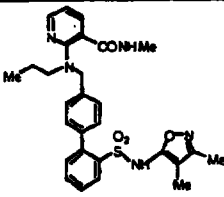
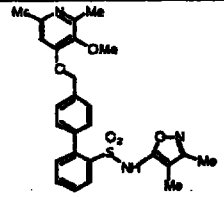
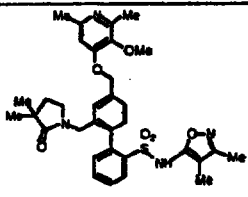
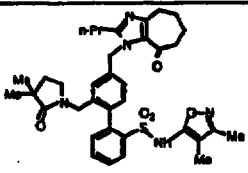
175		4-Chloro-1-((2'- [(3,4-dimethyl-5- isoxazolyl)amino]s ulfonyl)[1,1'- biphenyl]-4- yl)methyl)-2- propyl-1H- imidazole-5- carboxamide	P19	22 (87); 25 (47); 8, H ₂ O (99); 12 (35)	529	>98	3.69 (A)
176		N-(3,4-Dimethyl-5- isoxazolyl)-2'- fluoro-4'- [(1,4,5,6,7,8- hexahydro-8-oxo- 2-propyl-1- cycloheptimidazol yl)methyl][1,1'- biphenyl]-2- sulfonamide	P8	21 (15); 7 (16)	551	>98	5.78 (J)
177		4'-[(2-Butyl-4-oxo- 1,3- diazaspiro[4.4]non -1-en-3-yl)methyl]- 2'-[(1,2-dihydro-2- oxo-1- pyridinyl)methyl]- N-(3,4-dimethyl-5- isoxazolyl)[1,1'- biphenyl]-2- sulfonamide	42A	2 (67); 4 (72); 7 (21)	642	>97	13.59 (E)
178		4'-[(2-Butyl-4-oxo- 1,3- diazaspiro[4.4]non -1-en-3-yl)methyl]- N-(3,4-dimethyl-5- isoxazolyl)-2'-(1H- pyrazol-1- ylmethyl)[1,1'- biphenyl]-2- sulfonamide	P1	3 (98); 4, 11 (35); 3, 4, 7 (13)	615	97	3.42 (A)
179		2-Butyl-4-chloro-1- [[2'-[(3,4- dimethyl-5- isoxazolyl)amino]s ulfonyl][1,1'- biphenyl]-4- yl)methyl]-1H- imidazole-5- carboxamide	P19	22 (43); 25; 8, H ₂ O; 12 (19)	543	94	3.82 (A)

180		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-methyl-4-quinolinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide	P18	4 (79); 8, EtOH (26)	500	98	22.4 (B)
181		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-ethyl-4-quinolinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide	P18	4 (49); 8, EtOH (30)	514	93	23.25 (B)
182		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-ethyl-5,6,7,8-tetrahydro-4-quinolinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide	P18	4 (79); 8, EtOH (3)	518	93	3.49 (A)
183		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-propyl-4-quinolinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide	P18	4 (47); 8, EtOH (20)	528	97	3.50 (A)
184		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(5,6,7,8-tetrahydro-2,4-dimethyl-7-oxopyrido[2,3-d]pyrimidin-8-yl)methyl][1,1'-biphenyl]-2-sulfonamide	P18	4 (79); 8, EtOH (20)	518	>98	3.05 (A)
185		4'-[(2-Ethyl-4-quinolinyl)oxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide	P18	4 (20); 8, EtOH (33)	639	93	3.43 (A)

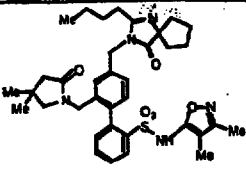
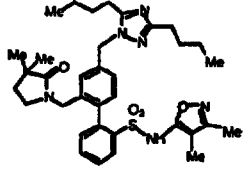
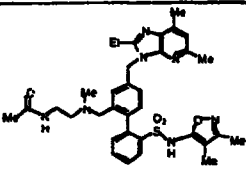
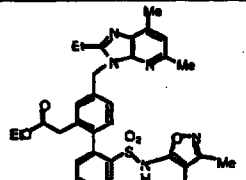
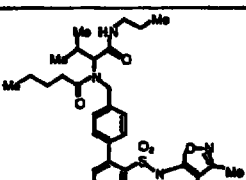
186		N-(3,4-Dimethyl-5-isoxazolyl)-2'-((3,3-dimethyl-2-oxo-1-pyrrolidiny)methyl)-4'-(((5,6,7,8-tetrahydro-2-ethyl-4-quinolinyloxy)methyl)[1,1'-biphenyl]-2-sulfonamide	P18	4 (63); 8, EtOH (8)	643	92	3.79 (C)
187		3-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-N-methyl-3H-benzimidazole-4-carboxamide	31	12 (12)	544	92	2.80 (A)
188		1-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-1H-benzimidazole-7-carboxylic acid phenylmethyl ester	31	20 (55)	621	96	3.95 (C)
189		1-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-1H-benzimidazole-7-carboxylic acid 2-phenylethyl ester	31	20 (12)	635	>98	4.03 (C)
190		1-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-2-ethyl-1H-benzimidazole-7-carboxylic acid 2-(2-oxo-1-pyrrolidiny)ethyl ester	31	20 (45)	642	>98	3.15 (C)

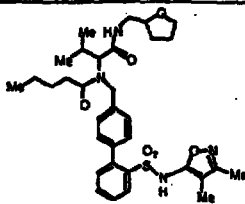
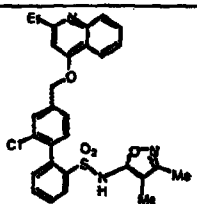
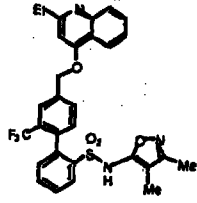
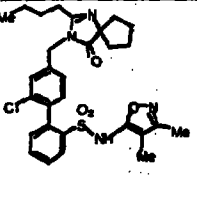
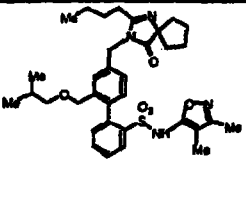
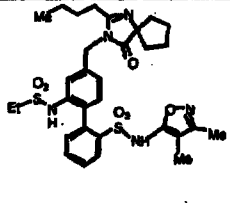
191		1-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 3-(2-oxo-1-pyrrolidinyl)propyl ester	31	20 (30)	656	>98	3.21 (C)
192		2'-Cyano-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[[(2-ethyl-4-quinolinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide	P3	3, 4 (59); 10 (60)	539	>98	3.01 (C)
193		2'-(Cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide	P12	16, 3 (73); 21 (46); 8, EtOH(16)	572	96	2.95 (A)
194		3-[[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-5-ethyl-N-methyl-2-propyl-3H-imidazole-4-carboxamide	40B	12, MeNH ₂ (12)	536	>98	2.88 (C)
195		1-[[[2-Chloro-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-4-ethyl-2-propyl-1H-imidazole-5-carboxamide	167	12, NH ₂ (17)	557	>98	3.08 (A)

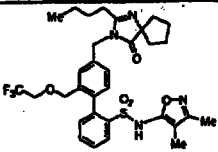
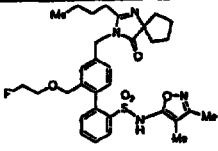
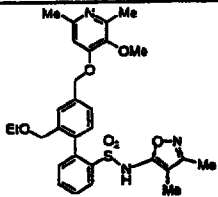
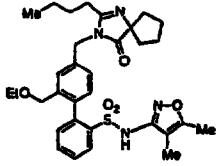
196		3-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-5-ethyl-2-propyl-3H-imidazole-4-carboxamide	40B	12, NH ₃ (16)	522	>98	2.79 (C)
197		3-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-N-methyl-3H-benzimidazole-4-carboxamide	29	12, MeNH ₂ (32)	560	>98	3.31 (A)
198		3-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-N,N-dimethyl-3H-benzimidazole-4-carboxamide	29	12, Me ₂ NH (5)	574	>98	3.42 (A)
199		2-((2'-((3,4-Dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)propylamine-3-pyridinecarboxylic acid	P18	4, 15, 7 (34)	521	99	23.4 (B)
200		4'-((3,5-Dibutyl-1H-1,2,4-triazol-1-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide	P18	4, 7 (77)	522	99	28.4 (B)
201		N-(3,4-Dimethyl-5-isoxazolyl)-4'-((1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl)-[1,1'-biphenyl]-2-sulfonamide	P18	21, 7 (55)	533	99	21.5 (B)

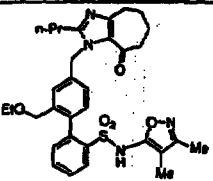
202		4'-[(2,7-Diethyl-5H-pyrazolo[1,5-b][1,2,4]triazol-5-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide	P18	4, 7 (33)	505	99	21.8 (B)
203		N-[2-Butyl-3-[[2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-3,4-dihydro-4-oxo-6-quinazolinyl]-N'-methyl-N'-(1-methylethyl)urea	P18	4, 7 (71)	657	99	28.7 (B)
204		2-[[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]propylamino]-N-methyl-3-pyridinecarboxamide	199	12 (98)	534	99	23.8 (B)
205		4'-[(3-Methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide	P18	4 (59); 8 (74)	494	98	6.99 (I)
206		N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide	20A	2 (82); 4 (82); 8 (81)	619	96	14.02 (E)
207		N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide	20A	2 (82); 21, 9 (54)	658	97	15.56 (E)

208		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide	P2	4 (45); 8 (63)	538	99	10.60 (E)
209		3-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl-2-ethyl-5-methyl-3H-imidazole-4-carboxamide	P19	22 (35); 7 (67)	494	>97	7.96 (E)
210		4'-[(2-Butyl-3,4-dihydro-4-oxo-3-quinazolinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide	P18	4, 7 (13)	543	98	25.52 (I)
211		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl[1,1'-biphenyl]-2-sulfonamide	17	5 (36)	660	98	14.51 (I)
212		N'-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-4-yl]methyl-N-methyl-N'-(1-oxopentyl)-L-valinamide	20A	17 (80); 5 (95); 6 (95); 7 (42)	680	97	13.13, 14.66 (F) migrates as diastereomers

213		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(4,4-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide	3	5 (58)	660	>98	24.60 (B)
214		4'-[(3,5-Dibutyl-1H-1,2,4-triazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide	20A	4 (52); 9 (57)	647	97	23.53 (I)
215		N-[2-[[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-yl)methyl]methylamino]ethyl]acetamide	23B	5, 12 (4); 8 (15)	644	89	2.69 (A)
216		4-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-acetic acid ethyl ester	113	8, EtOH (13)	602	90	3.41 (A)
217		N'-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N'-[1-oxopentyl]-N-propyl-L-valinamide	101	12 (65)	583	>98	14.97 (F)

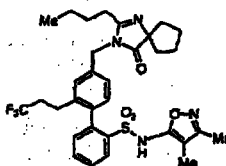
218		N'-((2'-((3,4-dimethyl-5-isoxazolyl)amino)sulfonyl)[1,1'-biphenyl]-4-yl)methyl)-N'-((1-oxopentyl)-N-((tetrahydro-2-furanyl)methyl))-L-valinamide	101	12 (43)	625	>98	14.06 (F)
219		2'-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-4'-((2-ethyl-4-quinolinyl)oxy)methyl[1,1'-biphenyl]-2-sulfonamide	P10	4 (90); 8 (65)	549	98	1.68 (D)
220		N-(3,4-Dimethyl-5-isoxazolyl)-4'-((2-ethyl-4-quinolinyl)oxy)methyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-sulfonamide	P9	4, 8 (30)	582	97	1.75 (D)
221		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2'-chloro-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide	P10	4, 8 (42)	570	98	2.13 (D)
222		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-((2-methylpropoxy)methyl)[1,1'-biphenyl]-2-sulfonamide	42A	2 (67); 4 (49); 7 (85)	621	>98	23.07 (B)
223		4'-((2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethyl-5-isoxazolyl)-2'-((ethylsulfonyl)amino)[1,1'-biphenyl]-2-sulfonamide	123	24 (33)	642	98	14.32 (E)

224		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(2,2,2-trifluoroethoxy)methyl][1,1'-biphenyl]-2-sulfonamide	P2A	4, F ₃ CCH ₂ OH (89); 14 (76); 1 (67); 11 (95); 2 (90); 4 (85); 7 (85)	647	>97	20.15 (E)
225		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(2-fluoroethoxy)methyl][1,1'-biphenyl]-2-sulfonamide	P2A	4, FCH ₂ CH ₂ OH (72); 14 (65); 1 (68); 11 (95); 2 (85); 4 (80); 7 (90)	611	>97	15.94 (E)
226		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxymethyl]-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide	P2A	4, EtOH (77); 14 (80); 1 (75); 11 (95); 2 (77); 22 (43); 7 (74)	552	97	12.60 (E)
227		4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2-ethoxy)methyl][1,1'-biphenyl]-2-sulfonamide	P2A	4, EtOH (77); 14 (80); 1 (70); 11 (98); 2 (80); 4 (83); 7 (86)	593	>98	18.75 (E)

228		N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide	P2A	4, EtOH (77); 14 (80); 1 (75); 11 (95); 2 (77); 21 (0); 7 (0)	591	>98	20.07 (B)
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Example 229

5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3,3,3-trifluoropropyl) [1,1'-biphenyl]-2-sulfonamide



10

A. 3-Bromo-4-methoxybenzaldehyde dimethyl acetal

A solution of 3-bromo-4-methoxybenzaldehyde (19.2 g, 89 mmol) and trimethylorthoformate (14.8 ml, 140 mmol) in 150 ml methanol was treated at RT with concentrated sulfuric acid (10 μ l). After stirring for 16 h, the mixture was treated with potassium carbonate (70 mg) and the solvent was evaporated. The residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated to provide 229A (22.6 g) as a brown oil, which was used without further purification.

20

B. 4-Methoxy-3-(3,3,3-trifluoropropyl)benzaldehyde dimethyl acetal

A solution of **229A** (15.8 g, 60 mmol) in dry THF (120 ml) was added to magnesium turnings (4.1 g, 170 mmol) at RT. The mixture was heated to 60 °C for 5 min, which initiated an exothermic reaction. The heating bath was removed and the mixture was allowed to reflux gently. Upon subsidence of the reaction (approximately 5 min), the mixture was heated to reflux for an additional 20 min and then was allowed to cool to RT. The clear green supernatant was transferred via canula away from excess magnesium and into a separate flask containing copper (I) iodide (575 mg, 3.0 mmol) under a nitrogen atmosphere. To this mixture was added 1-iodo-3,3,3-trifluoropropane (15 g, 67 mmol) and the resulting mixture was allowed to stir for 16 h, during which time a thick white precipitate developed. Aqueous ammonium chloride solution, ethyl acetate, and hexanes were added, and the organic layer was dried over sodium sulfate. Evaporation followed by silica gel chromatography of the residue using 3:1 hexanes/ethyl acetate as eluant provided 7.7 g of a mobile, slightly yellow oil, which was a 6:1 (mol ratio) mixture of **229B** and 4-methoxybenzaldehyde dimethyl acetal, as determined by proton NMR. This mixture was used without further purification.

20 C. 4-Methoxy-3-(3,3,3-trifluoropropyl)benzaldehyde

The **229B** mixture (7.7 g) was subjected to hydrochloric acid hydrolysis according to General Method 19. The resulting crude yellow oil (8.0 g) was a 6:1 mixture (mol ratio) of **229C** and 4-methoxybenzaldehyde, and was used without further purification.

25

D. 4-Hydroxy-3-(3,3,3-trifluoropropyl)benzaldehyde

A solution of the **229C** mixture (8.0 g, 35 mmol) in dichloromethane (5 ml) was treated at 0 °C with boron tribromide (55 ml of a 1.0 M solution in dichloromethane). The mixture was allowed to warm to RT and was stirred for 2 h. Aqueous 10% dipotassium hydrogen phosphate solution was added, and the aqueous layer was extracted with two portions of

30

dichloromethane. The combined organic extracts were dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel using 3:1 hexanes/ethyl acetate as eluant to provide 2.0 g of **229D** as an orange solid (contaminated with 4-hydroxybenzaldehyde).

5

E. 4-(trifluoromethanesulfonyloxy)-3-(3,3,3-trifluoropropyl)benzaldehyde

A solution of the **229D** mixture (2.0 g, 9 mmol) and N,N-diisopropylethylamine (2.4 ml, 14 mmol) in dichloromethane (40 ml) was treated dropwise at -78 °C with trifluoromethanesulfonic anhydride (1.9 ml, 11 mmol). The mixture was stirred at that temperature for 15 min following the completion of the addition. Aqueous sodium bicarbonate solution was added and the mixture was stirred and allowed to warm to RT. The layers were separated and the aqueous layer was extracted with two portions of dichloromethane. The combined organic extracts were dried over sodium sulfate, evaporated, and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluant to provide first recovered **229D** (540 mg), and then the product fraction (380 mg) as an orange oil. The product fraction was a 2:1 mixture (mol ratio) of **229E** and 4-(trifluoromethanesulfonyloxy)benzaldehyde, as determined by proton NMR.

F. N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(3,3,3-trifluoropropyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

A solution of **229E** (380 mg, 1.1 mmol) and [2-[(3,4-dimethyl-5-isoxazolyl)[(2-(trimethylsilyl)ethoxy)methyl]amino]-sulfonyl]phenyl]boronic acid (925 mg, 2.2 mmol) in dioxane (10 ml) was sparged with nitrogen for 15 min. Tetrakis(triphenylphosphine)palladium(0) (130 mg, 0.11 mmol) was added, followed by powdered potassium phosphate (460 mg, 2.2 mmol). The mixture was heated at 85 °C for 5 h, then the solvent was evaporated.

The residue was chromatographed on silica gel using hexanes/ethyl acetate as eluant to provide the product fraction (550 mg) as an orange oil. The product fraction was a 2:1 mixture (mol ratio) of **229F** and the corresponding 2'-H product, as judged by proton NMR.

5

G. N-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-(3,3,3-trifluoropropyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

The **229F** mixture (550 mg, 0.9 mmol) was subjected to sodium borohydride reduction according to General Method 14. The crude residue was chromatographed directly on silica gel using 3:1 hexanes/ethyl acetate as eluant to provide the product fraction (355 mg) as an amber oil. The product fraction was a 2:1 mixture (mol ratio) of **229G** and the corresponding 2'-H product, as judged by proton NMR.

15

H. N-(3,4-Dimethyl-5-isoxazolyl)-4'-(methanesulfonyloxy)methyl-2'-(3,3,3-trifluoropropyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

The **229G** mixture (350 mg, 0.63 mmol) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude product **229H** was used directly in the next step.

20

I. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(3,3,3-trifluoropropyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

25

229H was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude residue was chromatographed on silica gel using 2:1 hexanes/ethyl acetate as eluant to provide the product fraction (370 mg) as a slightly orange oil. The product fraction was a 2:1 mixture (mol ratio) of **229I** and the corresponding 2'-H product, as judged by proton NMR

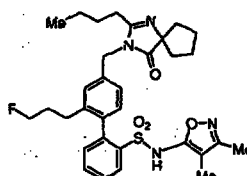
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J. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3,3,3-trifluoropropyl) [1,1'-biphenyl]-2-sulfonamide

5 The **229I** mixture was deprotected according to General Method 8. The crude product (which contained the 2'-H contaminant) was purified by reverse-phase preparative HPLC, followed by extraction with ethyl acetate from pH 8 potassium phosphate buffer. Finally, silica gel chromatography using 2:1 hexanes/acetone as eluant provided the title compound (120 mg)
 10 as a white foam; LRMS m/z 631 (ESI+ mode); HPLC retention time 3.78 min (Method C); HPLC purity >98%.

Example 230

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3-fluoropropyl) [1,1'-biphenyl]-2-sulfonamide



20 A. Methyl 3-(2-propenyl)-4-(trifluoromethanesulfonyloxy)benzoate
 Methyl 4-hydroxy-3-(2-propenyl)benzoate (12.0 g, 62.4 mmol, prepared according to W.J. Greenlee, et. al., WO 91/11999) was treated with trifluoromethanesulfonic anhydride according to the procedure of Example 229, Step E. The crude product was chromatographed on silica
 25 gel using 3:1 hexanes/ethyl acetate as eluant to yield 17.4 g of **230A** as a yellow oil.

B. Methyl 3-(3-hydroxypropyl)-4-
(trifluoromethanesulfonyloxy)benzoate

Borane-THF complex (1.0 M solution in THF, 32 ml, 32 mmol) was added to a solution of 230A (8.5 g, 26 mmol) in THF at 0 °C. The mixture
5 was stirred at RT for 16h and then cooled to 0 °C. A 1.0 M solution of sodium/potassium phosphate buffer (pH 7, 50 ml) was added, followed by 30% aqueous hydrogen peroxide (9.0 ml). The mixture was allowed to warm to RT, then water and EtOAc were added. The organic layer was dried over sodium sulfate and evaporated. The crude product was
10 chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to yield 4.3 g of 230B as a yellow oil.

C. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(3-hydroxypropyl)-4'-
(methoxycarbonyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-
15 biphenyl]-2-sulfonamide

Suzuki coupling of 230B (1.3 g, 3.8 mmol) according to the procedure of Example 229, step F, provided 230C (750 mg) as an orange oil following silica gel chromatography using 1:1 hexanes/ethyl acetate as eluant.

D. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(3-fluoropropyl)-4'-
(methoxycarbonyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-
20 biphenyl]-2-sulfonamide

A solution of 230C (750 mg, 1.3 mmol) in dichloromethane (3 ml)
25 was treated at -78 °C with (diethylamino)sulfur trifluoride (0.21 ml, 1.6 mmol). The mixture was allowed to warm to RT. After 15 min, water was added and the aqueous layer was extracted with two portions of dichloromethane. The organic extracts were dried over sodium sulfate, concentrated, and the residue was chromatographed on silica gel using 2:1
30 hexanes/ethyl acetate as eluant to provide 230D (175 mg) as a yellow oil.

E. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(3-fluoropropyl)-4'-(hydroxymethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

A solution of **230D** (175 mg, 0.3 mmol) in THF (5 ml) was treated with DIBAL-H (0.53 ml of a 1.5 M solution in toluene, 0.8 mmol) at -78 °C. The temperature was allowed to rise to -25 °C and the mixture was stirred for 2 h. Water (2 ml) and ether (10 ml) were added and the mixture was stirred at RT for 2 h. The mixture was filtered and the filtrate concentrated to provide crude **230E** (110 mg) as a colorless oil.

10

F. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(3-fluoropropyl)-4'-(methanesulfonyloxy)methyl-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

230E (110 mg, 0.2 mmol) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude product **230F** was used directly in the next step.

G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(3-fluoropropyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

20

230F was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4, to provide **230G** (124 mg) as a colorless oil, which was used without further purification.

H. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3-fluoropropyl) [1,1'-biphenyl]-2-sulfonamide

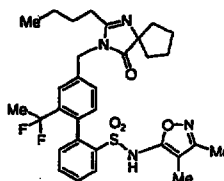
230G (124 mg, 0.2 mmol) was deprotected according to General Method 8 (EtOH). The crude product was purified by silica gel chromatography using 1:1 hexanes/ethyl acetate as eluant provided the

30

title compound (23 mg) as a white foam; LRMS m/z 595 (ESI+ mode); HPLC retention time 2.10 min (Method D); HPLC purity >98%.

Example 231

- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,1-difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl) [1,1'-biphenyl]-2-sulfonamide



10

A. 5-Bromo-2-(trifluoromethanesulfonyloxy)acetophenone

5-Bromo-2-hydroxyacetophenone (3.3 g, 15 mmol) was treated with trifluoromethanesulfonic anhydride according to the procedure of Example 229, Step E. The crude residue was taken up in ether and washed twice
15 with 10% aqueous potassium dihydrogenphosphate solution and once with brine. The ether solution was dried over magnesium sulfate and concentrated to provide crude **231A** (4.7 g) as an orange oil, which was used without further purification.

20 B. 3-(1,1-Difluoroethyl)-4-(trifluoromethanesulfonyloxy)bromobenzene

231A (4.4 g, 13 mmol) was treated at RT with neat (diethylamino)sulfur trifluoride (2.5 ml, 19 mmol) and the resulting solution was stirred at RT for 40 h. The mixture was poured onto ice, aqueous sodium bicarbonate solution was added, and the mixture was
25 extracted with three portions of dichloromethane. The combined extracts were dried over sodium sulfate and concentrated, and the residue was chromatographed on silica gel using 5:1 hexanes/ethyl acetate as eluant to provide **231B** (4.0 g) as an orange oil.

C. 3-(1,1-Difluoroethyl)-4-(trifluoromethanesulfonyloxy)benzaldehyde

A solution of **231B** (3.8 g, 10 mmol) and DMF (1.2 ml, 15 mmol) in dry THF (60 ml) was treated dropwise at -78 °C with n-butyllithium (5.0 ml of a 2.5 M solution in hexanes, 13 mmol). 10% aqueous potassium dihydrogenphosphate solution was added and the resulting mixture was allowed to warm to RT. 1:1 hexanes/ethyl acetate and brine were added and the organic layer was collected, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using 3:1 hexanes/ethyl acetate as eluant to provide recovered **231B** (1.4 g), followed by **231C** (1.0 g), which was an orange oil.

D. 2'-(1,1-Difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl)-4'-formyl-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

Suzuki coupling of **231C** (1.0 g, 3.2 mmol) according to the procedure of Example 229, step F, provided **231D** (640 mg) as an orange oil following silica gel chromatography using 3:1 hexanes/ethyl acetate as eluant.

E. 2'-(1,1-Difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl)-4'-hydroxymethyl-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

231D (640 mg, 1.2 mmol) was subjected to sodium borohydride reduction according to General Method 14. The crude residue was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide **231E** (550 mg) as a brown oil.

F. 2'-(1,1-Difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl)-4'-(methanesulfonyloxy)methyl-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

231E (360 mg, 0.7 mmol) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude product **231F** was used directly in the next step.

- 5 G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,1-difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

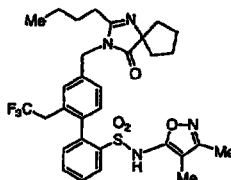
231F was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude residue was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide **231G** (170 mg) as a yellow oil.

- 15 H. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,1-difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl)-[1,1'-biphenyl]-2-sulfonamide

231G (150 mg, 0.2 mmol) was deprotected according to General Method 8 (EtOH). The crude product was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide the title compound (36 mg) as a white foam; LRMS m/z 599 (ESI+ mode); HPLC retention time 3.58 min (Method A); HPLC purity >98%.

Example 232

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2,2-trifluoroethyl)-N-(3,4-dimethylisoxazol-5-yl) [1,1'-biphenyl]-2-sulfonamide



A. Methyl 4-bromo-3-(bromomethyl)benzoate

Methyl 4-bromo-3-methylbenzoate (20 g, 87 mmol) was brominated according to General Method 13. The crude orange solid was triturated with 4:1 hexanes/ethyl acetate to provide **232A** (14.7 g) as a white solid.

5

B. Methyl 4-bromo-3-(2,2,2-trifluoroethyl)benzoate

Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (3.1 ml, 25 mmol) was added to a mixture of **232A** (7.0 g, 22 mmol) and copper(I) iodide (420 mg, 2.2 mmol) in DMF (45 ml) under a nitrogen atmosphere. The mixture was heated to 85 °C for 16 h. The mixture was cooled to RT and the solvent was evaporated. Hexanes and brine were added, and the organic layer was dried over sodium sulfate and concentrated to give a yellow solid (6.0 g), which contained **232A** and **232B**.

The solid was dissolved in DMF (15 ml) and stirred at RT with potassium acetate (1.0 g, 10 mmol) for 3 h. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated, and the residue was chromatographed on silica gel using 4:1 hexanes/ethyl acetate as eluant to provide **232B** (3.4 g) as a white solid.

20

C. N-(3,4-Dimethylisoxazol-5-yl)-4'-(methoxycarbonyl)-2'-(2,2,2-trifluoroethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

Suzuki coupling of **232B** (1.8 g, 5.9 mmol) according to the procedure of Example 229, step F, provided **232C** (1.3 g) as a yellow solid following silica gel chromatography using 3:1 hexanes/ethyl acetate as eluant.

25

D. N-(3,4-Dimethylisoxazol-5-yl)-4'-hydroxymethyl-2'-(2,2,2-trifluoroethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

232C (1.3 g, 2.2 mmol) was treated with DIBAL-H according to the
5 procedure of Example 230, step E, to provide 232D (650 mg) as an oil
following silica gel chromatography using 3:1 hexanes/ethyl acetate as
eluant.

E. N-(3,4-Dimethylisoxazol-5-yl)-4'-(methanesulfonyloxy)methyl-2'-(2,2,2-trifluoroethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

232D (650 mg, 1.1 mmol) was converted to the corresponding
methanesulfonate ester according to General Method 3. The entire crude
product 232E was used directly in the next step.

15

F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2,2,2-trifluoroethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

232E was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one
20 according to General Method 4. The crude residue was chromatographed
on silica gel using 2:1 hexanes/ethyl acetate as eluant to provide 232F
(440 mg) as a yellow oil.

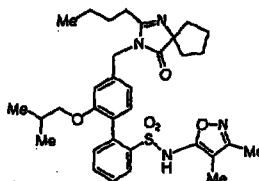
G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2,2,2-trifluoroethyl) [1,1'-biphenyl]-2-sulfonamide

232F was deprotected according to General Method 8 (EtOH). The
crude product was purified by reverse-phase preparative HPLC, followed
by an extraction with ethyl acetate from pH 5 sodium phosphate buffer to
30 provide the title compound (78 mg) as a white foam; LRMS m/z 617 (ESI+
mode); HPLC retention time 1.69 min (Method H); HPLC purity >98%.

Example 233

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-[(2-methyl)propoxy] [1,1'-biphenyl]-2-sulfonamide

5

**A. 2-Bromo-5-methylphenol**

10 A solution of sodium nitrite (2.8 g, 41 mmol) in 5 ml water was added rapidly with stirring to an ice-cooled mixture of 6-amino-m-cresol (5.0 g, 41 mmol) and 48% hydrobromic acid (17 ml, 100 mmol). The temperature was kept below 10 °C by addition of ice chips. The diazonium salt solution was then added in portions over a period of 30 min to a

15 boiling mixture of copper(I) bromide (6.4 g, 22 mmol) and 48% hydrobromic acid (5 ml). The resulting mixture was refluxed for an additional 30 min, then was cooled and extracted with ether (2x100ml). The combined organic extracts were washed with water, dried over magnesium sulfate, and evaporated. The residue was chromatographed on

20 silica gel using 98:2 hexanes/ethyl acetate to afford 233A (1.6 g, 20%) as an oil.

B. 4-Bromo-3-(2-methylpropoxy)toluene

Isobutyl bromide (0.70 ml, 6.4 mmol) was added to a mixture of

25 233A (800 mg, 4.3 mmol), potassium carbonate (1.2 g, 8.5 mmol), and DMF (2 ml). The mixture was stirred for 36 h at 45 °C and was then cooled and concentrated under vacuum. The residue was added to water and extracted with ethyl acetate (3 X 50ml). The combined organic extracts

were washed with water and dried over sodium sulfate to give **233B** (960 mg, 93%) as an oil.

C. 4-Bromomethyl-2-(2-methylpropoxy)-1-bromobenzene

5 **233B** (960 mg, 3.9 mmol) was subjected to NBS bromination according to General Method 13. The crude **233C** (1.1 g, 86%) was used without further purification.

10 D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-(2-methylpropoxy)-1-bromobenzene

233C (1.1 g, 3.4 mmol) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude residue was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide **233D** (550 mg, 40%) as an oil.

15

E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-[(2-methyl)propoxy]-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

20 Suzuki coupling of **233D** (550 mg, 1.3 mmol) according to General Method 1 provided **233E** (660 mg, 60%) as an oil following silica gel chromatography using 2:3 hexanes/ethyl acetate as eluant.

25 F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-[(2-methyl)propoxy][1,1'-biphenyl]-2-sulfonamide

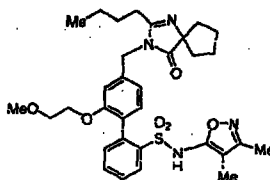
233E (660 mg) was deprotected according to General Method 8 (EtOH). Water was added to the crude residue and the mixture was extracted with ethyl acetate (3 X 50ml). The combined organic extracts were washed with water and dried and evaporated. The residue was
30 chromatographed on silica gel using 1:1 hexanes/ethyl acetate to provide the title compound (270 mg, 60%) as a white solid, mp 58-61°C ; LRMS

m/e 607 (ESI+ mode); HPLC retention time 26.32 min (Method B); HPLC purity >98%.

5

Example 234

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-methoxyethoxy) [1,1'-biphenyl]-2-sulfonamide



10

A. 4-Bromo-3-(2-methoxyethoxy)toluene

233A (800 mg, 4.3 mmol) was alkylated with 1-bromo-2-methoxyethane (0.89 g, 6.4 mmol) according to the procedure of Example 15 233, step B, to give **234A** (840 mg, 81%) as an oil.

B. 4-Bromomethyl-2-(2-methoxyethoxy)-1-bromobenzene

234A (840 mg, 3.4 mmol) was subjected to NBS bromination according to General Method 13. The crude **234B** (510 mg, 46%) was used 20 without further purification.

C. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-(2-methoxyethoxy)-1-bromobenzene

234B (510 mg, 1.6 mmol) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude 25 residue was chromatographed on silica gel using 4:1 hexanes/ethyl acetate as eluant to provide **234C** (600 mg, 88%) as an oil.

D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-methoxyethoxy)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

Suzuki coupling of **234C** (600 mg, 1.4 mmol) according to General

- 5 Method 1 provided **234D** (550 mg, 54%) as an oil following silica gel chromatography using 2:3 hexanes/ethyl acetate as eluant.

E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-methoxyethoxy)[1,1'-biphenyl]-2-sulfonamide

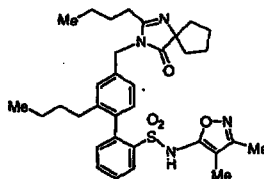
10

234D (550 mg, 0.8 mmol) was deprotected according to General Method 8 (EtOH). Water was added to the crude residue and the mixture was extracted with ethyl acetate (3 X 50ml). The combined organic extracts were washed with water and dried and evaporated. The residue

15 was purified by reverse-phase preparative HPLC to provide the title compound (125 mg, 30%) as a white solid, mp 55-58 °C ; MS m/e 609 (ESI+ mode); HPLC retention time 22.75 min (Method B); HPLC purity >98%.

Example 235

- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-butyl-N-(3,4-dimethylisoxazol-5-yl)[1,1'-biphenyl]-2-sulfonamide



25

A. 4-Bromo-3-(1-butenyl)benzonitrile

2A (4.0 g, 19 mmol) was reacted with propyltriphenylphosphonium bromide following the procedure of Example 27, step A. The crude residue

was chromatographed on silica gel using 9:1 hexanes/ethyl acetate to afford **235A** (2.2 g, 49%) as an E/Z mixture.

B. 4-Bromo-3-butylbenzonitrile

5 A mixture of **235A** (2.2 g, 9.3 mmol) and 210 mg of PtO_2 in 40 ml EtOH was hydrogenated at 35 PSI for 40 min. Filtration and concentration gave 1.4 g of **235B** (62%).

C. 4-Bromo-3-butylbenzaldehyde

10 **235B** (1.4 g, 5.8 mmol) was treated with DIBAL-H according to General Method 14 to provide crude **235C** (1.2 g, 90%) as an oil.

D. N-(3,4-Dimethyl-5-isoxazolyl)-2'-butyl-4'-formyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

15 **235C** (1.2 g, 5.1 mmol) was subjected to Suzuki coupling according to General Method 1 to provide **235D** as a crude oil.

E. N-(3,4-Dimethyl-5-isoxazolyl)-2'-butyl-4'-hydroxymethyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

20 **235D** (entire sample) was reduced with sodium borohydride in methanol according to General Method 11 to provide **235E** (1.4 g, 50% from **235C**) as an oil.

F. N-(3,4-Dimethyl-5-isoxazolyl)-4'-(methanesulfonyl)oxymethyl-2'-butyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

25 **235E** (1.4 g, 2.5 mmol) was converted to the corresponding methanesulfonate ester according to General Method 3 to provide **235F** (1.4 g, 90%) as an oil.

30

G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-butyl-N-[(2-trimethylsilyl)ethoxymethyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

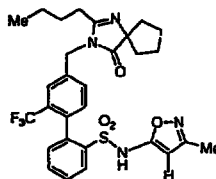
235F (1.3 g, 2.1 mmol) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. 235G (1.3 g, 85%) was produced as an oil.

H. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-butyl-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

235G (1.2 g, 1.7 mmol) was deprotected according to General Method 7. The crude product was purified by reverse-phase preparative HPLC to provide the title compound (620 mg, 62%) as a solid, mp 58-61 °C; MS m/e 591 (ESI+ mode); HPLC retention time 26.67 min (Method B); HPLC purity >98%.

Example 236

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3-methylisoxazol-5-yl)-2'-trifluoromethyl[1,1'-biphenyl]-2-sulfonamide



A. [2-[(3-methyl-5-isoxazolyl)][[(2-trimethylsilyl)ethoxy]methyl]aminol sulfonylphenyl]boronic acid

25B (14 g, 31 mmol) was converted to the corresponding boronic acid according to the procedure of Example 45, step B. The crude product 236A (16.5 g, estimated purity 60%) was produced as an amber oil, and was used without further purification.

B. 4'-Formyl-N-(3-methyl-5-isoxazolyl)-2'-trifluoromethyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

236A (8.0 g, 20 mmol) was subjected to Suzuki coupling with P6
5 according to General Method 1. Silica gel chromatography using 2:1 hexanes/ethyl acetate as eluant provided 1.8 g of a mixture of 236B and a highly crystalline impurity. Trituration with 2:1 hexanes/ethyl acetate to remove this impurity provided 236B (1.0 g) as an orange oil.

10 C. 4'-Hydroxymethyl-N-(3-methyl-5-isoxazolyl)-2'-trifluoromethyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

236B (880 mg, 1.6 mmol) was reduced with sodium borohydride (0.3 eq.) in ethanol according to General Method 11. The crude residue was chromatographed on silica gel using 2:1 hexanes/ethyl acetate as eluant to
15 provide 236C (450 mg) as a yellow oil.

D. 4'-(Methanesulfonyloxy)methyl-N-(3-methyl-5-isoxazolyl)-2'-trifluoromethyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

20 236C (450 mg) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude product 236D was used in the next reaction step.

25 E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]N-(3-methyl-5-isoxazolyl)-2'-trifluoromethyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

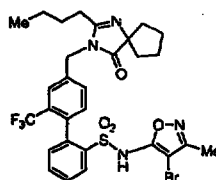
236D was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude residue was chromatographed on silica gel using 2:1 hexanes/acetone as eluant to
30 provide 236E (170 mg) as a yellow oil.

F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl] N-(3-methyl-5-isoxazolyl)-2'-trifluoromethyl [1,1'-biphenyl]-2-sulfonamide

236E (100 mg) was deprotected according to General Method 8 (ethanol) to provide the title compound as the hydrochloride salt (77 mg), which required no additional purification: MS m/e 589 (ESI+ mode); HPLC retention time 3.72 min (Method C); HPLC purity 97%.

Example 237

10 N-(4-Bromo-3-methyl-5-isoxazolyl)-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-trifluoromethyl [1,1'-biphenyl]-2-sulfonamide

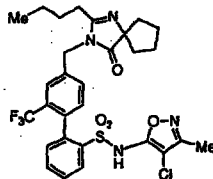


15

Bromine (33 mg/ml solution in acetic acid, 18 mg, 0.11 mmol) was added in portions to a solution of 236 (53 mg, 0.09 mmol) and sodium acetate (35 mg, 0.42 mmol) in acetic acid (4 ml) at RT. The solvent was evaporated, aqueous potassium phosphate solution was added, and the pH was adjusted to 8. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. The residue was chromatographed on silica gel using 1:3 hexanes/acetone as eluant to provide the title compound (31 mg) as a white powder following lyophilization: MS m/e 667, 669 (ESI+ mode); HPLC retention time 3.83 min (Method C); HPLC purity 94%.

Example 238

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-chloro-3-methyl-5-isoxazolyl)-2'-trifluoromethyl [1,1'-biphenyl]-2-sulfonamide



5

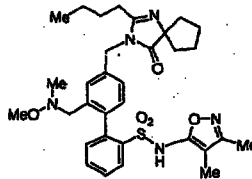
Clorox bleach (5.25% sodium hypochlorite solution, 225 μ l) was added in portions to a solution of 236 (32 mg, 0.054 mmol) in THF (2 ml) at RT. The solvent was evaporated and the residue was purified by reverse-phase preparative HPLC, followed by preparative thin-layer silica gel chromatography using 10% methanol in dichloromethane as eluant, providing the title compound (1.0 mg) as a white powder following lyophilization: MS m/e 624 (ESI+ mode); HPLC retention time 3.53 min (Method A); HPLC purity 95%.

15

Example 239

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(N-methoxy-N-methylaminomethyl) [1,1'-biphenyl]-2-sulfonamide

20



- A. N-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-(N-methoxy-N-methylaminomethyl)-N-[(2-methoxyethoxy)methyl] [1,1'-biphenyl]-2-sulfonamide

P21 (230 mg, 0.48 mmol) was subjected to reductive amination with
5 N-methoxy-N-methylamine according to General Method 5, yielding **239A**
(169 mg, 69%) as an oil.

- B. 4'-Bromomethyl-N-(3,4-dimethyl-5-isoxazolyl)-2'-(N-methoxy-N-methylaminomethyl)-N-[(2-methoxyethoxy)methyl] [1,1'-biphenyl]-2-sulfonamide

10 **239A** (165 mg, 0.33 mmol) was converted to the corresponding
bromide according to General Method 2, yielding **239B** (174 mg, 92%) as
an oil following silica gel chromatography using hexanes/ethyl acetate as
eluant.

- 15 C. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(N-methoxy-N-methylaminomethyl)-N-[(2-methoxyethoxy)methyl] [1,1'-biphenyl]-2-sulfonamide

239B (170 mg, 0.30 mmol) was used to alkylate 2-butyl-1,3-
20 diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude
residue was chromatographed on silica gel using hexanes/ethyl acetate as
eluant to provide **239C** (155 mg, 72%) as a yellow oil.

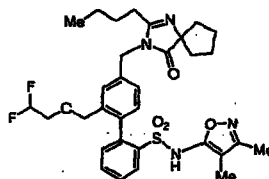
- 25 D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(N-methoxy-N-methylaminomethyl) [1,1'-biphenyl]-2-sulfonamide

239C (150 mg) was deprotected according to General Method 7. The
crude product was purified by reverse-phase preparative HPLC to provide
the title compound (117 mg, 89%) as a white solid: MS m/e 608 (ESI+
30 mode); HPLC retention time 17.75 min (Method E); HPLC purity >97%.

Example 240

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2-difluoroethoxymethyl)-N-(3,4-dimethylisoxazol-5-yl)[1,1'-biphenyl]-2-sulfonamide

5

A. Methyl 4-bromo-3-(hydroxymethyl)benzoate

10 A mixture of methyl 4-bromo-3-methylbenzoate (168 g, 735 mmol), N-bromosuccinimide (141 g, 792 mmol), benzoyl peroxide (3.5 g, 15 mmol), and carbon tetrachloride (900 ml) was refluxed for 17 h. The mixture was cooled and filtered, and the filtrate was washed once with water and once with brine. The filtrate was then dried over sodium sulfate and
15 concentrated to provide an orange oil (261 g), which was judged (¹H NMR) be about 70 mol% methyl 4-bromo-3-(bromomethyl)benzoate.

The crude orange oil (261 g) was dissolved in 400 ml DMF and treated with potassium acetate (74 g, 750 mmol) at 0 °C. The mixture was allowed to warm to RT and was stirred for 54 h. The solvent was
20 evaporated and the residue was taken up in 1:1 hexanes ethyl acetate and washed twice with half-saturated brine, then once with saturated brine. The organic layer was dried over sodium sulfate and concentrated to provide a new orange oil (208 g), which was judged to contain about 70 mol% methyl 4-bromo-3-(acetoxymethyl)benzoate.

25 The crude acetate mixture (208 g) was dissolved in methanol (1 l) and treated with potassium carbonate (12 g, 87 mmol) at 0 °C. The mixture was allowed to warm to RT and was stirred for 18 h. The solvent was evaporated and the residue was treated with 130 ml 1N hydrochloric

acid at 0 °C. The mixture was extracted once with 1:3 hexanes/ethyl acetate, once with 1:1 hexanes/ethyl acetate, and once with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated, and the residue was chromatographed on silica gel using 2:1
5 hexanes/ethyl acetate. The product fractions were combined, evaporated, and triturated with 1:1 hexanes/ethyl acetate to provide **240A** (102 g) as a white solid.

B. Methyl 4-bromo-3-[(tetrahydro-2H-pyran-2-yl)oxymethyl]benzoate
10 p-Toluenesulfonic acid hydrate (50 mg) was added to a solution of **240A** (10 g, 41 mmol) and 3,4-dihydro-2H-pyran (10 g, 120 mmol) in dichloromethane (100 ml) at 0 °C. After 1h aqueous sodium bicarbonate solution was added, the layers were separated, and the organic layer was dried over sodium sulfate and concentrated to provide crude **240B** (16 g)
15 as a slightly yellow oil.

C. N-(3,4-Dimethyl-5-isoxazolyl)-4'-methoxycarbonyl-2'-[(tetrahydro-2H-pyran-2-yl)oxymethyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide
20 Crude **240B** (10 g, approximately 25 mmol) was subjected to Suzuki coupling according to General Method 1. Silica gel chromatography using 3:1 hexanes/ethyl acetate as eluant provided **240C** (14 g) as a yellow oil.

D. N-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-[(tetrahydro-2H-pyran-2-yl)oxymethyl]-N-(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide
25

A solution of **240C** (10.5 g, 17 mmol) in THF (200 ml) was treated with DIBAL-H (23.4 ml of a 1.5 M solution in toluene, 35 mmol) at -78 °C. The temperature was allowed to rise to -25 °C and the mixture was
30 stirred for 2 h. Water (10 ml) and ether (100 ml) were added and the mixture was stirred at RT for 2 h. Ethyl acetate and hexanes were added,

and the mixture was washed three times with aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated to provide crude **240D** (9 g) as a deep maroon-colored oil.

- 5 **E.** N-(3,4-Dimethyl-5-isoxazolyl)-4'-(methanesulfonyloxy)methyl-2'-[(tetrahydro-2H-pyran-2-yl)oxymethyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

240D (4.5 g, 7.5 mmol) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude
10 product **240E** was used in the next reaction step.

- F.** 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(tetrahydro-2H-pyran-2-yl)oxymethyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

15 **240E** was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude residue was chromatographed on silica gel using 3:2 hexanes/ethyl acetate as eluant to provide **240F** (6.0 g) as a slightly yellow oil.

- 20 **G.** 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-hydroxymethyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

 A solution of **240F** (6.0 g, 7.7 mmol) and 2N hydrochloric acid (6 ml, 12 mmol) in methanol (150 ml) was stirred for 16 h at RT. The mixture
25 was neutralized with aqueous sodium bicarbonate solution and the methanol was evaporated. Aqueous sodium bicarbonate solution was added and the mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated to provide **240G** (5.0 g) as a crude orange oil.

30

H. 2'-Bromomethyl-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

240G (590 mg, 0.85 mmol) was converted to the corresponding
5 bromide according to General Method 2, providing 240H (373 mg, 58%) as
a yellow oil following silica gel chromatography using hexanes/ethyl
acetate as eluant.

I. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2-difluoroethoxymethyl)-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

10

240H (370 mg, 0.49 mmol) was used to alkylate 2,2-difluoroethanol
according to General Method 4. 240I (209 mg, 56%) was produced as a
yellow oil following silica gel chromatography using hexanes/ethyl acetate
15 as eluant.

J. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2-difluoroethoxymethyl)-N-(3,4-dimethylisoxazol-5-yl)[1,1'-biphenyl]-2-sulfonamide

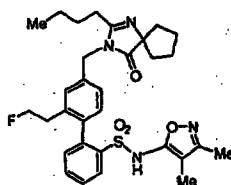
20

240I (205 mg, 0.27 mmol) was deprotected according to General
Method 7. The crude product was purified by reverse-phase preparative
HPLC to provide the title compound (104 mg, 60%) as a white solid: MS
m/e 629 (ESI+ mode); HPLC retention time 17.18 min (Method E); HPLC
purity >97%.

25

Example 241

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-fluoroethyl)[1,1'-biphenyl]-2-sulfonamide



A. Methyl 3-(2-hydroxyethyl)-4-(trifluoromethanesulfonyloxy)benzoate

5 An ozone/oxygen gas mixture was bubbled through a solution of **230A** (8.3 g, 26 mmol) in methanol (100 ml) at -78°C until a light blue color persisted. The solution was sparged with nitrogen to remove excess ozone, then triphenylphosphine (10 g, 38 mmol) was added in portions. The cooling bath was removed and the mixture was allowed to warm RT, then was concentrated. Ethanol (100 ml) was added to the residue and the resulting mixture was cooled to 0°C . Sodium borohydride (1.9 g, 51 mmol) was added. After 1h, the mixture was allowed to warm to RT and the solvent was evaporated. The residue was taken up in 10% aqueous potassium dihydrogen phosphate solution and was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated, and the residue chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to yield **241A** (4.5 g) as a colorless oil.

B. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2-hydroxyethyl)-4'-(methoxycarbonyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

Suzuki coupling of **241A** (4.5 g, 14 mmol) according to the procedure of Example 229, step F, provided **241B** (4.1 g) as a yellow solid following silica gel chromatography using 1:1 hexanes/ethyl acetate as eluant.

C. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2-fluoroethyl)-4'-(methoxycarbonyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

A mixture of **241B** (1.0 g, 1.8 mmol) and (diethylamino)sulfur trifluoride (0.71 ml, 5.4 mmol) was stirred at RT for 20 h. The mixture was poured onto ice. Aqueous sodium bicarbonate solution was added and the mixture was extracted with two portions of dichloromethane. The organic extracts were dried over sodium sulfate, concentrated, and the residue was chromatographed on silica gel using 1:1 hexanes/ethyl acetate as eluant to provide **241C** (230 mg) as a yellow oil.

D. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2-fluoroethyl)-4'-(hydroxymethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide
241C (230 mg, 0.41 mmol) was treated with DIBAL-H according to the procedure of Example 230, step E, to provide crude **241D** (320 mg) as a yellow oil

E. N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2-fluoroethyl)-4'-(methanesulfonyloxy)methyl-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide
241D (320 mg) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude product **241E** was used directly in the next step.

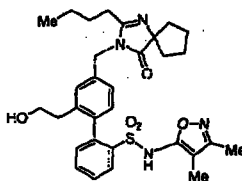
F. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(2-fluoroethyl)-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide
241E was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4, to provide **241F** (300 mg) as a yellow oil, which was used without further purification.

G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-fluoroethyl) [1,1'-biphenyl]-2-sulfonamide

Crude **241F** (300 mg) was deprotected according to General Method 8 (ethanol). The crude product was purified by silica gel chromatography using hexanes/ethyl acetate as eluant provided the title compound (16 mg) as a tan solid; LRMS m/z 581 (ESI+ mode); HPLC retention time 2.05 min (Method H); HPLC purity 97%.

Example 242

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide



A. N-(3,4-Dimethyl-5-isoxazolyl)-4'-methoxycarbonyl-2'-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

Pyridinium *p*-toluenesulfonate (2 mg) was added to a solution of **241B** (1.0 g, 1.8 mmol) and 3,4-dihydro-2H-pyran (0.48 ml, 5.4 mmol) in dichloromethane (4 ml) at 0 °C. After 48h aqueous sodium bicarbonate solution was added, the layers were separated, and the organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using 2:1 hexanes/ethyl acetate to provide **242A** (320 mg) as a slightly yellow oil.

B. N-(3,4-Dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-2'-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

242A (320 mg, 0.50 mmol) was treated with DIBAL-H according to the procedure of Example 230, step E, to provide crude 242B (250 mg) as a yellow oil.

5 C. N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(methanesulfonyloxy)methyl]-2'-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]-N-[(2-trimethylsilyl)ethoxymethyl] [1,1'-biphenyl]-2-sulfonamide

242B (250 mg) was converted to the corresponding methanesulfonate ester according to General Method 3. The entire crude
10 product 242C was used in the next reaction step.

D. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

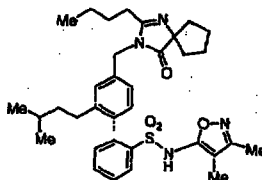
15 242C was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude 242D was used without further purification.

E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(2-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide

20 242D was deprotected according to General Method 8 (ethanol). The crude product was purified by silica gel chromatography using 3% methanol in dichloromethane as eluant to provide the title compound (45
25 mg) as a white solid following lyophilization: MS m/e 579 (ESI+ mode); HPLC retention time 1.42 min (Method H); HPLC purity >98%.

Example 243

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3-methylbutyl)[1,1'-biphenyl]-2-sulfonamide



A. 4-Bromo-3-(3-methyl-1-butenyl)benzonitrile

5 **2A** (2.0 g, 9.5 mmol) was reacted with isobutyltriphenylphosphonium bromide following the procedure of Example 27, step A. The crude residue was chromatographed on silica gel using 9:1 hexanes/ethyl acetate to afford **243A** (2.2 g, 91%) as an E/Z mixture.

10

B. 4-Bromo-3-(3-methylbutyl)benzonitrile

A mixture of **243A** (2.2 g) and 220 mg of PtO₂ in 30 ml EtOH was hydrogenated at 35 PSI for 20 min. Filtration and concentration gave 1.9 g of **243B** (86%).

15

C. 4-Bromo-3-(3-methylbutyl)benzaldehyde

243B (1.9 g) was treated with DIBAL-H according to General Method 14 to provide crude **243C** (810 mg, 43%) as an oil.

20 D. N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(3-methylbutyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

243C (810 mg) was subjected to Suzuki coupling according to General Method 1 to provide **243D** as a crude oil.

25 E. N-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-(3-methylbutyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

243D (entire sample) was reduced with sodium borohydride in methanol according to General Method 11 to provide **243E** (490 mg, 30%

from 243C) as an oil following silica gel chromatography using hexanes/ethyl acetate as eluant.

5 F. 4'-Bromomethyl-N-(3,4-dimethyl-5-isoxazolyl)-2'-(3-methylbutyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

243E (490 mg) was converted to the corresponding bromide according to General Method 2 to provide 243F (430 mg, 78%) as an oil following silica gel chromatography using hexanes/ethyl acetate as eluant.

10 G. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(3-methylbutyl)-N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

243F (430 mg) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. 243G (300 mg, 58%) was
15 produced as an oil following silica gel chromatography using hexanes/ethyl acetate as eluant.

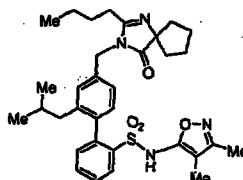
20 H. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3-methylbutyl)[1,1'-biphenyl]-2-sulfonamide

243G was deprotected according to General Method 7. The crude product was purified by reverse-phase preparative HPLC to provide the title compound (165 mg, 63%) as a white solid: mp 50-53 °C; MS m/e 605 (ESI+ mode); HPLC retention time 27.42 min (Method B); HPLC purity
25 >97%.

Example 244

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide

30



A. 4-[(2-Methyl-2-propenyl)oxyl]benzonitrile

5 A mixture of 4-cyanophenol (9.0 g, 75 mmol), potassium carbonate (21 g, 150 mmol), and DMF (50 ml) was treated with methallyl bromide (7.8 ml, 77 mmol) at 0 °C. The mixture was stirred at RT for 16 h, then was added to water and extracted with ethyl acetate (3 X 100 ml). The combined organic extracts were washed with water and dried and
10 evaporated to give **244A** (13 g, 99%) as an oil.

B. 4-Cyano-2-(2-methyl-2-propenyl)phenol

A solution of **244A** (13 g, 75 mmol) and BHT (165 mg) in 1,2,4-trichlorobenzene (40 ml) was heated at 200 °C for 5 days. The mixture
15 was cooled and diluted with ethyl acetate, then the organic layer was extracted with 10% NaOH solution (3 X 200ml). The aqueous phase was made acidic with hydrochloric acid and extracted with ether (3 X 100ml). The combined ether extracts were washed with water and dried and evaporated. The residue was chromatographed on silica gel using 9:1
20 hexanes/ethyl acetate to afford **244C** (5.8 g, 45%) as a solid.

C. 4-Cyano-2-(2-methylpropyl)phenol

A mixture of **244B** (1.1 g) and 110 mg of PtO₂ in 20 ml EtOH was hydrogenated at 35 PSI for 15 min. Filtration and concentration gave
25 0.73 g of **244C** (66%).

D. 4-Hydroxy-3-(2-methylpropyl)benzaldehyde

244C (0.73 g) was treated with DIBAL-H according to General Method 14 to provide crude 244D (530 mg, 72%) as an oil.

- 5 E. 3-(2-Methylpropyl)-4-(trifluoromethanesulfonyloxy)benzaldehyde
244D (530 mg) was converted to the corresponding trifluoromethanesulfonate ester according to the procedure of Example 229, step E. The residue was chromatographed on silica gel using 4:1 hexanes/ethyl acetate to give 244E (295 mg, 33%) as an oil.
- 10 F. N-(3,4-Dimethyl-5-isoxazolyl)-4'-formyl-2'-(2-methylpropyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide
Suzuki coupling of 244E (295 mg) according to the procedure of Example 229, step F, provided 244F (170 mg, 36%) as a yellow solid following silica gel chromatography using hexanes/ethyl acetate as eluant.
- 15 G. N-(3,4-Dimethyl-5-isoxazolyl)-4'-hydroxymethyl-2'-(2-methylpropyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide
244F (170 mg) was reduced with sodium borohydride in methanol according to General Method 11 to provide 244G (67 mg, 39%) as an oil.
- 20 H. 4'-Bromo-methyl-N-(3,4-dimethyl-5-isoxazolyl)-2'-(2-methylpropyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide
244G (67 mg) was converted to the corresponding bromide according to General Method 2 to provide 244H (42 mg, 56%) as an oil.
- 25 I. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2-methylpropyl)-N-[(2-methoxyethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide
244H (42 mg) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. 244I (36 mg, 45%) was produced
- 30

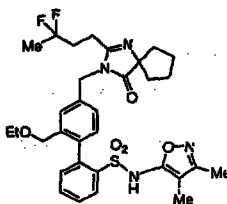
as an oil following silica gel chromatography using hexanes/ethyl acetate as eluant.

- J. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2-methylpropyl)-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide

244I (36 mg) was deprotected according to General Method 7. The crude product was purified by reverse-phase preparative HPLC to provide the title compound (25 mg, 86%) as a white solid: mp 58-61 °C; MS m/e 591 (ESI+ mode); HPLC retention time 28.21 min (Method B); HPLC purity >98%.

Example 245

- 4'-[[2-(3,3-Difluorobutyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide



- A. Methyl 1-[(3,3-difluorobutanoyl)amino]cyclopentane-1-carboxylate
- A solution of 4,4-Difluoropentanoic acid (600 mg, 4.4 mmol, prepared according to Larsson, U.; Carlson, R.; Leroy, J. *Acta Chem. Scand.* **1993**, *47*, 380-90) in dichloromethane (10 ml) was treated at RT with oxalyl chloride (4.4 ml of a 2.0 M solution in dichloromethane, 8.8 mmol) and DMF (10 µl). After 20 min the mixture was evaporated and 10 ml fresh dichloromethane was added. The mixture was cooled to 0 °C and methyl 1-aminocyclopentane-1-carboxylate hydrochloride (1.6 g, 8.8 mmol)

was added, followed by triethylamine (3.6 ml, 26 mmol) and DMAP (10 mg). The mixture was stirred at RT for 3 hours. Aqueous sodium bicarbonate solution was added and the mixture was extracted three times with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using 1:2 hexanes/ethyl acetate as eluant to give **245A** (520 mg, 46%) as an orange oil.

B. 2-(3,3-Difluorobutyl)-1,3-diazaspiro[4.4]non-1-en-4-one

245A (520 mg, 2.0 mmol) was treated according to the procedure of Example 22, step B. The crude residue was chromatographed on silica gel using 1:3 hexanes/ethyl acetate as eluant to yield **245B** (150 mg, 33%) as a yellow oil.

C. 4'-[[2-(3,3-Difluorobutyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl]methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(ethoxymethyl)-N-(2-methoxyethoxy)methyl[1,1'-biphenyl]-2-sulfonamide

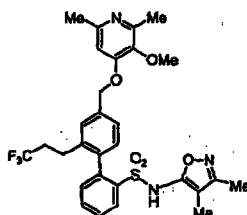
245B (75 mg, 0.42 mmol) was alkylated with 4'-bromomethyl-N-(3,4-dimethyl-5-isoxazolyl)-2'-ethoxymethyl-N-(2-methoxyethoxy)methyl[1,1'-biphenyl]-2-sulfonamide (prepared as described in Example 226) according to General Method 4. Crude **245C** (220 mg) was used without further purification.

D. 4'-[[2-(3,3-Difluorobutyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl]methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide

245C (220 mg) was deprotected according to General Method 8 (EtOH). The crude product was purified by preparative thin-layer silica gel chromatography using 1:1 hexanes/acetone to provide the title compound (57 mg) as a white lyophilized powder; MS m/e 629 (ESI+ mode); HPLC retention time 3.79 min (Method A); HPLC purity 96%.

Example 246

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)][1,1'-biphenyl]-2-sulfonamide

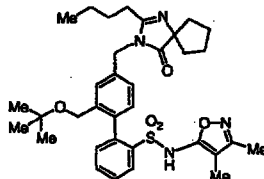


- 10 A. **N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)-N-[(2-trimethylsilyl)ethoxymethyl]][1,1'-biphenyl]-2-sulfonamide**
229H (400 mg, 0.60 mmol) was used to alkylate 3-methoxy-2,6-dimethyl-4-(4H)-pyridinone according to General Method 22. The crude
 15 product was purified by silica gel chromatography using 1:2 hexanes/ethyl acetate as eluant to provide **246A** (130 mg) as a slightly yellow oil.

- 20 B. **N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)][1,1'-biphenyl]-2-sulfonamide**
246A (130 mg, 0.18 mmol) was deprotected according to General Method 8 (EtOH). The crude product was purified by silica gel chromatography using 5% methanol in chloroform as eluant to provide the
 25 title compound (82 mg) as a pale orange powder after lyophilization; MS m/e 590 (ESI+ mode); HPLC retention time 3.35 min (Method A); HPLC purity 97%.

Example 247

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-[(1,1-dimethylethoxy)methyl][1,1'-biphenyl]-2-sulfonamide



5

A. Methyl 4-bromo-3-[(1,1-dimethylethoxy)methyl]benzoate

To a solution of **240A** (4.90 g, 20 mmol) in 40 ml cyclohexane and 20
 10 ml dichloromethane was added t-butyl 2,2,2-trichloroacetimidate (4.81 g,
 22 mmol) followed by 0.4 ml boron trifluoride diethyl etherate. The
 mixture was stirred at RT for 4 hours. 1 g solid sodium bicarbonate was
 added and the mixture was stirred for 10 min. The mixture was
 chromatographed directly on silica gel eluting with 20:1 hexanes/ethyl
 15 acetate to give compound **247A** as an oil (5.33 g, 88%).

B. N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(1,1-dimethylethoxy)methyl]-4'-methoxycarbonyl-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

247A (5.3 g, 17.5 mmol) was subjected to Suzuki coupling according
 20 to General Method 1. Silica gel chromatography using hexanes/ethyl
 acetate as eluant provided **247B** (6.4 g, 88%) as an oil.

C. N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(1,1-dimethylethoxy)methyl]-4'-hydroxymethyl-N-(2-trimethylsilyl)ethoxymethyl[1,1'-biphenyl]-2-sulfonamide

25

247B (6.4 g, 10.7 mmol) was reduced with DIBAL-H according to the procedure of Example 230, step E, to provide crude **247C** (5.5 g, 89%) as an orange oil.

- 5 D. 4'-Bromomethyl-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(1,1-dimethylethoxy)methyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

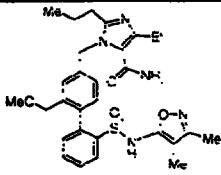
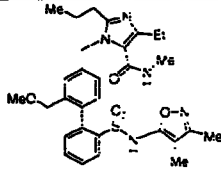
247C (5.5 g, 9.6 mmol) was converted to the corresponding bromide according to General Method 2, providing **247D** (5.6 g, 92%) as a yellow oil
10 following silica gel chromatography using hexanes/ethyl acetate as eluant.

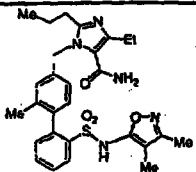
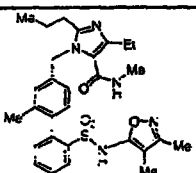
- E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(1,1-dimethylethoxy)methyl]-N-[(2-trimethylsilyl)ethoxymethyl][1,1'-biphenyl]-2-sulfonamide

15 **247D** (380 mg, 0.60 mmol) was used to alkylate 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one according to General Method 4. The crude residue was chromatographed on silica gel using hexanes/ethyl acetate as eluant to provide **247E** (410 mg, 92%) as a slightly yellow oil.

- 20 E. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(1,1-dimethylethoxy)methyl][1,1'-biphenyl]-2-sulfonamide

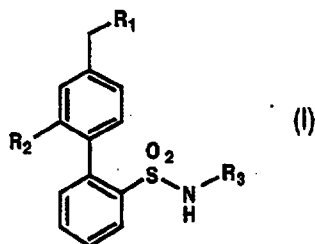
247E (410 mg, 0.55 mmol) was deprotected with TBAF according to General Method 10. The crude product was purified by reverse-phase
25 preparative HPLC to provide the title compound (230 mg, 66%) as a white solid: MS m/e 621 (ESI+ mode); HPLC retention time 20.97 min (Method E); HPLC purity 96%.

E X A M P L E	S T R U C T U R E	N A M E	S T A R T I N G M A T E R I A L	General Methods Applied (yield, %)	M/z (MH) ⁺	HPLC % Purity	HPLC ret time, min (method)
248		4'-[4-Ethyl-1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methoxymethyl][1,1'-biphenyl]-4-yl)methyl]-2-propyl-1H-imidazole-5-carboxamide	P2	22 (39); 8, EtOH, 15 (96); 12 (38)	566	95	2.79 (C)
249		4'-[4-Ethyl-1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methoxymethyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide	P2	22 (39); 8, EtOH, 15 (96); 12 (34)	580	96	2.90 (C)

250		4'-[4-Ethyl-1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-yl)methyl]-2-propyl-1H-imidazole-5-carboxamide	P13	22 (56); 8, EtOH, 15 (94); 12 (38)	536	95	2.90 (C)
251		4'-[4-Ethyl-1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide	P13	22 (56); 8, EtOH, 15 (94); 12 (37)	550	97	2.99 (C)

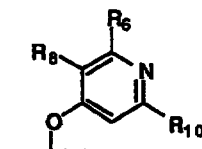
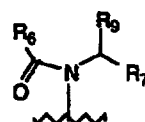
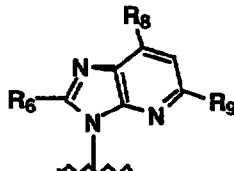
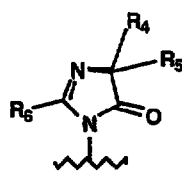
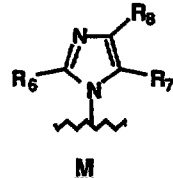
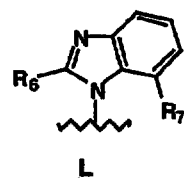
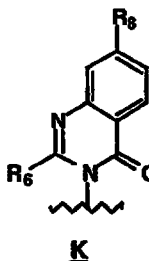
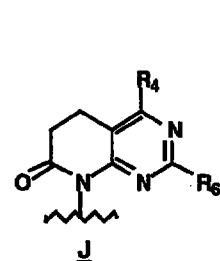
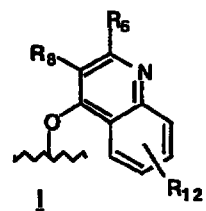
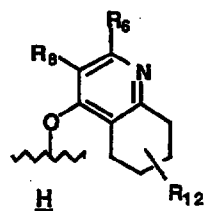
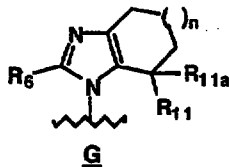
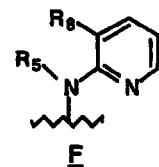
What is claimed is:

1. A compound of the following formula I or a salt thereof:

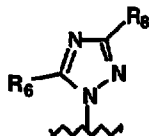


5

wherein:

R₁ is

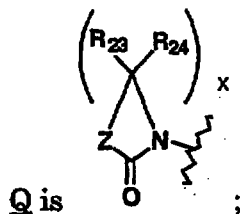
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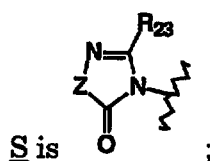
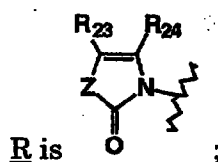


or



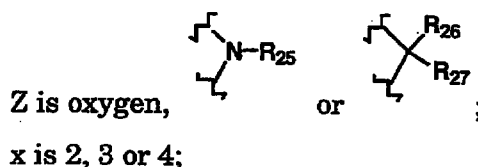
- R_2 is hydrogen, halogen, -CHO, alkyl, , haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, -CH(OR₁₃)(OR₁₄), -(CH₂)_wY; with the proviso that when R_1 is B, R_2 is not hydrogen,
- 5 halogen, alkyl, haloalkyl, alkoxy, hydroxyalkyl, nitro, -(CH₂)_wNR₁₉R₂₀ or NHSO₂R₂₂;
- R_3 is heteroaryl;
- R_4 and R_5 are each independently alkyl, cycloalkyl or alkoxyalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl, cyclohexyl,
- 10 tetrahydrofuranyl or tetrahydropyranyl ring;
- R_6 is alkyl, haloalkyl, cycloalkyl, alkoxy or alkoxyalkyl;
- R_7 is -CO₂R₁₅, -(C=O)NR₁₆R₁₇, -CH₂OH, tetrazolyl, oxadiazolyl or triazolyl wherein said tetrazolyl, oxadiazolyl or triazolyl may optionally be substituted with hydrogen, alkyl or halogen;
- 15 R_8 , R_9 , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylthioalkyl, alkoxy or alkoxyalkyl;
- R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;
- 20 R_{13} and R_{14} are alkyl or together form a five to six-membered ring;
- R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, cycloalkyl or aryl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;
- n is 1 or 2;
- w is 0, 1, or 2;
- 25 Y is -COOH, -COOR₁₈, -NR₁₉R₂₀, -NR₂₁(C=O)R₂₂, -NR₂₁(C=O)NR₁₉R₂₀, -NR₂₁(C=O)OR₁₈, -NR₂₁SO₂R₂₂, -SO₂R₂₂, Q, R or S;





R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

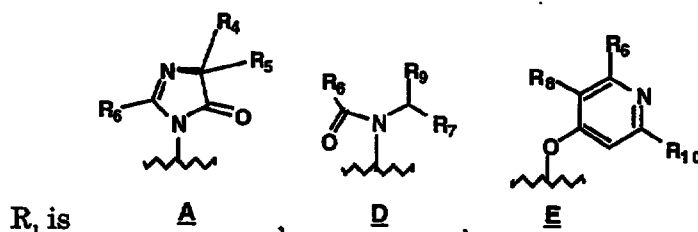
R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

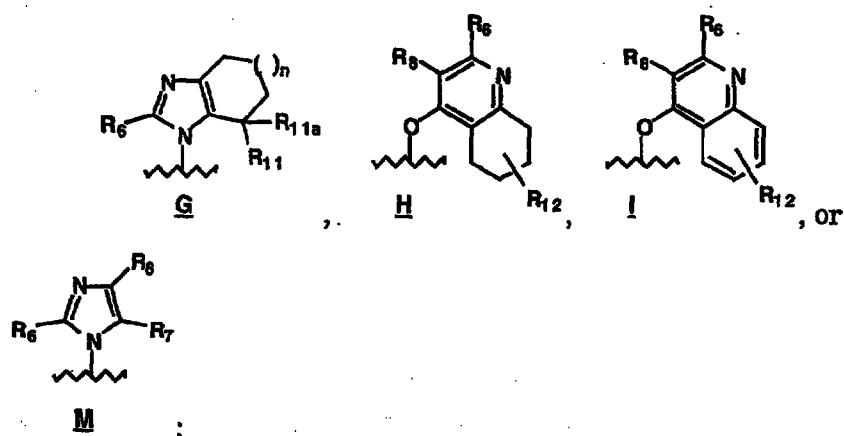


R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

wherein said rings; aryl alone or as part of another group; or heteroaryl alone or as part of another group may each optionally be substituted by one or more hydrogen, halogen, cyano, alkyl, alkoxy, nitro or trifluoromethyl groups.

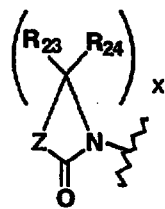
2. A compound of claim 1, wherein:





- R_2 is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(\text{CH}_2)_w\text{Y}$;
- 5 R_3 is isoxazolyl pyridizynyl, pyrazinyl or pyrimidinyl, each optionally substituted with one to three of the following substituents:
hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;
- R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;
- 10 R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;
 R_7 is $-\text{CO}_2R_{15}$, $-(\text{C}=\text{O})\text{NR}_{16}R_{17}$ or $-\text{CH}_2\text{OH}$;
 R_8 , R_9 , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;
- R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;
- 15 R_{16} , R_{16} and R_{17} are independently hydrogen, alkyl or cycloalkyl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;
- n is 1 or 2;
 w is 0, 1, or 2;
- 20 Y is $-\text{COOR}_{18}$, $-\text{NR}_{21}(\text{C}=\text{O})R_{22}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{NR}_{19}R_{20}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{OR}_{18}$, $-\text{NR}_{21}\text{SO}_2R_{22}$, $-\text{SO}_2R_{22}$ or Q ;

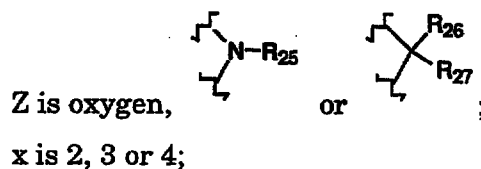




Q is

R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

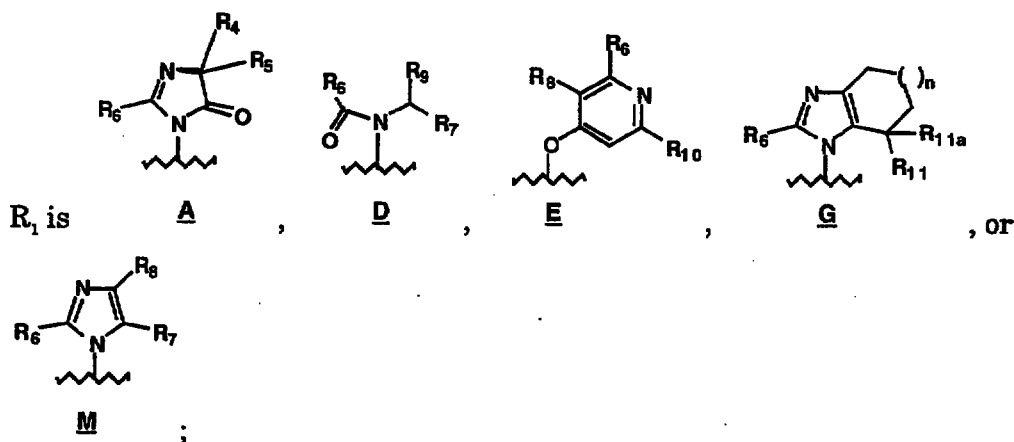
- 5 R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;



x is 2, 3 or 4;

- 10 R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring.

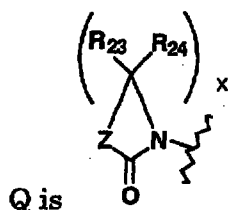
3. A compound of claim 1, wherein:



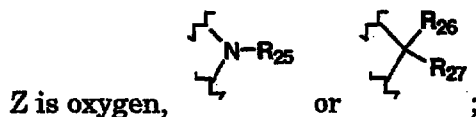
R_2 is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, hydroxyalkyl, or $-(CH_2)_w Y$;



- R_3 is isoxazolyl, optionally substituted with one or two of the following substituents: hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;
- R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;
- R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;
- R_7 is $-\text{CO}_2R_{15}$ or $-(\text{C}=\text{O})\text{NR}_{16}R_{17}$;
- R_8 , R_9 and R_{10} are each independently hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;
- 10 R_{11} and R_{11a} together form a carbonyl;
- R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, or cycloalkyl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;
- n is 2;
- w is 0, 1, or 2;
- 15 Y is $-\text{NR}_{21}(\text{C}=\text{O})R_{22}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{NR}_{19}R_{20}$, $-\text{NR}_{21}(\text{C}=\text{O})\text{OR}_{18}$, $-\text{NR}_{21}\text{SO}_2R_{22}$, $-\text{SO}_2R_{22}$ or Q ;



- R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;
- 20 R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

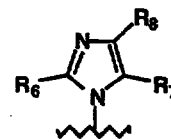
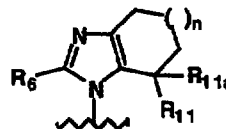
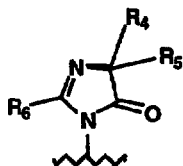


x is 2, 3 or 4;

- 25 R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring.



4. A compound of claim 1, wherein:



R_1 is A, E, G, or M;

R_2 is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl,

5 alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY$;

R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two of following substituents: alkyl or halogen;

R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;

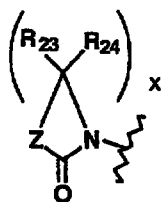
10 R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;

R_7 is $-(C=O)NR_{16}R_{17}$;

R_8 and R_{10} are independently H, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;
n is 2;

w is 0, 1, or 2;

15 Y is $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$ or Q;



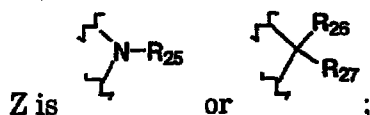
Q is ;

R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four-, five-, six- or to seven-membered heterocyclic ring;

20

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

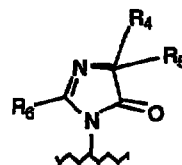




x is 2;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three-, four-, five-, six- or seven-membered cycloalkyl ring.

5. A compound of claim 1, wherein R_1 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two of following substituents: alkyl or halogen.

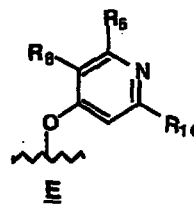


6. A compound of claim 5, wherein R_1 is

7. A compound of claim 6, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.

8. A compound of claim 6, wherein R_2 is $-\text{CH}_2\text{Y}$;

9. A compound of claim 8, wherein Y is Q;



10. A compound of claim 5, wherein R_1 is

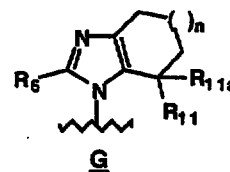
11. A compound of claim 10, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.



12. A compound of claim 10, wherein R_2 is $-\text{CH}_2\text{Y}$;

13. A compound of claim 12, wherein Y is Q;

5



14. A compound of claim 5, wherein R_1 is G

15. A compound of claim 14, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.

10

16. A compound of claim 14, wherein R_2 is $-\text{CH}_2\text{Y}$;

17. A compound of claim 16, wherein Y is Q;

15

18. A compound of claim 1, wherein R_2 is alkoxyalkyl alkyl, haloalkyl or haloalkoxyalkyl

19. A compound of claim 18, wherein R_2 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two of following substituents:
20 alkyl or halogen.

20. A compound of claim 1, wherein R_2 is $-\text{CH}_2\text{Y}$.

21. A compound of claim 20, wherein R_2 is isoxazol-5-yl or
25 isoxazol-3-yl independently substituted with two of following substituents:
alkyl or halogen.

22. A compound of claim 20, wherein Y is Q.



23. A compound of claim 22, wherein R₃ is isoxazol-5-yl or isoxazol-3-yl independently substituted with two of following substituents: alkyl or halogen.

5

24. A compound of claim 1, wherein said compound is selected from the group consisting of:

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(methylamino)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(2-pyrazinyl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3-chloro-2-pyrazinyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;



4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(3,6-dimethyl-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide;

5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-N-(3-methoxy-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

(S)-N-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pentanamide;

15 N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[2-(2-methoxyethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

20 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[2-(2-ethoxymethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(2-oxo-1-pyrrolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

(S)-2-[N-[2'-[[N-(3-Methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;

30 (S)-2-[N-[2'-[[N-(4-Bromo-3-methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;



- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-
-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;
4'-[(7-Methoxycarbonyl-2-ethoxybenzimidazol-1-yl)methyl]-
N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
5 4'-[(7-Carboxy-2-ethoxybenzimidazol-1-yl)methyl]-N-
(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
4'-[(7-Methoxycarbonyl-2-ethylbenzimidazol-1-yl)methyl]-N-
(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
4'-[(7-Carboxy-2-ethylbenzimidazol-1-yl)methyl]-N-
10 (3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-
(methoxycarbonyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-
isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-
15 (carboxy)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-
biphenyl]-2-sulfonamide;
2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(N-
methylcarbamoyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-
[1,1'-biphenyl]-2-sulfonamide;
20 2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(N,N-
dimethylcarbamoyl)benzimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-
isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(1,3,5-trimethylpyrazol-4-yl)
[1,1'-biphenyl]-2-sulfonamide;
25 4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(3-methylisoxazol-5-yl) [1,1'-
biphenyl]-2-sulfonamide;
4'-[(5-Acetyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-
dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
4'-[(5-Methoxycarbonyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-
30 (3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;



- 4'-[(5-(N,N-dimethylcarbamoyl)-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-hydroxymethyl[1,1'-biphenyl]-2-sulfonamide
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidiny)methyl]-N-(3-methoxy-5-methyl-2-pyrazinyl)[1,1'-biphenyl]-2-sulfonamide;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-bromo-3-methyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidiny)methyl][1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(formylmethylamino)methyl][1,1'-biphenyl]-2-sulfonamide;
- N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylpropanamide;
- 20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclopropanecarbox-amide;
- N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,2-dimethylpropanamide;
- 25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbutanamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
methoxy-N-methylacetamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-4-pentynamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylcyclobutanecarboxamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3-dimethylbutanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
15 N,2,2-trimethylpropanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
methoxy-N-methylpropanamide;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
ethoxy-N-methylacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-2-furancarboxamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,4-dimethylpentanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[3,4-dimethyl-5-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
30 methylbenzamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-3-thiophenecarboxamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylcyclopentaneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylcyclohexanecarboxamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3-dimethylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
15 methylbenzeneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
fluoro-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
20 [[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
fluoro-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-
fluoro-N-methylbenzamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylcyclohexaneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
30 fluoro-N-methylbenzeneacetamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
fluoro-N-methylbenzeneacetamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-
fluoro-N-methylbenzeneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,N',N'-trimethylurea;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N'-
(1,1-dimethylethyl)-N-methylurea;

[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-
15 yl)methyl]methylcarbamic acid ethyl ester;

[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-
yl)methyl]methylcarbamic acid 2-methylpropyl ester;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3,3-trimethylbutanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-2-pyridinecarboxamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-3-pyridinecarboxamide;

30 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-3-pyridinecarboxamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,1-dimethyl-1H-pyrrole-2-carboxamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-1,2,3-thiadiazole-4-carboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,5-dimethyl-2-pyrazinecarboxamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3,5-trimethyl-4-isoxazolecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
15 N,3-dimethyl-2-thiophenecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,5-dimethyl-2-thiophenecarboxamide;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
cyano-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-
cyano-N-methylbenzamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
methoxy-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
30 chloro-N-methylbenzamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-chloro-N-methylbenzamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-chloro-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2,3-difluoro-N-methylbenzamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3,4-difluoro-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3,5-difluoro-N-methylbenzamide;

15 4-Acetyl-N-[[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-ethoxy-N-methyl-2-thiophenecarboxamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(propylsulfonyl)amino][1,1'-biphenyl]-2-sulfonamide;

N-[[2'-[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)-L-valine methyl ester;

30 N-[[2'-[[3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)-L-valine methyl ester;



N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-propyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

5 N-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide;

N2-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N2-(1-oxopentyl)-L-valinamide;

10 N2-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

N2-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N,N-dimethyl-N2-(1-oxopentyl)-L-valinamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(2,2,2-trifluoroethyl)amino]methyl][1,1'-biphenyl]-2-sulfonamide;

4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxylic acid;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-sulfonamide;

20 4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxylic acid methyl ester;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide;

2'-(Cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;



- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
- 5 2'-Cyano-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-methyl[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(2,2,2-trifluoroethyl)amino]methyl[1,1'-biphenyl]-2-sulfonamide;
- 10 N-[4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl]benzeneacetamide;
- 15 N-[4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl]-3,3-dimethylbutanamide;
- 2'-Amino-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-nitro[1,1'-biphenyl]-2-sulfonamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopropyl)-L-isoleucinamide;
- N2-(Cyclopropylcarbonyl)-N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-isoleucinamide;
- 25 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxo-3-phenylpropyl)-L-isoleucinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(3-methyl-1-oxobutyl)-L-isoleucinamide;
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- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxohexyl)-L-isoleucinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxobutyl)-L-isoleucinamide;
- 5 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxopropyl)-L-leucinamide;
- N2-(Cyclopropylcarbonyl)- N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-leucinamide;
- 10 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxo-3-phenylpropyl)-L-leucinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(phenylacetyl)-L-leucinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(3-methyl-1-oxobutyl)-L-leucinamide;
- 15 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxohexyl)-L-leucinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxobutyl)-L-leucinamide;
- 20 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxopropyl)-L-valinamide;
- N2-(Cyclopropylcarbonyl)- N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;
- 25 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxo-3-phenylpropyl)-L-valinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(phenylacetyl)-L-valinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(3-methyl-1-oxobutyl)-L-valinamide;
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- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxohexyl)-L-valinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxobutyl)-L-valinamide;
- 5 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-ethyl- N2-(1-oxopentyl)-L-valinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-hexyl- N2-(1-oxopentyl)-L-valinamide;
- N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-cyano[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- 10 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- 4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide;
- 15 N,N-Dimethyl-4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide;
- N-Methyl-4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide;
- 20 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide;
- 25 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide;



N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(methoxymethyl)[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

5 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide;

2'-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[[(5,6,7,8-tetrahydro-2-ethyl-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

10 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(phenoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

15 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(1H-pyrazol-1-ylmethyl)[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

N2-(Cyclopropylcarbonyl)-N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-L-valinamide;

20 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-N2-(1-oxobutyl)-L-valinamide;

N2-(Cyclopropylcarbonyl)-N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(methoxymethyl)[1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-L-valinamide;

25 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(methoxymethyl)[1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-N2-(1-oxobutyl)-L-valinamide;

N2-[[2-Chloro-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

30 N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;



N2-(Cyclobutylcarbonyl)-N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;

1-[[2-Chloro-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-4-ethyl-2-propyl-1H-imidazole-5-carboxylic acid;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(methylsulfonyl)amino][1,1'-biphenyl]-2-sulfonamide;

(S)-N-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-[(4-methyl-1-piperaziny]carbonyl]propyl]pentanamide;

(S)-N-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-[(4-methyl-1-piperaziny]carbonyl]propyl]pentanamide;

N-(3,3-Dimethylbutyl)-N2-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N2-(1-oxopentyl)-L-valinamide;

N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[(4-fluorophenyl)methyl]-N2-(1-oxopentyl)-L-valinamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(methylethoxy)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(propoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

4-Chloro-1-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

N-(3,4-Dimethyl-5-isoxazolyl)-2'-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(1,2-dihydro-2-oxo-1-pyridinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;



4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(1H-pyrazol-1-ylmethyl)[1,1'-biphenyl]-2-sulfonamide;

2-Butyl-4-chloro-1-[[2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-methyl-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-ethyl-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-ethyl-5,6,7,8-tetrahydro-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(2-propyl-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(5,6,7,8-tetrahydro-2,4-dimethyl-7-oxopyrido[2,3-d]pyrimidin-8-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Ethyl-4-quinolinyloxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyloxy)methyl]-4'-[(5,6,7,8-tetrahydro-2-ethyl-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

3-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-N-methyl-3H-benzimidazole-4-carboxamide;

1-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid phenylmethyl ester;

1-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 2-phenylethyl ester;

1-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 2-(2-oxo-1-pyrrolidinyloxy)ethyl ester;



1-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 3-(2-oxo-1-pyrrolidinyl)propyl ester;

2'-Cyano-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[2-ethyl-4-quinolinyl]oxy]methyl][1,1'-biphenyl]-2-sulfonamide;

2'-(Cyanomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

3-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-5-ethyl-N-methyl-2-propyl-3H-imidazole-4-carboxamide;

1-[[2-Chloro-2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-4-ethyl-2-propyl-1H-imidazole-5-carboxamide;

3-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-5-ethyl-2-propyl-3H-imidazole-4-carboxamide;

3-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethoxy-N-methyl-3H-benzimidazole-4-carboxamide;

3-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethoxy-N,N-dimethyl-3H-benzimidazole-4-carboxamide;

2-[[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]propylamino]-3-pyridinecarboxylic acid;

4'-[(3,5-Dibutyl-1H-1,2,4-triazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2,7-Diethyl-5H-pyrazolo[1,5-b][1,2,4]triazol-5-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

N-[2-Butyl-3-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-3,4-dihydro-4-oxo-6-quinazolinyl]-N'-methyl-N'-(1-methylethyl)urea;

2-[[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]propylamino]-N-methyl-3-pyridinecarboxamide;



- 4'-[[[(3-Methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
- 5 N-(3,4-Dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide;
- 10 3-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-2-ethyl-5-methyl-3H-imidazole-4-carboxamide;
- 4'-[(2-Butyl-3,4-dihydro-4-oxo-3-quinazolinyl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- N2-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(4,4-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 4'-[(3,5-Dibutyl-1H-1,2,4-triazol-1-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 25 N-[2-[[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-4-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-yl)methyl]methylamino]ethyl]acetamide;



4-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-
 [[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-acetic acid
 ethyl ester;

N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-
 5 4-yl)methyl]-N2-(1-oxopentyl)-N-propyl-L-valinamide;

N2-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-
 4-yl)methyl]-N2-(1-oxopentyl)-N-[(tetrahydro-2-furanyl)methyl]-L-
 valinamide;

2'-Chloro-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[[(2-ethyl-4-
 10 quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2-ethyl-4-quinolinyloxy)methyl]-
 2'-(trifluoromethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-chloro-
 N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
 dimethyl-5-isoxazolyl)-2'-[(2-methylpropoxy)methyl][1,1'-biphenyl]-2-
 sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
 dimethyl-5-isoxazolyl)-2'-[(ethylsulfonyl)amino][1,1'-biphenyl]-2-
 20 sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
 dimethyl-5-isoxazolyl)-2'-[(2,2,2-trifluoroethoxy)methyl][1,1'-biphenyl]-2-
 sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
 25 dimethyl-5-isoxazolyl)-2'-[(2-fluoroethoxy)methyl][1,1'-biphenyl]-2-
 sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-
 pyridinyloxy)methyl]-2'-ethoxymethyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-
 30 propyl-1-cycloheptimidazolyl)methyl]-2'-(ethoxymethyl)[1,1'-biphenyl]-2-
 sulfonamide;



4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3,3,3-trifluoropropyl) [1,1'-biphenyl]-2-sulfonamide;

5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3-fluoropropyl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,1-difluoroethyl)-N-(3,4-dimethylisoxazol-5-yl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2,2-trifluoroethyl)-N-(3,4-dimethylisoxazol-5-yl) [1,1'-biphenyl]-2-sulfonamide;

10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-[(2-methyl)propoxy] [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-methoxyethoxy) [1,1'-biphenyl]-2-sulfonamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-butyl-N-(3,4-dimethylisoxazol-5-yl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3-methylisoxazol-5-yl)-2'-trifluoromethyl[1,1'-biphenyl]-2-sulfonamide;

20 N-(4-Bromo-3-methyl-5-isoxazolyl)-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-trifluoromethyl [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-chloro-3-methyl-5-isoxazolyl)-2'-trifluoromethyl [1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(N-methoxy-N-methylaminomethyl) [1,1'-biphenyl]-2-sulfonamide;

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2-difluoroethoxymethyl)-N-(3,4-dimethylisoxazol-5-yl)[1,1'-biphenyl]-2-sulfonamide;



- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-fluoroethyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(3-methylbutyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(2-methylpropyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[[2-(3,3-Difluorobutyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;
- 10 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)[1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethylisoxazol-5-yl)-2'-[(1,1-dimethylethoxy)methyl][1,1'-biphenyl]-2-sulfonamide;
- 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methoxymethyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-
- 20 carboxamide;
- 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methoxymethyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;
- 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-
- 25 methyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;
- 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide; and salts thereof.

- 30 25. A compound of claim 1, wherein said compound is selected from the group consisting of:



4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(methylamino)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3-methyl-2-oxo-1-imidazolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-formyl-N-(3,4-dimethyl-5-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

(S)-N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pentanamide;

N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-dimethyl-3-isoxazolyl)-4'-[2-(2-methoxyethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-dimethyl-3-isoxazolyl)-4'-[2-(2-ethoxymethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;



4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-
 [(2-oxo-1-pyrrolidinyl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-
 2-sulfonamide;

4'-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-
 5 [(3-methyl-2-oxo-1-imidazolidinyl)methyl]-N-(4,5-dimethyl-3-
 isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

(S)-2-[N-[2'-[[N-(3-Methyl-5-isoxazolyl)amino]sulfonyl][1,1'-
 biphenyl]-4-yl)methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;

(S)-2-[N-[2'-[[N-(4-Bromo-3-methyl-5-isoxazolyl)amino]sulfonyl][1,1'-
 10 biphenyl]-4-yl)methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-
 -N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(7-Methoxycarbonyl-2-ethoxybenzimidazol-1-yl)methyl]-
 N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

15 4'-[(7-Carboxy-2-ethoxybenzimidazol-1-yl)methyl]-N-
 (4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(7-Methoxycarbonyl-2-ethylbenzimidazol-1-yl)methyl]-N-
 (4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(7-Carboxy-2-ethylbenzimidazol-1-yl)methyl]-N-
 20 (4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-
 (methoxycarbonyl)benzimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-
 isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-
 25 (carboxy)benzimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-
 biphenyl]-2-sulfonamide;

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(N-
 methylcarbamoyl)benzimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-
 [1,1'-biphenyl]-2-sulfonamide;

2'-[(3,3-Dimethyl-2-oxopyrrolidin-1-yl)methyl]-4'-[(2-ethoxy-7-(N,N-dimethylcarbamoyl)benzimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(3-methylisoxazol-5-yl)
5 [1,1'-biphenyl]-2-sulfonamide;

4'-[(5-Acetyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(5-Methoxycarbonyl-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

10 4'-[(5-(N,N-dimethylcarbamoyl)-2-n-propyl-4-chloroimidazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-hydroxymethyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-bromo-3-methyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(formylmethylamino)-methyl][1,1'-biphenyl]-2-sulfonamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylpropanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclopropanecarbox-amide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,2-dimethylpropanamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylbutanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-methoxy-N-methylacetamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-4-pentynamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-15 methylcyclobutanecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3-dimethylbutanamide;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,2,2-trimethylpropanamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-methoxy-N-methylpropanamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-ethoxy-N-methylacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-30 methyl-2-furancarboxamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,4-dimethylpentanamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-3-thiophenecarboxamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylcyclopentaneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
15 methylcyclohexanecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3-dimethylbenzamide;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methylbenzeneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
fluoro-N-methylbenzamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
fluoro-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-
30 fluoro-N-methylbenzamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methylcyclohexaneacetamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-fluoro-N-methylbenzeneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-fluoro-N-methylbenzeneacetamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-fluoro-N-methylbenzeneacetamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,N',N'-trimethylurea;

15 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-(1,1-dimethylethyl)-N-methylurea;

20 [[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]methylcarbamic acid ethyl ester;

[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]methylcarbamic acid 2-methylpropyl ester;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide;

30 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-2-pyridinecarboxamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-3-pyridinecarboxamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-3-pyridinecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,1-dimethyl-1H-pyrrole-2-carboxamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-
methyl-1,2,3-thiadiazole-4-carboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
15 N,5-dimethyl-2-pyrazinecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3,5-trimethyl-4-isoxazolecarboxamide;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,3-dimethyl-2-thiophenecarboxamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
N,5-dimethyl-2-thiophenecarboxamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
cyano-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-4-
30 cyano-N-methylbenzamide;



N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
methoxy-N-methylbenzamide;

5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-2-
chloro-N-methylbenzamide;

10 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
chloro-N-methylbenzamide;

15 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
2,3-difluoro-N-methylbenzamide;

N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
3,4-difluoro-N-methylbenzamide;

20 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-
3,5-difluoro-N-methylbenzamide;

4-Acetyl-N-[[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-
yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-
yl)methyl]-N-methylbenzamide;

25 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-
[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-3-
ethoxy-N-methyl-2-thiophenecarboxamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-
dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;



4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(propylsulfonyl)amino][1,1'-biphenyl]-2-sulfonamide;

5 N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)-L-valine methyl ester;

N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)-L-valine methyl ester;

10 N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(2-propyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-yl)methyl]-N,3,3-trimethylbutanamide;

15 N2-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N2-(1-oxopentyl)-L-valinamide;

N2-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

N2-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N,N-dimethyl-N2-(1-oxopentyl)-L-valinamide;

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2,2,2-trifluoroethyl)amino]methyl][1,1'-biphenyl]-2-sulfonamide;

4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxylic acid;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-sulfonamide;

4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxylic acid methyl ester;

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide;



- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide;
- 2'-(Cyanomethyl)-N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(cyanomethyl)-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(cyanomethyl)-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
- 2'-Cyano-N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-sulfonamide;
- N2-[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-2-methyl[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- 15 N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[(2,2,2-trifluoroethyl)amino]methyl][1,1'-biphenyl]-2-sulfonamide;
- N-[4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl]benzeneacetamide;
- 20 N-[4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl]-3,3-dimethylbutanamide;
- 25 2'-Amino-4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-nitro[1,1'-biphenyl]-2-sulfonamide;
- N2-[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopropyl)-L-isoleucinamide;
- 30



N2-(Cyclopropylcarbonyl)- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-isoleucinamide;

5 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxo-3-phenylpropyl)-L-isoleucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(3-methyl-1-oxobutyl)-L-isoleucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxohexyl)-L-isoleucinamide;

10 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxobutyl)-L-isoleucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxopropyl)-L-leucinamide;

15 N2-(Cyclopropylcarbonyl)- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-leucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxo-3-phenylpropyl)-L-leucinamide;

20 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(phenylacetyl)-L-leucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(3-methyl-1-oxobutyl)-L-leucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxohexyl)-L-leucinamide;

25 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxobutyl)-L-leucinamide;

N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl- N2-(1-oxopropyl)-L-valinamide;

30 N2-(Cyclopropylcarbonyl)- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;



- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl- N2-(1-oxo-3-phenylpropyl)-L-valinamide;
- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl- N2-(phenylacetyl)-L-valinamide;
- 5 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl- N2-(3-methyl-1-oxobutyl)-L-valinamide;
- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl- N2-(1-oxohexyl)-L-valinamide;
- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl- N2-(1-oxobutyl)-L-valinamide;
- 10 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-ethyl- N2-(1-oxopentyl)-L-valinamide;
- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-hexyl- N2-(1-oxopentyl)-L-valinamide;
- 15 N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-2-cyano[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- N2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-2-hydroxymethyl[1,1'-biphenyl]-4-yl)methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;
- 20 4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide;
- N,N-Dimethyl-4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide;
- 25 N-Methyl-4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-carboxamide;
- N-(4,5-dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(methoxymethyl)[1,1'-biphenyl]-2-
- 30 sulfonamide;



N-(4,5-dimethyl-3-isoxazolyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide;

N-(4,5-dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-methyl[1,1'-biphenyl]-2-sulfonamide;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-2-(methoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

N-(4,5-dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide;

2'-Chloro-N-(4,5-dimethyl-3-isoxazolyl)-4'-[[[5,6,7,8-tetrahydro-2-ethyl-4-quinolinyl]oxy]methyl][1,1'-biphenyl]-2-sulfonamide;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-2-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(phenoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-2-(1H-pyrazol-1-yl)methyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

N2-(Cyclopropylcarbonyl)-N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-L-valinamide;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-N2-(1-oxobutyl)-L-valinamide;

N2-(Cyclopropylcarbonyl)-N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-2-(methoxymethyl)[1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-L-valinamide;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-2-(methoxymethyl)[1,1'-biphenyl]-4-yl]methyl]-N,N-dimethyl-N2-(1-oxobutyl)-L-valinamide;



N2-[[2-Chloro-2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

5 N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-2-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

N2-(Cyclobutylcarbonyl)-N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;

10 1-[[2-Chloro-2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-4-ethyl-2-propyl-1H-imidazole-5-carboxylic acid;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(methylsulfonyl)amino][1,1'-biphenyl]-2-sulfonamide;

15 (S)-N-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-[(4-methyl-1-piperazinyl)carbonyl]propyl]pentanamide;

(S)-N-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[2-methyl-1-[(4-methyl-1-piperazinyl)carbonyl]propyl]pentanamide;

20 N-(3,3-Dimethylbutyl)-N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N2-(1-oxopentyl)-L-valinamide;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-[(4-fluorophenyl)methyl]-N2-(1-oxopentyl)-L-valinamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(methylethoxy)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(propoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

30 4-Chloro-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;



- N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;
4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[(1,2-dihydro-2-oxo-1-pyridinyl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-
5 biphenyl]-2-sulfonamide;
4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(1H-pyrazol-1-ylmethyl)[1,1'-biphenyl]-2-sulfonamide;
2-Butyl-4-chloro-1-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-carboxamide;
10 isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-carboxamide;
N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-methyl-4-quinolinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-ethyl-4-quinolinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
15 [1,1'-biphenyl]-2-sulfonamide;
N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-ethyl-5,6,7,8-tetrahydro-4-quinolinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
N-(4,5-dimethyl-3-isoxazolyl)-4'-[(2-propyl-4-quinolinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
20 N-(4,5-dimethyl-3-isoxazolyl)-4'-[(5,6,7,8-tetrahydro-2,4-dimethyl-7-oxopyrido[2,3-d]pyrimidin-8-yl)methyl][1,1'-biphenyl]-2-sulfonamide;
4'-[(2-Ethyl-4-quinolinyl)oxy]methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;
25 N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(5,6,7,8-tetrahydro-2-ethyl-4-quinolinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
3-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-2-ethyl-N-methyl-3H-benzimidazole-4-carboxamide;
30 1-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid phenylmethyl ester;



- 1-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 2-phenylethyl ester;
- 1-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 2-(2-oxo-1-
- 5 pyrrolidinyl)ethyl ester;
- 1-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-1H-benzimidazole-7-carboxylic acid 3-(2-oxo-1-pyrrolidinyl)propyl ester;
- 2'-Cyano-N-(4,5-dimethyl-3-isoxazolyl)-4'-[[[(2-ethyl-4-
- 10 quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;
- 2'-(Cyanomethyl)-N-(4,5-dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 3-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-
- 15 yl]methyl]-5-ethyl-N-methyl-2-propyl-3H-imidazole-4-carboxamide;
- 1-[[2-Chloro-2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-4-ethyl-2-propyl-1H-imidazole-5-carboxamide;
- 3-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-5-ethyl-2-propyl-3H-imidazole-4-carboxamide;
- 20 3-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethoxy-N-methyl-3H-benzimidazole-4-carboxamide;
- 3-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethoxy-N,N-dimethyl-3H-benzimidazole-4-carboxamide;
- 2-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-
- 25 yl]methyl]propylamino]-3-pyridinecarboxylic acid;
- 4'-[(3,5-Dibutyl-1H-1,2,4-triazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 30 4'-[(2,7-Diethyl-5H-pyrazolo[1,5-b][1,2,4]triazol-5-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;



N-[2-Butyl-3-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-3,4-dihydro-4-oxo-6-quinazolinyl)-N'-methyl-N'-(1-methylethyl)urea;

2-[[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]propylamino]-N-methyl-3-pyridinecarboxamide;

4'-[[3-Methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-2'-(methoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

3-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-2-ethyl-5-methyl-3H-imidazole-4-carboxamide;

4'-[(2-Butyl-3,4-dihydro-4-oxo-3-quinazolinyl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N2-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-2-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxopentyl)-L-valinamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(4,4-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(3,5-Dibutyl-1H-1,2,4-triazol-1-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;



N-[2-[[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino)sulfonyl]-4-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl][1,1'-biphenyl]-2-yl)methyl)methylamino]ethyl]acetamide;

5 4-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2'-[[[4,5-dimethyl-3-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-2-acetic acid ethyl ester;

N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N2-(1-oxopentyl)-N-propyl-L-valinamide;

10 N2-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino)sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N2-(1-oxopentyl)-N-[(tetrahydro-2-furanyl)methyl]-L-valinamide;

2'-Chloro-N-(4,5-dimethyl-3-isoxazolyl)-4'-[[[2-ethyl-4-quinolinyloxy)methyl][1,1'-biphenyl]-2-sulfonamide;

15 N-(4,5-dimethyl-3-isoxazolyl)-4'-[[[2-ethyl-4-quinolinyloxy)methyl]-2'-(trifluoromethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-chloro-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2-methylpropoxy)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(ethylsulfonyl)amino][1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2,2,2-trifluoroethoxy)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-[(2-fluoroethoxy)methyl][1,1'-biphenyl]-2-sulfonamide;

30 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl]-2'-ethoxymethyl[1,1'-biphenyl]-2-sulfonamide;



N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(3,3,3-trifluoropropyl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(3-fluoropropyl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(1,1-difluoroethyl)-N-(4,5-dimethylisoxazol-3-yl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2,2-trifluoroethyl)-N-(4,5-dimethylisoxazol-3-yl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-[(2-methyl)propoxy] [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(2-methoxyethoxy) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-butyl-N-(4,5-dimethylisoxazol-3-yl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(N-methoxy-N-methylaminomethyl) [1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-(2,2-difluoroethoxymethyl)-N-(4,5-dimethylisoxazol-3-yl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(2-fluoroethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(2-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(3-methylbutyl)[1,1'-biphenyl]-2-sulfonamide;



- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(2-methypropyl)[1,1'-biphenyl]-2-sulfonamide;
4'-[[2-(3,3-Difluorobutyl)-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethylisoxazol-3-yl)-2'-(ethoxymethyl)[1,1'-biphenyl]-
5 2-sulfonamide;
N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl]-2'-(3,3,3-trifluoropropyl)[1,1'-biphenyl]-2-sulfonamide;
4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-
10 dimethylisoxazol-3-yl)-2'-[(1,1-dimethylethoxy)methyl][1,1'-biphenyl]-2-sulfonamide;
4'-[4-Ethyl-1-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-methoxymethyl][1,1'-biphenyl]-4-yl)methyl]-2-propyl-1H-imidazole-5-carboxamide;
15 4'-[4-Ethyl-1-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-methoxymethyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;
4'-[4-Ethyl-1-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-yl)methyl]-2-propyl-1H-imidazole-5-carboxamide;
20 4'-[4-Ethyl-1-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide; and salts thereof.

26. A method for the treatment of an endothelin-dependent or
25 angiotensin II-dependent disorder, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

27. A method for the treatment of hypertension, comprising the
30 step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.



28. A method for the treatment of pulmonary hypertension, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

5

29. A method for the treatment of primary pulmonary hypertension, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

10

30. A method for the treatment of low renin hypertension, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

31. A method for the treatment of male erectile dysfunction, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

15

32. A method for the treatment of male or female sexual dysfunction, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

20

33. A method for the treatment of heart failure, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

25

34. A method for the treatment of atherosclerosis, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.



35. A method for the treatment of restenosis, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

5 36. A method for the treatment of endotoxemia, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

10 37. A method for the inhibition of cell growth, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

15 38. A method for the treatment of cancer, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

20 39. A method for the treatment of migraine, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

40. A method for the treatment of asthma, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

25 41. A method for the treatment of ischemia, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

30 42. A method for the treatment of subarachnoid hemorrhage, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.



43. A method for the treatment of benign prostatic hypertrophy, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

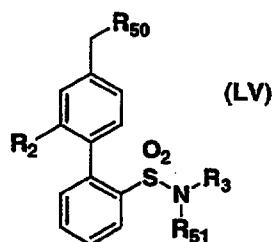
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44. A method for the treatment of renal, glomerular or mesangial cell disorders, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

10 45. A method for the treatment of acute or chronic renal failure, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

15 46. A pharmaceutical composition for the treatment of an endothelin-dependent or angiotensin II-dependent disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1 in an amount effective therefor.

47. A compound of the formula



20

wherein

R_2 and R_3 are as defined in claim 1;

R_{50} is hydroxy, chloro, bromo, iodo, $-\text{OSO}_2\text{-alkyl}$, or $-\text{OSO}_2\text{-aryl}$; and

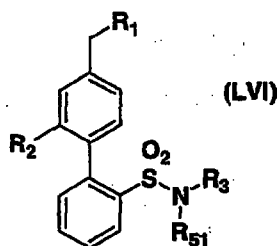
R_{51} is hydrogen, or a suitable nitrogen protecting group.

25

48. The compound of claim 47, wherein R_{51} is $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{OCH}_3$, or $-\text{CH}_2\text{OCH}_2\text{-aryl}$.



49. A compound of the formula

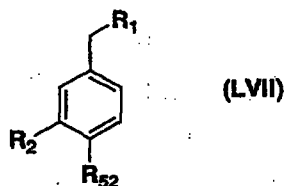


wherein R_1 , R_2 and R_3 are as defined in claim 1; and

5 R_{51} is a suitable nitrogen protecting group.

50. The compound of claim 49, wherein R_{51} is $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{OCH}_3$, or $-\text{CH}_2\text{OCH}_2$ -aryl.

10 51. A compound of the formula



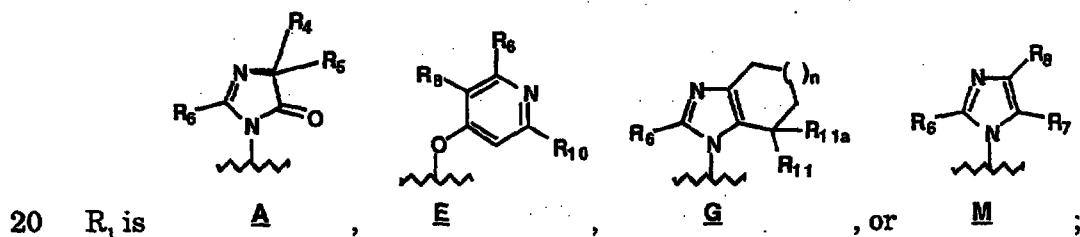
wherein

R_1 and R_2 are as defined in claim 1; and

15 R_{52} is chloro, bromo, iodo, or $-\text{OSO}_2\text{CF}_3$.

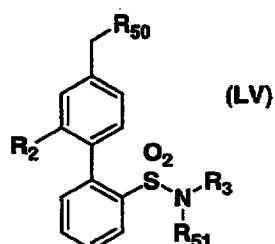
52. A compound of claim 51

wherein



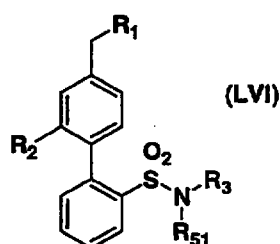
53. A process for the preparation of a compound of claim 1, comprising the following steps:

- a) displacement of a leaving group R_{50} via the anion of a compound R_1 -H from a compound of the formula



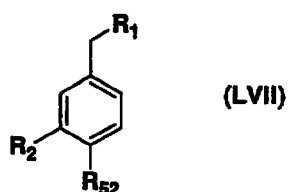
wherein R_1 , R_2 and R_3 are as defined in claim 1, R_{50} is hydroxy, chloro, bromo, iodo, -OSO₂-alkyl or -OSO₂-aryl, and R_{51} is hydrogen or a suitable nitrogen protecting group, using a Mitsunobu reaction or S_N1 or S_N2 displacement reaction, with removal of said nitrogen protecting group as appropriate;

- b) removal of the nitrogen protecting group R_{51} from a compound of formula

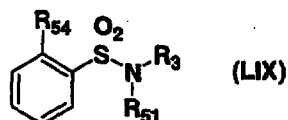


wherein R_1 , R_2 and R_3 are as defined in claim 1, and R_{51} is a suitable nitrogen protecting group;

- c) organometallic coupling of a compound of formula

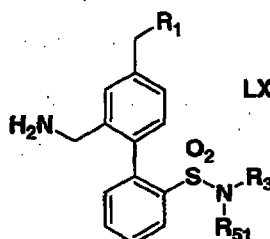


with a compound of formula



wherein R_1 , R_2 and R_3 are as defined for a compound of formula I and R_{51} is a suitable nitrogen protecting group; when R_{52} is chloro, bromo, iodo or
 5 $-\text{OSO}_2\text{CF}_3$, R_{54} is a boronic acid, boronic ester or stannane derivative; when R_{52} is a boronic acid, boronic ester or stannane derivative, R_{54} is chloro, bromo, iodo or $-\text{OSO}_2\text{CF}_3$.

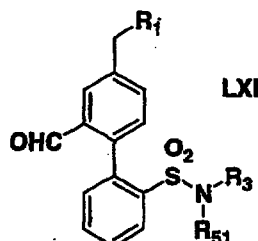
d) acylation of a compound of the formula



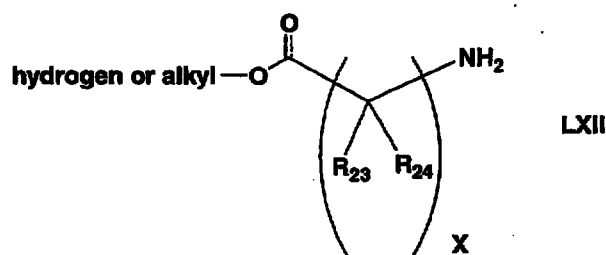
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wherein R_1 and R_3 are as defined in claim 1, and R_{51} is hydrogen or a suitable nitrogen protecting group, with an acylating agent of the formula $R_{55}-(\text{C}=\text{O})R_{22}$, $R_{19}\text{N}=\text{C}=\text{O}$, $R_{55}-\text{CO}_2R_{18}$, $R_{55}\text{SO}_2R_{22}$, wherein R_{18} , R_{19} and R_{22} are
 15 as defined in claim 1 and R_{55} is an activating group for an acid, or made using an acid activating agent, with removal of said nitrogen protecting group as appropriate; or

e) reductive amination of a compound of formula



20 wherein R_1 and R_3 are as defined in claim 1, and R_{51} is hydrogen or a suitable nitrogen protecting group, with an amine of the formula



wherein R_{23} , R_{24} , and x are as defined in claim 1, with removal of said nitrogen protecting group as appropriate.

5

54. A compound of claim 1, wherein said compound is selected from the group consisting of:

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-ethyl[1,1'-biphenyl]-2-sulfonamide;

10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(2,2-dimethylpropyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(2-ethoxyethyl)[1,1'-biphenyl]-2-sulfonamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-ethyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(2,2-dimethylpropyl)[1,1'-biphenyl]-2-sulfonamide;

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(2-ethoxyethyl)[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-2'-ethyl-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl][1,1'-biphenyl]-2-sulfonamide;

25 N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2,2-dimethylpropyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl][1,1'-biphenyl]-2-sulfonamide;



N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2-ethoxyethyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide;

2'-[(1,1-Dimethylethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethyl-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-2'-(2,2-dimethylpropyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-2'-(2-ethoxyethyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide;

2'-[(1,1-Dimethylethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[[3-methoxy-2,6-dimethyl-4-pyridinyl)oxy)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-4-isoxazolyl)-2'-ethyl-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2,2-dimethylpropyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-2'-(2-ethoxyethyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

2'-[(1,1-Dimethylethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethyl-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-2'-(2,2-dimethylpropyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;



N-(4,5-Dimethyl-3-isoxazolyl)-2'-(2-ethoxyethyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

2'-[(1,1-Dimethylethoxy)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4'-
5 [(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(1-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-
10 dimethyl-5-isoxazolyl)-2'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(1,2,3,4-tetrahydrofuran-1-yl)[1,1'-biphenyl]-2-sulfonamide;

15 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-2-sulfonamide;

20 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1,2,3,4-tetrahydrofuran-1-yl)[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1-hydroxyethyl)[1,1'-biphenyl]-2-
25 sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-
30 propyl-1-cycloheptimidazolyl)methyl]-2'-(1,2,3,4-tetrahydrofuran-1-yl)[1,1'-biphenyl]-2-sulfonamide;



- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(1-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-2-sulfonamide;
- 5 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;
- 10 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1,2,3,4-tetrahydrofuran-1-yl)[1,1'-biphenyl]-2-sulfonamide;
- 15 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1-hydroxyethyl)[1,1'-biphenyl]-2-sulfonamide;
- 20 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1,2,3,4-tetrahydrofuran-1-yl)[1,1'-biphenyl]-2-sulfonamide;
- 25 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)[1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)[1,1'-biphenyl]-2-sulfonamide;
- 30



N-(4,5-Dimethyl-3-isoxazolyl)- 4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(3,3,3-trifluoropropyl)[1,1'-biphenyl]-2-sulfonamide;

5 N-(3,4-Dimethyl-5-isoxazolyl)- 4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(3,3,3-trifluoropropyl)[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)- 4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

10 N-(4,5-Dimethyl-3-isoxazolyl)- 4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)- 4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

15 N-(3,4-Dimethyl-5-isoxazolyl)- 4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)- 4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-2'-(2-fluoroethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

20 N-(4,5-Dimethyl-3-isoxazolyl)- 4'-[[3-methoxy-2,6-dimethyl-4-pyridinyl]oxy]methyl]-2'-(2-fluoroethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

25 N-(4,5-Dimethyl-3-isoxazolyl)- 4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(2-fluoroethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)- 4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(2-fluoroethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

30 4'-[[2-(2,2-Difluorobutyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;



4'-[[2-(2,2-Difluorobutyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

5 4'-[[2-(3,3,3-Trifluorobutyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[[2-(3,3,3-Trifluorobutyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

10 4'-[[2-(3,3,3-Trifluorobutyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

4'-[[2-(3,3,3-Trifluorobutyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

15 4'-[[2-(3,3,3-Trifluoropropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[[2-(3,3,3-Trifluoropropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[[2-(3,3,3-Trifluoropropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

25 4'-[[2-(3,3,3-Trifluoropropyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-propyl[1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1,1-difluoropropyl)[1,1'-biphenyl]-2-sulfonamide;

30 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(1,1-difluoropropyl)[1,1'-biphenyl]-2-sulfonamide;



N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1,1-difluoropropyl)[1,1'-biphenyl]-2-sulfonamide;

5 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl]-2'-(1,1-difluoropropyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(1,1-difluoropropyl)[1,1'-biphenyl]-2-sulfonamide;

10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(1,1-difluoropropyl)[1,1'-biphenyl]-2-sulfonamide; and salts thereof;

4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-ethyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

15 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-propyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

20 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-(2-fluoroethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-(ethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

25 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-ethyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-propyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

30 4'-[4-Ethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-(2-fluoroethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;



4'-[4-Ethyl-1-[[2'-[[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-(ethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

5 4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-ethyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-propyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

10 4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-(2-fluoroethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

15 4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-(ethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-N-methyl-2-propyl-1H-imidazole-5-carboxamide;

4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-ethyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

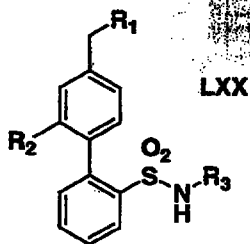
4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-propyl][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

20 4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-(2-fluoroethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

25 4'-[4-Ethyl-1-[[2'-[[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-(ethoxymethyl)][1,1'-biphenyl]-4-yl]methyl]-2-propyl-1H-imidazole-5-carboxamide;

55. A compound of formula LXX

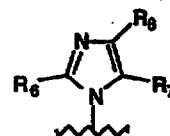




wherein R_2 is as defined in claim 1;

R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two of following substituents: alkyl or halogen; and

- 5 R_1 is any group such that the resulting compound demonstrates affinity (IC_{50}) for both the AT_1 receptor and ET_A receptor of less than 5 micromolar at both receptors.



56. A compound of claim 5, wherein R_1 is

- 10 57. A compound of claim 56, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.

58. A compound of claim 56, wherein R_2 is $-CH_2Y$;

- 15 59. A compound of claim 58, wherein Y is Q;

