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(54) Title: ARYL AND HETEROARYL COMPOUNDS, COMPOSITIONS, AND METHODS OF USE

(57) Abstract: This invention provides aryl and heteroaryl compounds of Formula (I) as described herein, and methods of their preparation. Also provided are pharmaceutical compositions made with the compounds of Formula (I) and methods for making such compositions. Compounds of Formula (I) may be useful for treating viral infections including orthopox viruses, either alone or in combination with other therapeutic agents.

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Aryl and Heteroaryl Compounds, Compositions, and Methods of Use

STATEMENT OF RELATED APPLICATIONS

The present application claims priority under 35 USC 119 from the following U.S. Provisional Patent Applications: Serial No. 60/493,879, filed August 8, 2003, entitled "Aryl and Heteroaryl Compounds as Antviral agents"; Serial No. 60/493,878, filed August 8, 2003, entitled "Aryl and Heteroaryl Componds and Methods to Modulate Red Blood Cell Production"; Serial No. 60/493,903, filed August 8, 2003, entitled "Aryl and Heteroaryl Compounds and Methods to Modulate Coagulation", which are herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

This invention relates to aryl and heteroaryl compounds and compositions that may possess antiviral activity, and methods of use of such compounds and compositions.

BACKGROUND OF THE INVENTION

Viruses may infect cells to take over the host cell machinery and produce new viral particles via transcription and translation processes. Interception of either of these processes, including pre- and post translation events, may cripple virus propagation.

Since the discovery of non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI), nonnucleoside organic molecules have been designed to combat viral infections by inhibiting a variety of targets responsible for viral replication. Examples of such targets include reverse transcriptases, DNA polymerases, viral proteases (e.g., serine, cysteine, aspartyl, metalloproteases), integrases, helicases, fusion proteins, chemokines (CCR5, CXCR4), and chemokine receptors. For example, there are drugs which may prevent fusion of the viral envelope with the cell membrane and therefore inhibit the entry of viruses, such as human immunodeficiency virus (HIV), into the cell. Also, other drugs may act at the late stage of the viral replication cycle to prevent propagation of virus that is already in the cell.

Smallpox is a member of the highly homologous orthopox family of viruses. As of the 1990s, it was belileved that smallpox virus was no longer a health concern as the last known case of smallpox had occurred in 1977. Also, universal vaccination programs in the U.S. were discontinued in 1972 because the risk of complications from the vaccine was actually greater than the risk of being infected with the disease. Recently, however, cases of

smallpox have been documented. In addition, due to the highly homologous nature of the orthopox family, therapeutics developed against smallpox are also potential candidate therapies for related viruses that continue to plague society such as monkeypox, a virus that recently reemerged in the Africa and spread to the US through exotic animals, and mulluscipox virus, which results in a common cutaneous infection that may be problematic with immunocompromised individuals. Thus, there is a renewed interest in developing antiviral agents to treat orthopox viruses, and more particularly, smallpox.

A wide spectrum of antiviral agents have been investigated using different strains of variola as well as other orthopoxviruses (Baker, et al., Antiviral research, 57, 13, 2003). Among antiviral compounds found to be useful were cidofovir (DNA polymerase), ribavrin and tiazofurin (IMP dehydrogenase), C-ca3-ADO, and C3-Npc-A (SAH hydrolase). Also, HPMPC (Cidofovir), a DNA Polymerase Inhibitor for the treatment of CMV retinitis in AIDS patients, may have therapeutic potential for treatment of various other herpes viruses, as well as polyomavirus, papillomavirus, adenovirus as well as poxvirus. For example, in vitro evidence demonstrates that HPMPC may be active against all poxviruses studied to date as well as vaccinia and cowpox virus infections. However, treatment with HPMPC is only currently available in either topical or intravenous forms. Also, side effects, including significant nephrotoxicity, may result.

While useful anti-viral compounds have been identified, viruses can rapidly acquire resistance to drugs. Thus, new anti-viral agents are needed that can be used alone or in a cocktail of drugs where the cocktail can cripple a virus by hitting a multitude of targets.

SUMMARY OF THE INVENTION

Embodiments of the present invention provide aryl and heteroaryl compounds, compositions, and methods of use of such compounds and compositions. The present invention may be embodied in a variety of ways.

In one embodiment, the present invention provides compounds of Formula (I) as described herein. In another embodiment, the present invention provides methods for the preparation of compounds of Formula (I).

The present invention also provides pharmaceutical compositions comprising compounds of Formula (I). In another embodiment, the present invention also provides methods for the preparation of compositions comprising the compounds of Formula (I). The pharmaceutical compositions may comprise pharmaceutically acceptable carriers, excipients, and/or diluents.

In another embodiment, the present invention provides methods for the use of compounds of Formula (I) and pharmaceutical compositions comprising compounds of Formula (I). In one embodiment, the compounds and pharmaceutical compositions of the present invention may be used for treating human or animal disorders. For example, the compounds and pharmaceutical compositions of the present invention may be used for treating or preventing viral infection in a subject. Compounds of Formula (I) may be useful in a variety of applications including treating or preventing viral infections in a subject such as, but not limited to, orthopox infections including smallpox, vaccinia virus, monkey pox, or cowpox viral infections. Thus, in one embodiment, the compounds and pharmaceutical compositions of the present invention may be used for treating or preventing orthopox viral infection in a subject. In an example embodiment, the the compounds and pharmaceutical compositions of the present invention may be used for treating or preventing smallpox viral infection.

The compounds and pharmaceutical compositions of the present invention may provide a number of advantages when used for treating human or animal disorders. In one embodiment, the compounds and pharmaceutical compositions of the present invention may provide a variety of treatment options. As small molecule therapeutics, example embodiments of the compounds and pharmaceutical compositions of the present invention may be administered orally, topically, or parentally. Also, the compounds and pharmaceutical compositions of the present invention may comprise a primary therapeutic or may be used as an adjunct to other therapeutics. For example, compounds of Formula (I) may also be useful in a combination therapy with an antiviral agent where administration of a the combination of a compound of Formula (I) and an antiviral agent may prevents viruses from bypassing or becoming resistant to an inhibitory effect of a compound of Formula (I) or the antiviral agent.

Additional features of the present invention will be described hereinafter. It is to be understood that the invention is not limited in its application to the details set forth in the foregoing or following description but is capable of other embodiments and of being practiced or carried out in various ways.

DETAILED DESCRIPTION

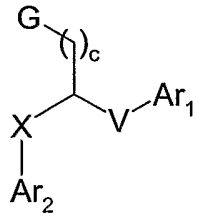
Embodiments of the present invention provide compounds, compositions and methods of use for such compounds. In certain embodiments, the compounds and compositions of the present invention may be used as antiviral agents for the treatment, preventions, or amelioration of viral infection.

Embodiments of the present invention comprise compounds of Formula (I) as depicted below. Embodiments of the present invention also comprise methods of the preparation of compounds of Formula (I) and/or pharmaceutical compositions comprising compounds of Formula (I).

In other embodiments, the present invention provides methods for the use of compounds of Formula (I) and pharmaceutical compositions comprising compounds of Formula (I) in treating human or animal disorders. Compounds of Formula (I) and pharmaceutical compositions comprising compounds of Formula (I) may be useful in a variety of applications. For example, the present invention provides methods of treating or preventing viral infections in a subject. The present invention also provides methods for the preparation of compounds of Formula (I) and methods of preparation of pharmaceutical compositions comprising compounds of Formula (I).

Compounds of Formula (I) may be useful in a variety of applications including treating or preventing viral infections in a subject such as, but not limited to, orthopox infections such as smallpox, vaccinia virus, monkey pox, or cowpox viral infections. Compounds of Formula (I) may also be useful in a combination therapy with an antiviral agent where administration of a the combination of a compound of Formula (I) and an antiviral agent may prevents viruses from bypassing or becoming resistant to an inhibitory effect of a compound of Formula (I) or antiviral agent.

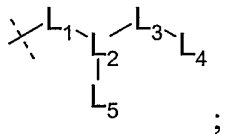
Thus, in one aspect, the present invention provides compounds of Formula (I):



(I)

wherein c is equal to 0, 1, or 2; wherein the values of 0, 1, and 2 comprise a direct bond, -CH_2-, and -CH_2-CH_2-, optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl. In an embodiment, c is equal to 0 or 1. In another embodiment, c is equal to 0.

G comprises: -hydrogen, -alkyl, -heteroaryl, -aryl, -heterocyclycl, -CH=CH-CO_2R_1, –CO_2R_1, –CH_2OR_1, –CH_2SR_1 –C(O)-R_1, -C(O)NR_1R_2, -C(R_1)=N-O-R_2, -C(O)C(O)R_1, -C(O)C(O)NR_1R_2, -CH=CH-NO_2, -CH=CH-CN, -C(O)-C(O)-OR_1, an acid isostere, or an ester isostere; wherein R_1 and R_2 independently comprise: -hydrogen, -alkyl, -aryl, -alkenyl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -heterocyclyl, or -heteroaryl, or when R_1 and R_2 are bonded to a nitrogen group in G, R_1 and R_2 may be taken together to form a ring having the formula -$(CH_2)_m$-Z_2-$(CH_2)_n$, wherein m and n are, independently, 1, 2, 3, or 4; Z_2 comprises -CH_2-, -C(O)-, -O-, -N(H)-, -S-, -S(O)-, -$S(O_2)$-, -CON(H)-, -NHC(O)-, -NHC(O)N(H)-, -$NH(SO_2)$-, -$S(O_2)$N(H)-, -(O)CO-, -$NHS(O_2)NH$-, -OC(O)-, -N(R_{21})-, -N(C(O)R_{21})-, -N(C(O)NHR_{21})-, -N($S(O_2)NHR_{21}$)-, -N(SO_2R_{21})-, or -N(C(O)OR_{21})-; wherein R_{21} comprises hydrogen, aryl, alkyl, or alkylene-aryl; or when when R_1 and R_2 are bonded to a nitrogen group in G, R_2 may be optionally substituted with a substituent of the formula



;

wherein

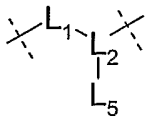
L_1 comprises a direct bond, alkylene, -O-alkylene-, alkylene-O-, -NH-C(O)-, -C(O)-NH- or –NH-C(O)-NH-;

L_2 comprises alkyline, alkenyline, heteroaryline, aryline, or heterocyclyline;

L_3 comprises –O-, -N(R_3)-, -C(O)-N(R_3)-, -C(O)-O-, -C(O)-, –N(R_3)-C(O)-N(R_4)-, -CH=CH-CO_2R_1, -C(O)R_1, -C(O)C(O)R_1, or -C(O)C(O)NR_1R_2;

L_4 comprises hydrogen, alkyl, alkenyl, alkynyl, heterocyclyl, heteroaryl, or -alkylene-aryl;

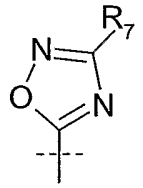
L_5 comprises hydrogen, alkyl, alkenyl, alkynyl, -akylene-aryl, -alkylene-heteroaryl, alkylene-O-alkylene-aryl, -alkylene-S-alkylene-aryl, -alkylene-O-alkyl, -alkylene-S-alkyl, -alkylene-NH_2, -alkylene-OH, -alkylene-SH, -alkylene-C(O)-OR_5, -alkylene-C(O)-NR_5R_6, -alkylene-NR_5R_6, -alkylene-N(R_5)-C(O)-R_6,
–alkylene-N(R_5)-$S(O_2)$-R_6; or



may be taken together to constitute a direct bond; and

wherein R_3, R_4, R_5, and R_6 independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or, -alkylene-heteroaryl.

In an embodiment, G comprises: -hydrogen, $-CO_2R_1$, $-C(O)NR_1R_2$, or $-C(O)R_1$, wherein R_1 and R_2 independently comprise -hydrogen, -alkyl, -alkenyl, -aryl. In another embodiment, G comprises an ester isostere comprising the substituted oxadiazole:



, wherein R_7 comprises alkyl, aryl, alkylene-sulfonyl-alkyl or alkylene-sulfonyl-aryl. In another embodiment R_7 comprises an alkyl group. In another embodiment, G comprises - hydrogen. In another embodiment, G comprises $-CO_2R_1$ wherein R_1 comprises alkyl.

V comprises: $-(CH_2)_b-O-(CH_2)_a-$, $-(CH_2)_b-N(R_8)-(CH_2)_a-$, $-(CH_2)_b-O-$, $-(CH_2)_b-N(R_8)$, $-(CH_2)_a-$, $-CH=CH-(R_8)-$ or a direct bond; in which a is equal to 0, 1, or 2, b is equal to 1 or 2, and R_8 comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; wherein the $-CH_2-$ groups may be optionally substituted 1 to 4 times with a substituent group comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, –hydroxyl, -S-alkyl, or -S-aryl. In an embodiment, V comprises: $-(CH_2)_a-$, $-(CH_2)_b-O-(CH_2)_a-$, or a direct bond, wherein a is equal to 1 or 2, and b is equal to 1. In another embodiment, V comprises: $-(CH_2)_a-$ or a direct bond, wherein a is equal to 1.

X comprises: $-N(R_9)-$, $-CON(R_9)-$, $-N(R_9)CO-$, $-N(R_9)CON(R_{10})-$, $-OC(O)N(R_8)-$, $-SO_2N(R_9)-$, $-N(R_9)\ SO_2-$, or $-N(R_9)SO_2N(R_{10})-$; wherein R_9 and R_{10} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, or $-(CH_2)_dY-$, wherein d is equal to 0, 1, or 2, wherein Y comprises: -hydrogen, $-CO_2R_{11}$, $-CH_2OR_{11}$, $-C(O)-R_{11}$, $-C(O)NR_{11}R_{12}$, $-C(R_{11})=N-O-R_{12}$, $-NR_{11}R_{12}$, or an acid isostere; wherein R_{11} and R_{12} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -heterocyclyl, or -heteroaryl. In an embodiment, X comprises: $-N(R_9)-$, $-CON(R_9)-$, $-N(R_9)CO-$, or $-N(R_9)CON(R_{10})-$, wherein R_9 and R_{10} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl. In another embodiment, X comprises $-N(R_9)-$, $-CON(R_9)-$, or $-N(R_9)CO-$, wherein R_9 comprises -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl. In another embodiment, X comprises $-CON(R_9)-$, wherein R_9 comprises -hydrogen.

Ar_1 comprises an aryl, heteroaryl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, or fused heterocyclylheteroaryl group optionally substituted 1 to 7 times. In another embodiment, Ar_1 comprises a mono- or bicyclic aryl or heteroaryl group optionally substituted 1 to 7 times. In another embodiment, Ar_1 comprises a phenyl group having 1 to 5 substituents. In various embodiments of Ar_1, the substituents of Ar_1 may independently comprise:

a) -fluoro;

b) -chloro;

c) -bromo;

d) -iodo;

e) -cyano;

f) -nitro;

g) -perfluoroalkyl;

h) -D-R_{12};

i) -alkyl;

j) -aryl;

k) -heteroaryl;

l) -heterocyclyl;

m) -cycloalkyl;

n) -alkylene-aryl;

o) -alkylene-arylene-aryl;

p) -alkylene-arylene-alkyl;

q) -arylene-alkyl;

r) -arylene-arylene-alkyl;

s) -D-alkyl;

t) -D-aryl;

u) -D-alkylene-aryl;

v) -D-arylene-alkyl;

w) -D-alkylene-arylene-aryl;

x) -D-arylene-arylene-aryl;

y) -D-alkylene-arylene-alkyl;

z) -alkylene-D-alkylene-aryl;

aa) -arylene-D-alkyl;

bb) -alkylene-D-aryl;

cc) -alkylene-D-heteroaryl;

dd) -alkylene-D-cycloalkyl;

ee) -alkylene-D-heterocyclyl;

ff) -alkylene-D-arylene-alkyl;

gg) -alkylene-D-alkylene-arylene-alkyl;

hh) -alkylene-D-alkyl;

ii) -alkylene-D-R_{13};

jj) -arylene-D-R_{13};

jj) -arylene-T-R_{17};

kk) -T-alkylene-arylene-heteroaryl;

ll) -T-alkylene-heterocyclyl;

mm) -T-alkylene-heteroaryl;

nn) -T-heteroaryl;

oo) -T-fused heterocyclylaryl;

pp) -T-fused cycloalkylaryl;

qq) -T-fused arylcycloalkyl;

rr) -T-fused fused heterocyclylaryl;

ss) -T-fused fused arylheterocyclyl;

tt) -T-fused fused cycloalkylheteroaryl;

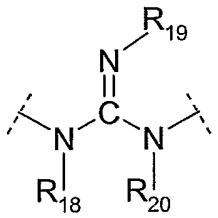
uu) -T-fused fused heteroarylcycloalkyl;

vv) -T-fused heterocyclylheteroaryl;

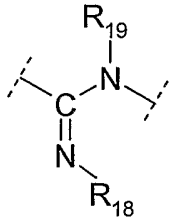
ww) -T-fused heteroarylheterocyclyl; or

xx) -hydrogen;

wherein T comprises a direct bond, $-CH_2-$, -O-, $-N(R_{18})-$, -C(O)-, $-CON(R_{18})-$, $-N(R_{18})C(O)-$, $-N(R_{18})CON(R_{19})-$, $-N(R_{18})C(O)O-$, $-OC(O)N(R_{18})-$, $-N(R_{18})SO_2-$, $-SO_2N(R_{18})-$, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, $-S(O_2)-$, $-N(R_{18})SO_2N(R_{19})-$,



, or



and wherein R_{17}, R_{18}, R_{19} and R_{20}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl. In another embodiment, Ar_1 comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl, -arylene-alkyl, -D-aryl,

-D-alkylene-arylene-alkyl, or -arylene-D-alkyl; wherein D comprises -O-, -N(R_{14})-, -CON(R_{14})-, or -N(R_{14})C(O)-, and wherein R_{14} comprises: -hydrogen; -alkyl; or -aryl.

In another embodiment, Ar_1 comprises: 2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl, 2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl, 2'-phenoxy-biphenyl-4-yl, 2'-trifluoromethyl-biphenyl-4-yl, 3',4'-dichloro-biphenyl-4-yl, 3',4'-difluoro-biphenyl-4-yl, 3',5'-bis-trifluoromethyl-biphenyl-4-yl, 3',5'-difluoro-biphenyl-4-yl, 3'-chloro-4'-fluoro-6-methoxy-biphenyl-3-yl, 3'-chloro-4'-fluoro-biphenyl-2-yl, 3'-chloro-4'-fluoro-biphenyl-3-yl, 3'-chloro-4'-fluoro-biphenyl-4-yl, 3'-chloro-biphenyl-4-yl, 3'-nitro-biphenyl-4-yl, 3'-trifluoromethoxy-biphenyl-4-yl, 3'-trifluoromethyl-biphenyl-4-yl, 4'-benzyloxy-3'-fluoro-biphenyl-4-yl, 4-benzyloxy-phenyl, 4'-chloro-biphenyl-4-yl, 4'-fluoro-biphenyl-4-yl, 4'-methanesulfonyl-biphenyl-4-yl, 4-naphthalen-2-yl-phenyl, 4'-nitro-biphenyl-4-yl, 4'-phenoxy-biphenyl-4-yl, 4-pyridin-3-yl-phenyl4'-tert-butyl-biphenyl-4-yl, 4'-trifluoromethyl-biphenyl-4-yl, 6-methoxy-4'-nitro-biphenyl-3-yl, biphenyl, biphenyl-4-yl, chlorofluorophenoxy-phenyl, or (cyano-phenoxy)-phenyl.

In another embodiment, Ar_1 comprises: [2-(4-chloro-phenyl)-ethoxy]-phenyl, (4-nitro-phenoxy)-phenyl, (3-phenyl-propylamino)-phenyl, 4-methoxy-4'-nitro-biphenyl-3-yl, (4'-methanesulfonyl-4-methoxy-biphenyl-3-yl), or (4'-methanesulfonyl-4-hydroxy-biphenyl-3-yl).

In another embodiment, Ar_1 comprises an unsubstituted biphenyl group.

In yet another embodiment, Ar_1 comprises a biphenyl group substituted with at least one of the following groups fluoro, chloro, trifluoroalkyl, trifluoroalkoxy, nitro, benzyloxy, phenoxy, and alkylsulfonyl.

Ar_2 comprises an aryl or heteroaryl group optionally substituted 1 to 7 times. In one embodiment, Ar_2 comprises a phenyl, naphthyl, pyridyl, isoquinolyl, pyrimidyl or quinazolyl group optionally substituted 1 to 7 times. In another embodiment, Ar_2 comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents. In various embodiments of Ar_2, the substituents of Ar_2 may independently comprise:

a) -fluoro;

b) -chloro;

c) -bromo;

d) -iodo;

e) -cyano;

f) -nitro;

g) -perfluoroalkyl;

h) -T-R_{17};

i) -alkyl;

j) -aryl;

k) -heteroaryl;

l) -heterocyclyl;

m) -cycloalkyl;

n) -alkylene-aryl;

o) -alkylene-arylene-aryl;

p) -alkylene-arylene-alkyl;

q) -arylene-alkyl;

r) -arylene-arylene-alkyl;

s) -T-alkyl;

t) -T-aryl;

u) -T-alkylene-aryl;

v) -T-arylene-alkyl;

w) -T-alkylene-arylene-aryl;

x) -T-arylene-arylene-aryl;

y) -T-alkylene-arylene-alkyl;

z) -alkylene-T-alkylene-aryl;

aa) -arylene-T-alkyl;

bb) -alkylene-T-aryl;

cc) -alkylene-T-heteroaryl;

dd) -alkylene-T-cycloalkyl;

ee) -alkylene-T-heterocyclyl;

ff) -alkylene-T-arylene-alkyl;

gg) -alkylene-T-alkylene-arylene-alkyl; or

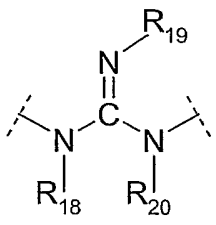
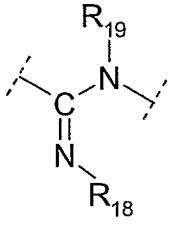
hh) -alkylene-T-alkyl;

ii) -alkylene-T-R_{17};

jj) -arylene-T-R_{17}; or

kk) -hydrogen;

wherein T comprises $-CH_2-$, -O-, -$N(R_{18})$-, -C(O)-, -$CON(R_{18})$-, -$N(R_{18})C(O)$-, -$N(R_{18})CON(R_{19})$-, -$N(R_{18})C(O)O$-, -$OC(O)N(R_{18})$-, -$N(R_{18})SO_2$-, -$SO_2N(R_{18})$-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -$S(O_2)$-, -$N(R_{18})SO_2N(R_{19})$-,

, or , and wherein R_{17}, R_{18}, R_{19} and R_{20}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl. In another embodiment, Ar_2 comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents independently comprising:

a) -fluoro;

b) -chloro;

c) -bromo;

d) -iodo;

e) -cyano;

f) -nitro;

g) -perfluoroalkyl;

h) -T-R_{17};

i) -alkyl;

j) -aryl;

k) -arylene-alkyl;

l) -T-alkyl;

m) -T-alkylene-aryl;

n) -T-alkylene-arylene-aryl;

o) -T-alkylene-arylene-alkyl; or

p) -arylene-T-alkyl;

wherein T comprises $-CH_2-$, -O-, -N(R_{18})-, -CON(R_{18})-, or -N(R_{18})C(O)-; wherein R_{17}, and R_{18}, independently comprise: -hydrogen, -alkyl, or -aryl.

In another embodiment, Ar_2 comprises: 3'-chloro-4'-fluoro-4-hydroxy-biphenyl, 2-hydroxy-5-[2-(4'-trifluoromethyl-biphenyl-3-yl)-acetylamino]-phenyl, 2-hydroxy-5-pyridin-3-yl-phenyl, 3',5'-difluoro-4-hydroxy-biphenyl, 3'-chloro-4'-fluoro-4-hydroxy-biphenyl, 3'-fluoro-4-hydroxy-biphenyl, 3'-trifluoromethyl-biphenyl-4-yl, 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl, 4'-amino-4-hydroxy-biphenyl, 4'-fluoro-4-hydroxy-biphenyl, 4-hydroxy-2'-trifluoromethyl-biphenyl, 4-hydroxy-3',5'-bis-trifluoromethyl-biphenyl, 4-hydroxy-3'-nitro-biphenyl, 4-hydroxy-4'-trifluoromethoxy-biphenyl, 4-Hydroxy-4'-trifluoromethyl-biphenyl,

4-hydroxy-biphenyl, 5-benzo[1,3]dioxol-5-yl-2-hydroxy-phenyl, 5-bromo-2-hydroxy-phenyl, 5-chloro-4-hydroxy-4'-trifluoromethyl-biphenyl, 5-fluoro-4-hydroxy-4'-trifluoromethyl-biphenyl, or 6-benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl.

In another embodiment, Ar_2 comprises 3'-chloro-4'-fluoro-4-hydroxy-biphenyl, or 4-Hydroxy-4'-trifluoromethyl-biphenyl.

In another embodiment, Ar_2 comprises: [2-(3,4-bis-benzyloxy-benzyloxy)-benzyloxy]-5-bromo-phenyl, 2-(4-tert-butyl-benzyloxy)-5-chlorophenyl, 3-bromo-5-chloro-2,6-dimethoxy-phenyl, 4-(4-tert-butyl-benzyloxy)-4'-trifluoromethyl-biphenyl, 4-acetoxy-2-phneyl-4'-trifluoromethyl-biphenyl, 4-acetoxy-4'-trifluoromethyl-biphenyl, 4-amino-4'-trifluoromethyl-biphenyl, 4-butoxy-3'-chloro-4'-fluoro-biphenyl, 4-methanesulfonylamino-4'-trifluoromethyl-biphenyl, 4-methoxy-4'-trifluoromethyl-biphenyl, 5-bromo-2-(4-[1,2,4]triazol-1-yl-benzyloxy)-phenyl, 5-bromo-2-(4-tert-butyl-benzyloxy)-phenyl, 5-bromo-2-cyclohexyloxy-phenyl, 5-bromo-2-heptyloxy-phenyl, 5-chloro-2,4-dimethoxy-4'-trifluoromethyl-biphenyl, 5-chloro-2-heptyloxy-phenyl.

In another embodiment, Ar_2 comprises: 5-bromo-2-(3-pyridin-4-yl-propoxy)-phenyl, 5-bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-ethoxy]-phenyl, 5-bromo-2-(2-morpholin-4-yl-ethoxy)-phenyl, 5-bromo-2-(4,4,4-trifluoro-butoxy)-phneyl, or 5-bromo-2-(2-piperidin-1-yl-ethoxy)-phenyl.

In another embodiment, Ar_2 comprises 3-hydroxy-naphthalene.

In another embodiment, Ar_2 comprises a phenyl or biphenyl group containing a hydroxy, alkyloxy, or acetoxy group ortho to the Ar_2 group's point of attachment to X.

In yet another embodiment, Ar_2 comprises a phenyl or biphenyl group containing a hydroxy, alkyloxy, or acetoxy group ortho to the Ar_2 group's point of attachment to X and further substituted with at least one of the following groups fluoro, chloro, trifluoroalkyl, trifluoroalkoxy, nitro, benzyloxy, phenoxy, phenyl, and alkylsulfonyl.

The alkyl, aryl, heteroaryl, alkylene, and arylene groups in Ar_1, Ar_2, G, R_1-R_{21}, may be optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising:

a) -hydrogen;

b) -fluoro;

c) -chloro;

d) -bromo;

e) -iodo;

f) -cyano;

g) -nitro;

h) -perfluoroalkyl;

i) -Q-R_{22};

j) -Q-alkyl;

k) -Q-aryl;

l) -Q-alkylene-aryl;

m) -Q-alkylene-$NR_{23}R_{24}$; or

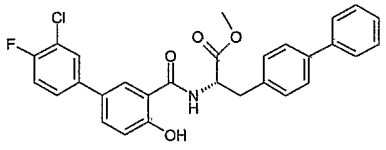
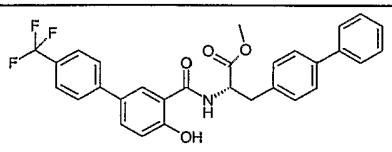
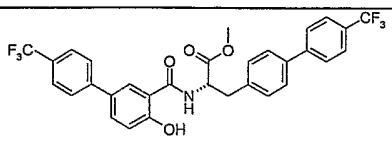
n) -Q-alkyl-W-R_{25};

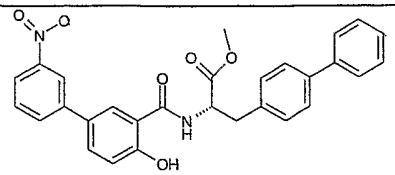
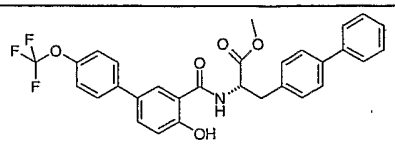
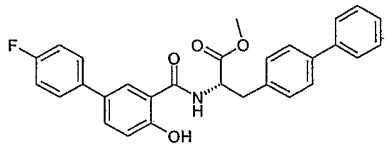
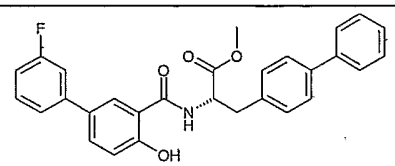
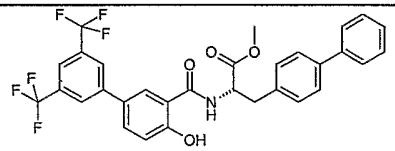
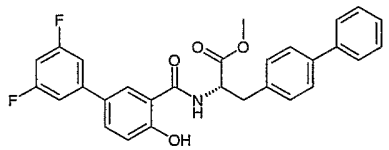
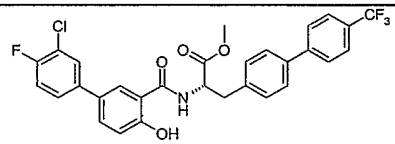
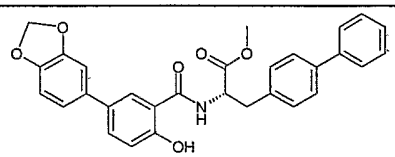
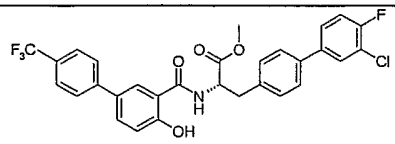
wherein Q and W independently comprise: $-CH_2-$, -O-, -$N(R_{26})$-, -C(O)-, -$CON(R_{26})$-, -$N(R_{26})C(O)$-, -$N(R_{26})CON(R_{27})$-, -$N(R_{26})C(O)O$-, -$OC(O)N(R_{26})$-, -$N(R_{26})SO_2$-, -$SO_2N(R_{26})$-, -C(O)-O-, -O-C(O)-, or -$N(R_{26})SO_2N(R_{27})$-, wherein R_{22}, R_{23}, R_{24}, R_{25}, R_{26} and R_{27}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

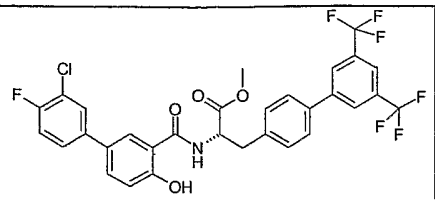
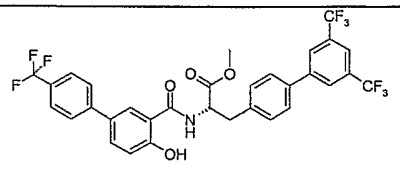
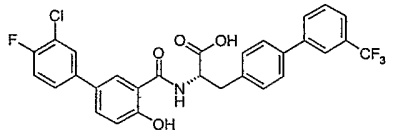
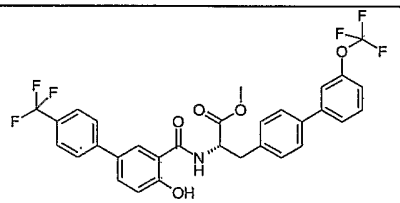
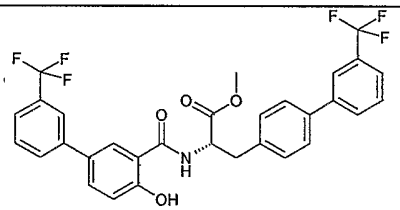
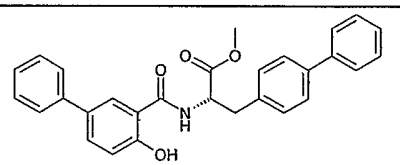
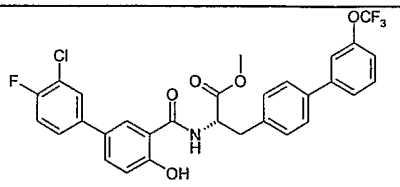
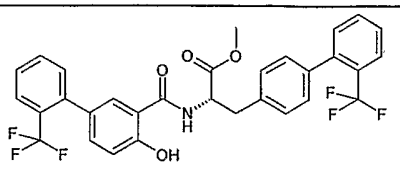
Also included within the scope of the invention are the individual enantiomers of the compounds represented by Formula (I) above as well as any wholly or partially racemic mixtures thereof. The present invention also covers the individual enantiomers of the compounds represented by formula above as mixtures with diastereoisomers thereof in which one or more stereocenters are inverted.

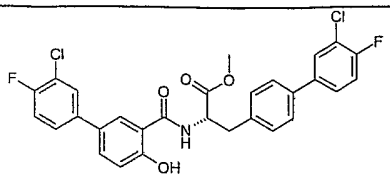
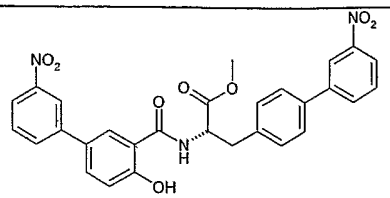
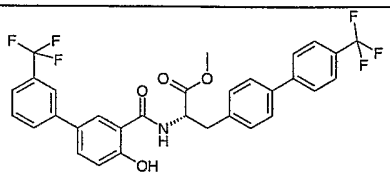
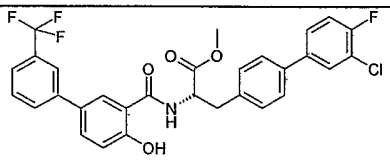
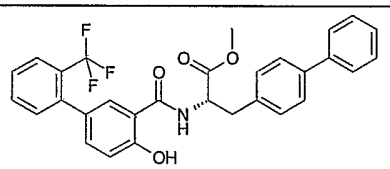
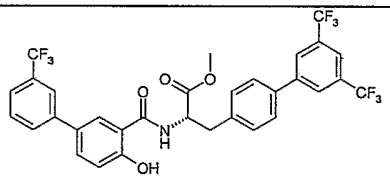
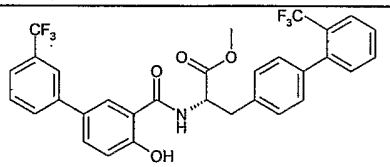
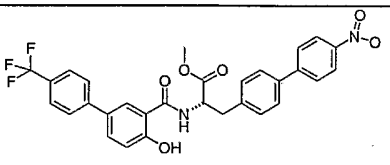
Compounds of the present invention are listed in Table 1.

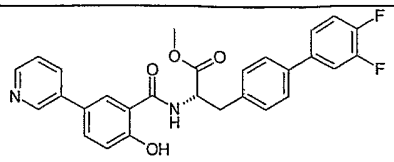
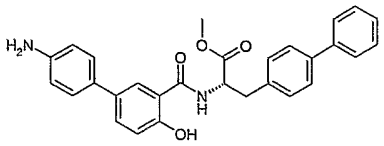
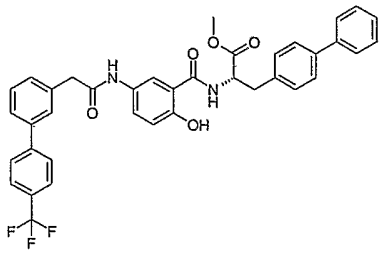
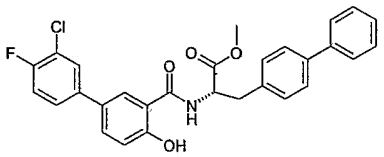
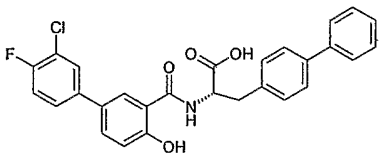
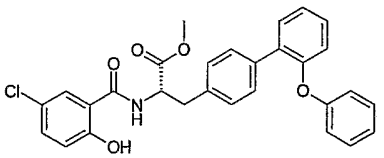
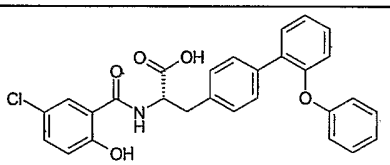
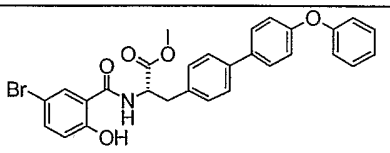
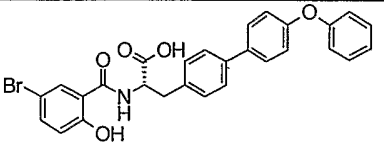
Table 1

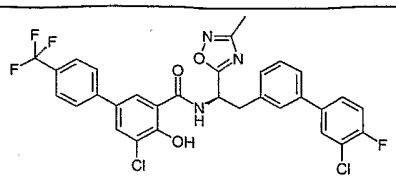
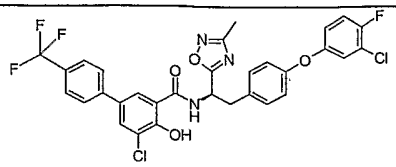
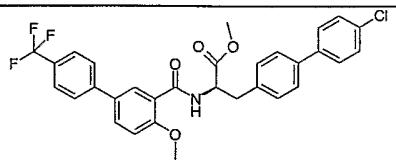
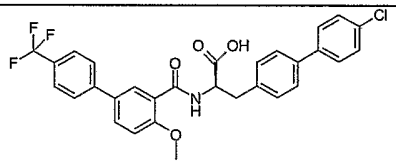
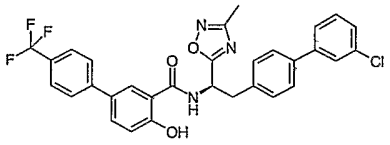
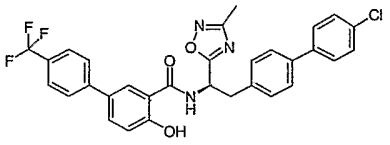
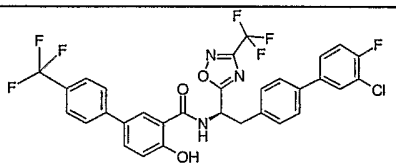
Ex.	Structure	Chemical Name
1		3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-4 -hydroxy- biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
2		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid biphenyl-4-yl-1(S)-formyl-ethyl)-amide; compound with methoxymethane
3		2-(S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)propionic

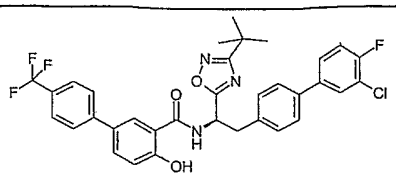
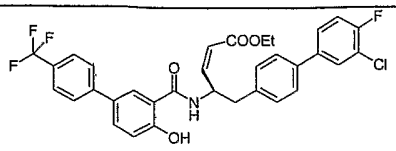
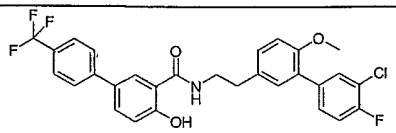
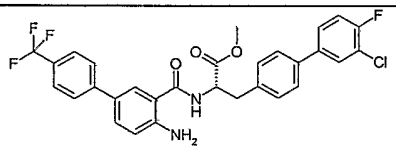
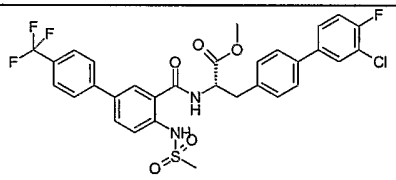
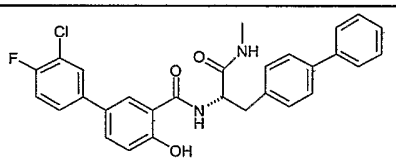
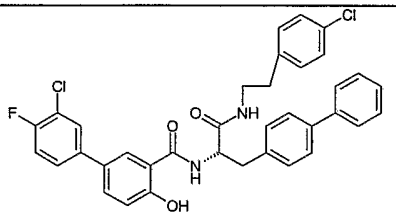
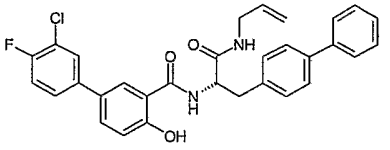
		acid methyl ester
4		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
5		3-Biphenyl-4-yl-2-(S)-[(4-hydroxy-4'-trifluoromethoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
6		3-Biphenyl-4-yl-2-(S)-[(4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
7		3-Biphenyl-4-yl-2-(2S)-[(3'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
8		3-Biphenyl-4-yl-2-(2S)-[(4-hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
9		3-Biphenyl-4-yl-2-(2S)-[(3',5'-difluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
10		2-(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
11		2-(2S)-(5-Benzo[1,3]dioxol-5-yl-2-hydroxy-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester
12		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(2S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

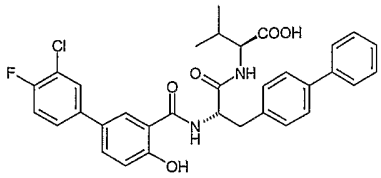
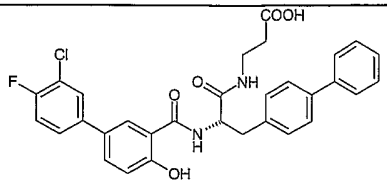
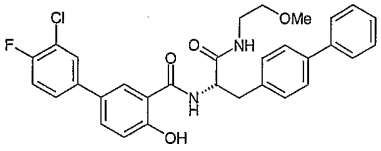
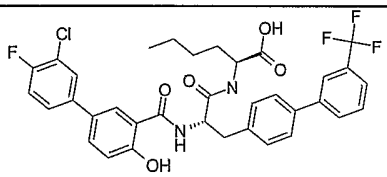
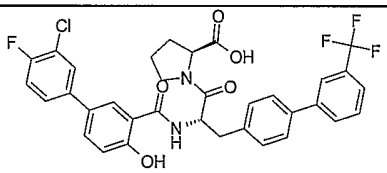
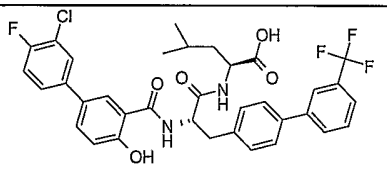
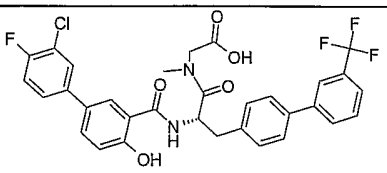
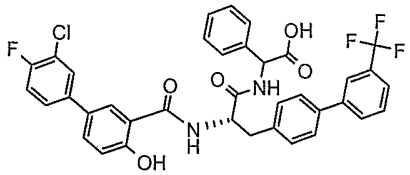
13		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
14		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(2S)-[(3'chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)amino]-propionic acid methyl ester
15		2-(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid
16		2-(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester
17		2-(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
18		3-Biphenyl-4-yl-2-(S)-[(4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
19		2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester
20		2-(S)-[(4-Hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester

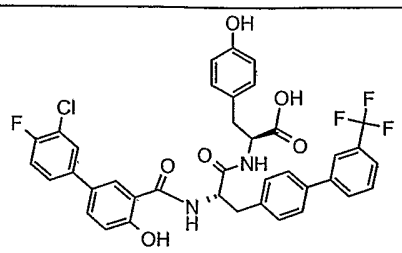
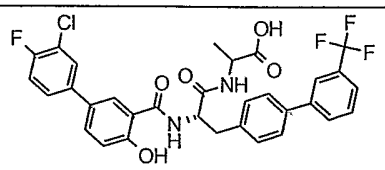
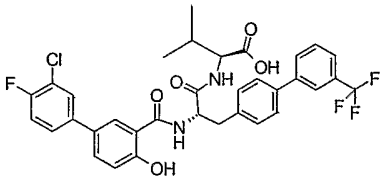
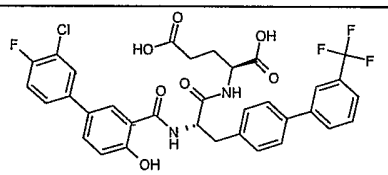
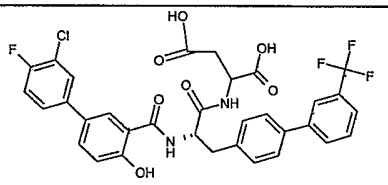
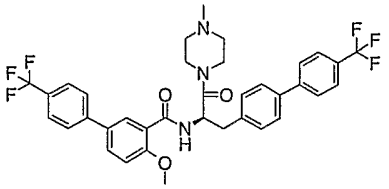
21		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
22		2-(S)-[(4-Hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester
23		2-(S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
24		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
25		3-Biphenyl-4-yl-2-(S)-[(4-hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
26		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
27		2-(S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
28		2-(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-nitro-biphenyl-4-yl)-propionic acid methyl ester

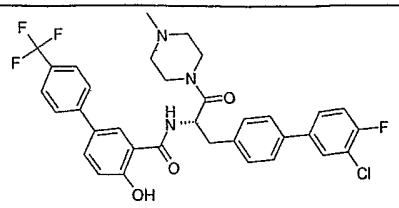
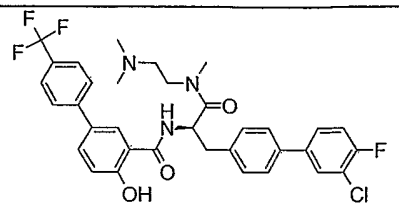
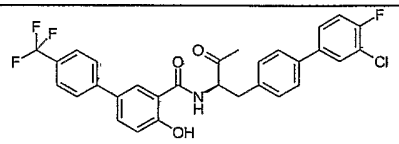
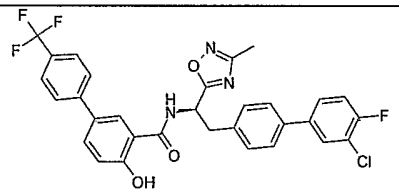
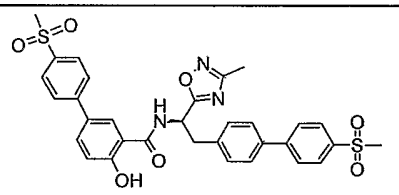
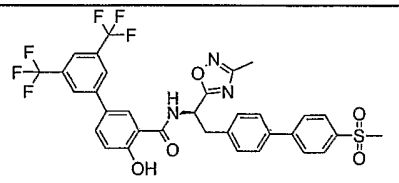
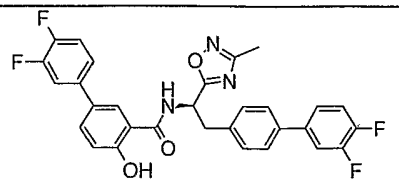
29		3-(3',4'-Difluoro-biphenyl-4-yl)-2-(S)(2-hydroxy-5-pyridin-3-yl-benzoylamino)-propionic acid methyl ester
30		2-(S)-[(4'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-biphenyl-4yl-propionic acid methyl ester
31		3-Biphenyl-4-yl-2-(2S)-{2-hydroxy-5-[2-(4'-trifluoromethyl-biphenyl-3-yl)-acetylamino]-benzoylamino] propionic acid methyl ester
32		3-Biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
33		3-Biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid
34		2-(S)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
35		2-(S)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
36		2-(S)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
37		2-(S)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid

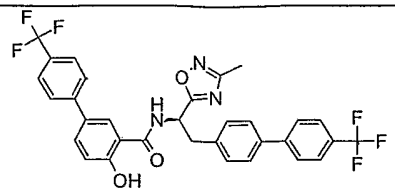
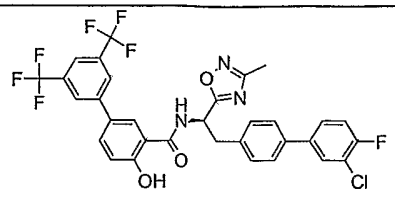
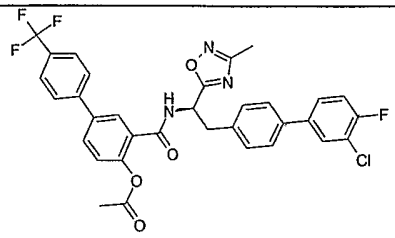
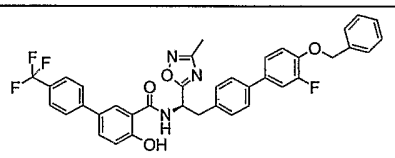
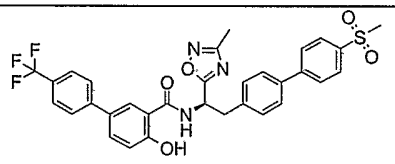
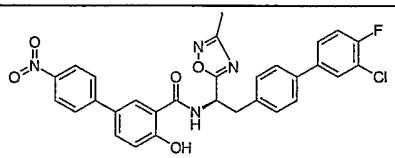
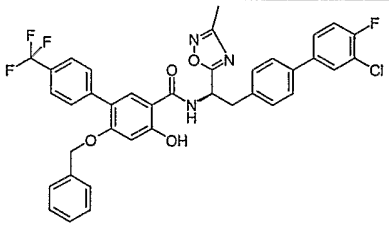
38		5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
39		5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluorophenoxy)-phenyl]-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
40		3-(4'-Chloro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
41		3-(4'-Chloro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid
42		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-biphenyl-4-yl)-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
43		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-chloro-biphenyl-4-yl)-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
44		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1(R)-(3-trifluoromethyl[1,2,4]oxadiazol-5-yl)-ethyl]-amide

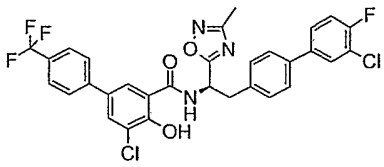
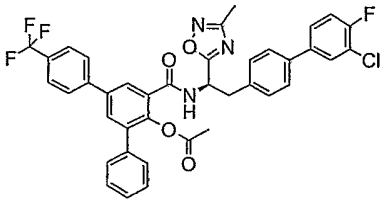
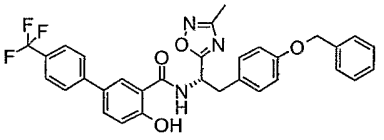
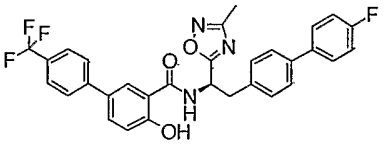
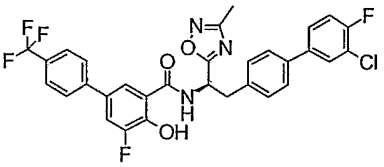
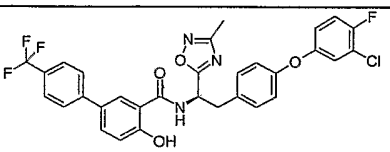
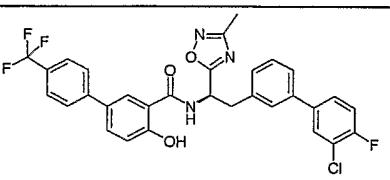
45		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1(R)-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-ethyl]-amide
46		5-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-4-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3(R)-carbonyl) amino]-pent-2-enoic acid ethyl ester
47		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-6-methoxy-biphenyl-3-yl)-ethyl]-amide
48		2-(S)-[(4-Amino-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester
49		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-methanesulfonyl amino-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]propionic acid methyl ester
50		3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (2-biphenyl-4-yl-1(S)-methylcarbamoyl-ethyl)-amide
51		3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid {2-biphenyl-4-yl-1-(S)-[2-(4-chloro-phenyl)-ethylcarbamoyl]-ethyl}-amide
52		3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (1-(S)-allylcarbamoyl-2-biphenyl-4-yl-ethyl)-amide

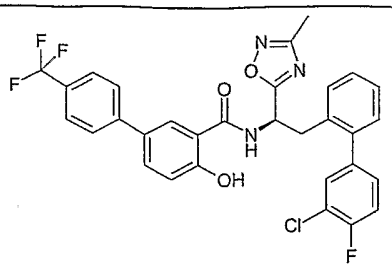
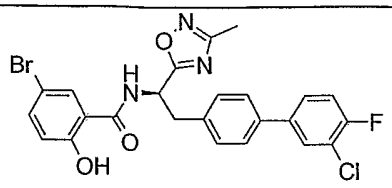
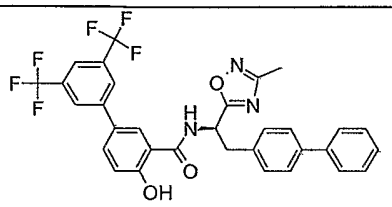
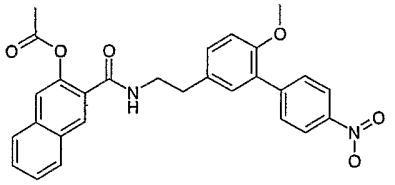
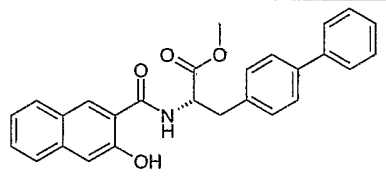
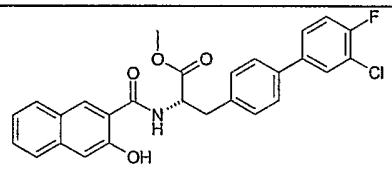
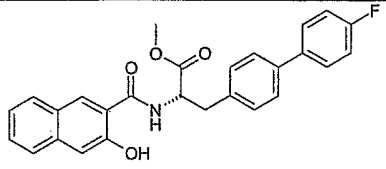
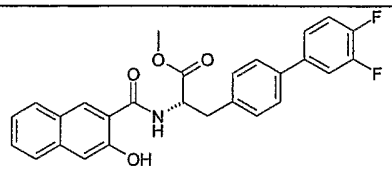
53		2-(S)-{3-Biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)amino]propionylamino}-3-methyl-butyricacid
54		3-(S)-{3-Biphenyl-4-yl-2-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]propionylamino}-propionic acid
55		3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(S)-(2-methoxy-ethylcarbamoyl)-ethyl]-amide
56		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-hexanoic acid
57		1-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionyl]-pyrrolidine-2-(S)-carboxylic acid
58		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-4-methylpentanoic acid
59		{[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionyl]-methyl-amino}-acetic acid
60		[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-

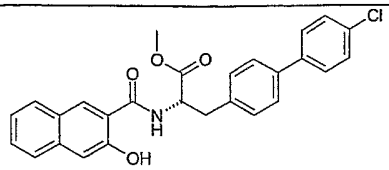
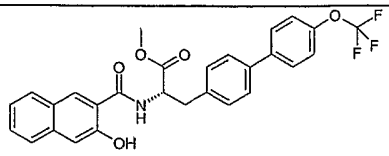
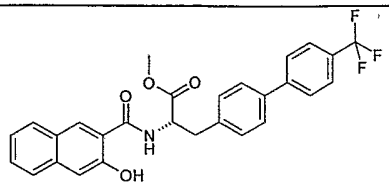
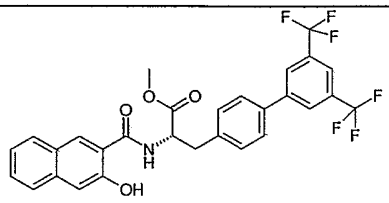
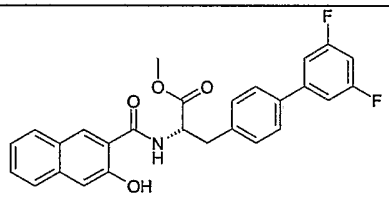
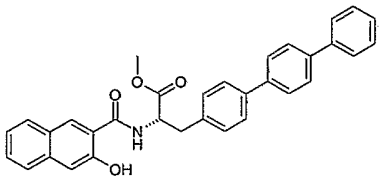
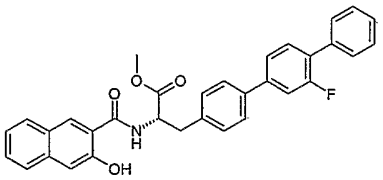
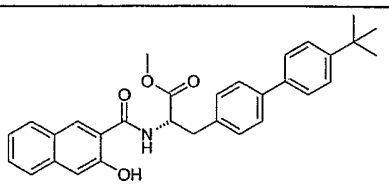
		propionylamino]-2-(S)-phenyl-acetic acid
61		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-3-(4-hydroxy-phenyl)-propionic acid
62		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-propionic acid
63		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-3-methyl-butyric acid
64		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-pentanedioic acid
65		2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-succinic acid
66		4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(R)-(4-methyl-piperazin-1-yl)-2-oxo-1-(4'-trifluoromethyl-biphenyl-4-ylmethyl)-ethyl]-amide

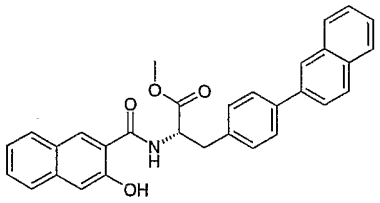
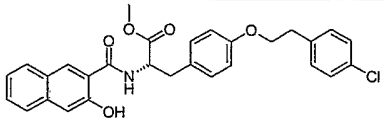
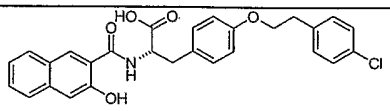
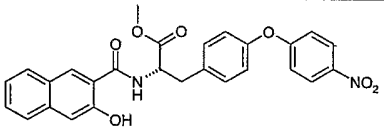
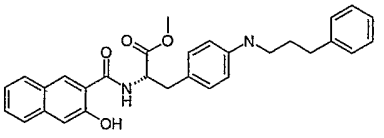
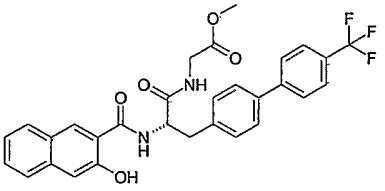
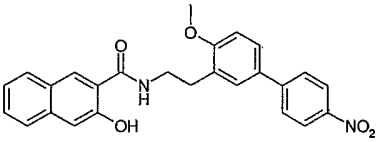
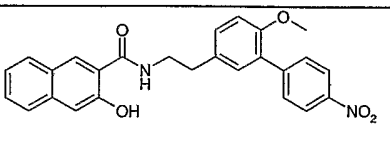
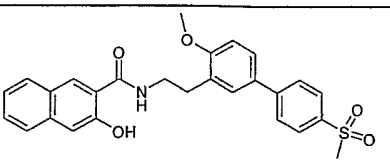
67		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(S)-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide
68		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid {2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-[(2-dimethylamino-ethyl)-methyl-carbamoyl]-ethyl}-amide
69		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-oxo-propyl]-amide
70		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
71		4-Hydroxy-4'-methanesulfonyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
72		4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
73		3',4'-Difluoro-4-hydroxy-biphenyl-3-carboxylic acid [2-(3',4'-difluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

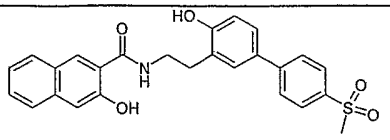
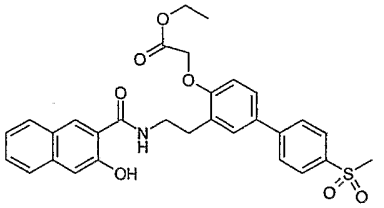
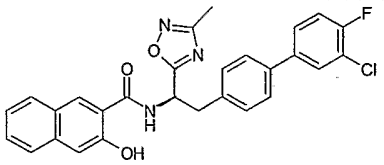
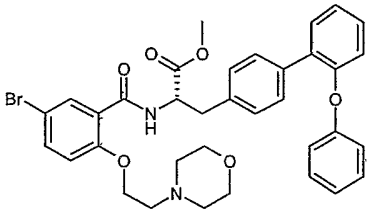
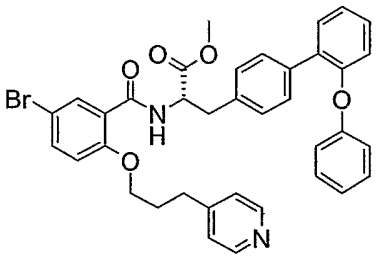
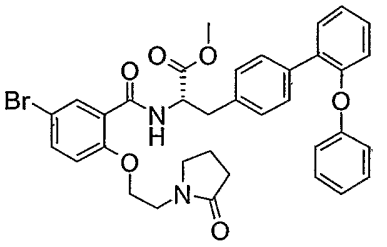
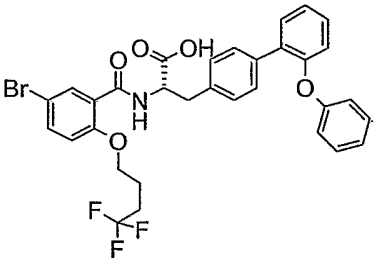
74		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-(4'-trifluoromethyl-biphenyl-4-yl)-ethyl]-amide
75		4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
76		Acetic acid 3-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-4'-trifluoromethyl-biphenyl-4-yl ester
77		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-benzyloxy-3'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
78		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
79		4-Hydroxy-4'-nitro-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
80		6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

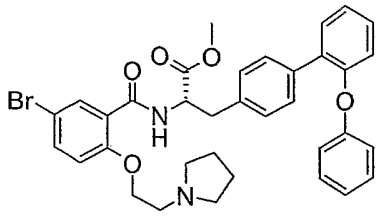
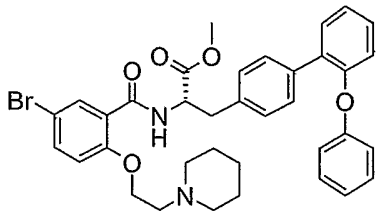
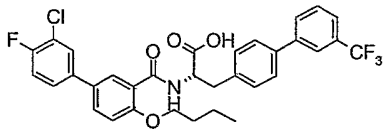
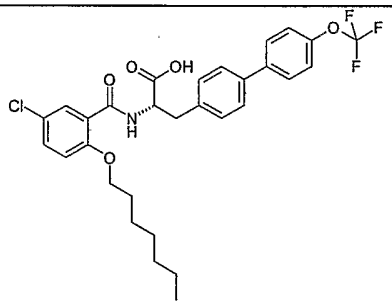
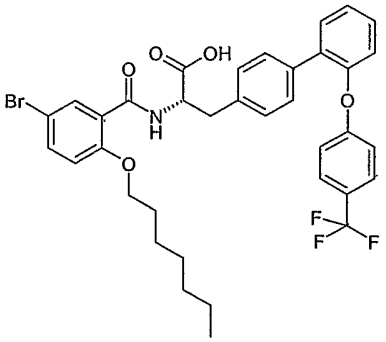
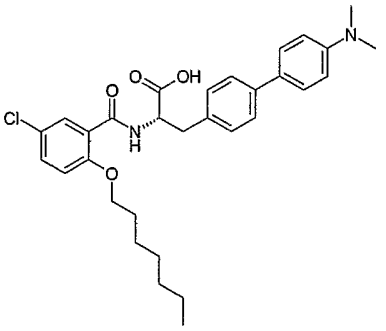
81		5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
82		Acetic acid 5'-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl) ethylcarbamoyl]-4-trifluoromethyl[1,1';3',1"]terphenyl-4'-yl ester
83		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4-benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
84		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
85		5-Fluoro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
86		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl 1,2,4]oxadiazol-5-yl)-ethyl]-amide
87		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

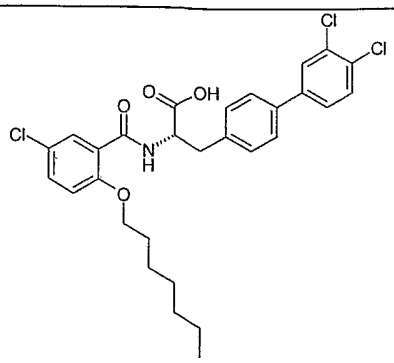
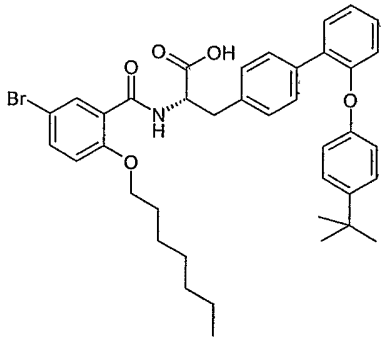
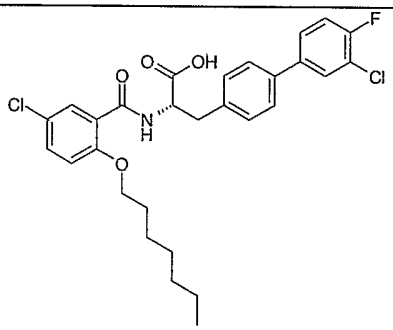
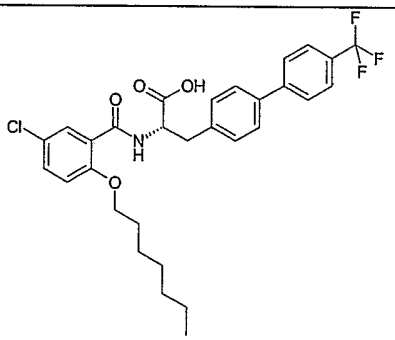
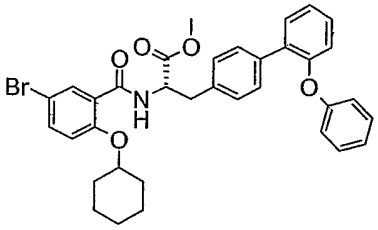
88		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
89		5-Bromo-N-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-2-hydroxy-benzamide
90		4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
91		Acetic acid 3-[2-(6-methoxy-4'-nitro-biphenyl-3-yl)-ethylcarbamoyl]-naphthalen-2-yl ester
92		3-Biphenyl-4-yl-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
93		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
94		3-(4'-Fluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
95		3-(3',4'-Difluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester

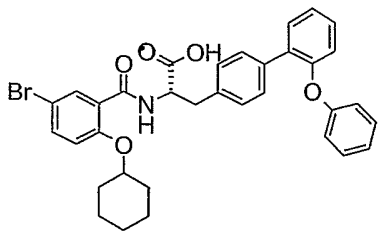
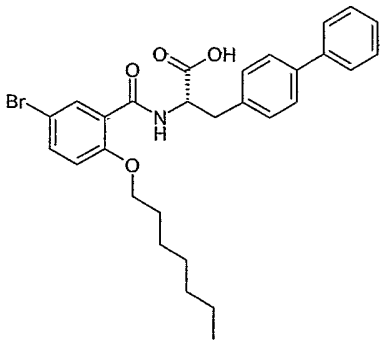
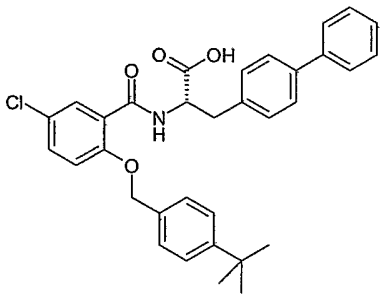
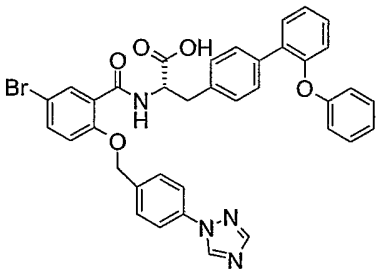
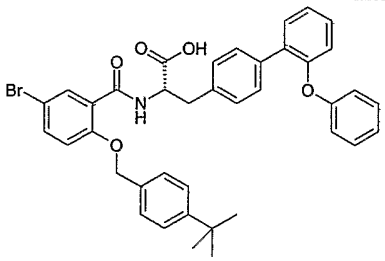
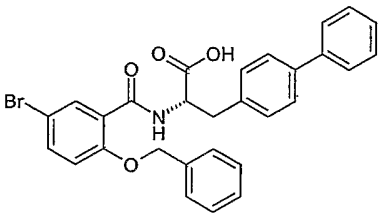
96		3-(4'-Chloro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
97		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester
98		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
99		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
100		3-(3',5'-Difluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
101		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-[1,1';4',1"]terphenyl-4-yl-propionic acid methyl ester
102		3-(2'-Fluoro-[1,1';4',1"]terphenyl-4"-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
103		3-(4'-tert-Butyl-biphenyl-4-yl)-2-[(3-hydroxy-naphthalene-2-(S)-carbonyl)-amino]-propionic acid methyl ester

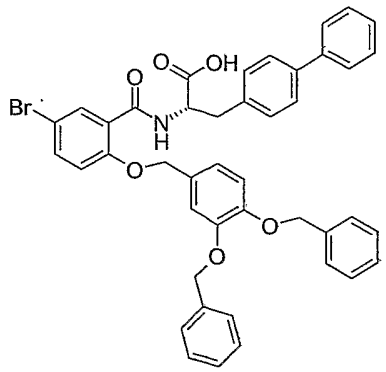
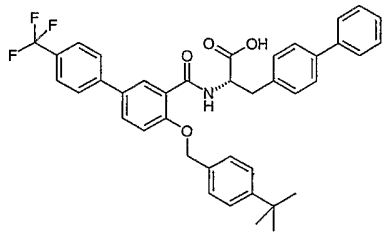
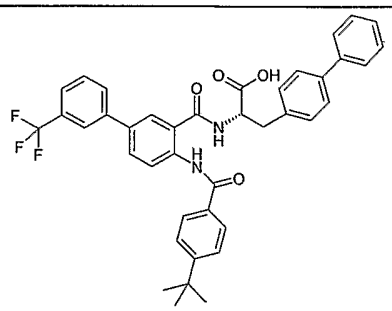
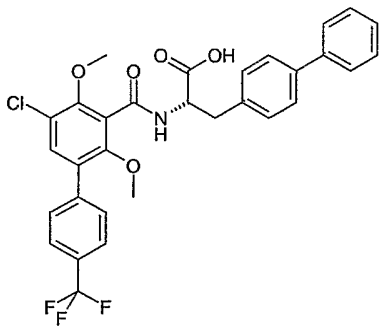
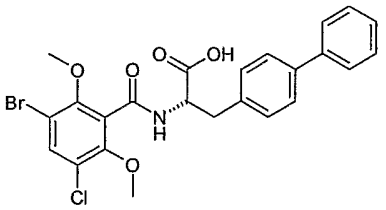
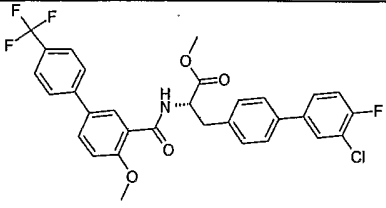
104		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4-naphthalen-2-yl-phenyl)-propionic acid methyl ester
105		3-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester
106		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4-naphthalen-2-ylphenyl)-propionic acid methyl ester
107		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-[4-(4-nitro-phenoxy)-phenyl]propionic acid methyl ester
108		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-[4-(3-phenyl-propylamino)-phenyl]-propionic acid methyl ester
109		[2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-acetic acid methyl ester
110		3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-methoxy-4'-nitro-biphenyl-3-yl)-ethyl]-amide
111		3-Hydroxy-naphthalene-2-carboxylic acid [2-(6-methoxy-4'-nitro-biphenyl-3-yl)-ethyl]-amide
112		3-Hydroxy-naphthalene-2-carboxylic acid [2-(4'-methanesulfonyl-4-methoxy-biphenyl-3-yl)-ethyl]-amide

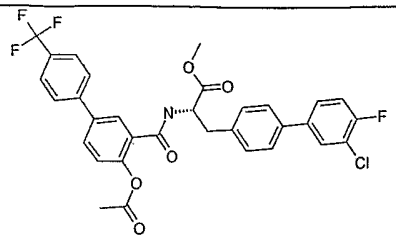
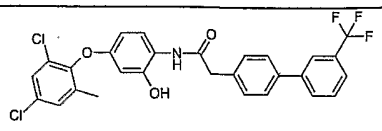
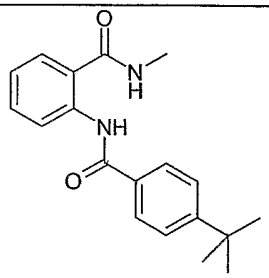
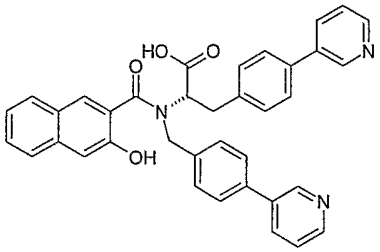
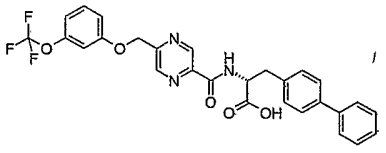
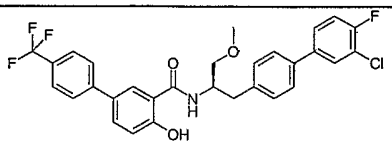
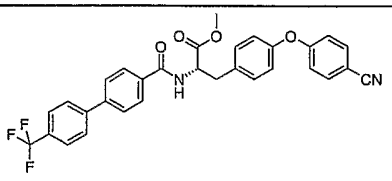
113		3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-hydroxy-4'-methanesulfonyl-biphenyl-3-yl)-ethyl]-amide
114		(3-{2-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-ethyl}-4'-methanesulfonyl-biphenyl-4-yloxy)-acetic acid ethyl ester
115		3-Hydroxy-naphthalene-2-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide
116		2-(S)-[5-Bromo-2-(2-morpholin-4-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
117		2-(S)-[5-Bromo-2-(3-pyridin-4-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
118		2-(S)-{5-Bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
119		2-(S)-[5-Bromo-2-(4,4,4-trifluoro-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

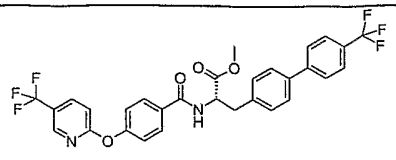
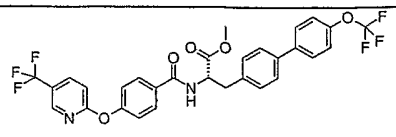
120		2-(S)-[5-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
121		2-S)-[5-Bromo-2-(2-piperidin-1-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
122		2-(S)-[(4-Butoxy-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid
123		2-(S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
124		2-(S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid
125		2-(S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid

126		2-S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(3',4'-dichloro-biphenyl-4-yl)-propionic acid
127		2-(S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl]-propionic acid
128		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid
129		2-(S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
130		2-(S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

131		2-S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
132		3-Biphenyl-4-yl-2-(5-bromo-2-heptyloxy-benzoylamino)-propionic acid
133		3-Biphenyl-4-yl-2-(S)-[2-(4-tert-butyl-benzyloxy)-5-chlorobenzoyl amino] -propionic acid
134		2-(S)-[5-Bromo-2-(4-[1,2,4]triazol-1-yl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
135		2-(S)-[5-Bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
136		2-S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-biphenyl-4-yl-propionic acid

137		3-Biphenyl-4-yl-2-(S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]-propionic acid
138		3-Biphenyl-4-yl-2-(S)-{[4-(4-tert-butyl-benzyloxy)-4'-trifluoromethyl-biphenyl-3-carbonyl]-amino}-propionic acid
139		3-Biphenyl-4-yl-2-(S)-{[4-(4-tert-butyl-benzoylamino)-3'-trifluoromethyl biphenyl-3-carbonyl]-amino}-propionic acid
140		3-Biphenyl-4-yl-2-(S)-[(5-chloro-2,4-dimethoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid
141		3-Biphenyl-4-yl-2-(S)-(3-bromo-5-chloro-2,6-dimethoxy-benzoylamino)-propionic acid
142		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

143		2-(S)-[(4-Acetoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester
144		N-[4-(2,4-Dichloro-6-methyl-phenoxy)-2-hydroxy-phenyl]-2-(3'-trifluoromethyl-biphenyl-4-yl)-acetamide
145		2-(4-t-butyl-1-Benzoylamino)-N-methyl-benzamide
146		2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-(4-pyridin-3-yl-benzyl)-amino]-3-(4-pyridin-3-yl-phenyl)-propionic acid
147		3-Biphenyl-4-yl-2-(S)-{[5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carbonyl]-amino}-propionic acid
148		4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-methoxymethyl-ethyl]-amide
149		3-[4-(4-Cyano-phenoxy)-phenyl]-2-(S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]propionic acid methyl ester

150		3-(4'-Trifluoromethyl-biphenyl-4-yl)-2-(S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid methyl ester
151		3-(4'-Trifluoromethoxy-biphenyl-4-yl)-2-(S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid methyl ester

Unless otherwise indicated, the structures of examples of compounds of Formula (I) having vacant connectivity for heteroatoms, such as oxygen and nitrogen, are assumed to have a hydrogen atom attached thereto.

As used herein, the term "lower" refers to a group having between one and six carbons.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkyl" group may containing one or more O, S, S(O), or $S(O)_2$ atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, n-butyl, t-butyl, n-pentyl, isobutyl, and isopropyl, and the like.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkylene"

group may containing one or more O, S, S(O), or $S(O)_2$ atoms. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon double bond, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkenyl" group may containing one or more O, S, S(O), or $S(O)_2$ atoms.

As used herein, the term "alkenylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon double bonds, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkenylene" group may containing one or more O, S, S(O), or $S(O)_2$ atoms. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like.

As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon triple bond, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkynyl" group may containing one or more O, S, S(O), or $S(O)_2$ atoms.

As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon triple bonds, optionally substituted with substituents selected from the group consisting of

halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkynylene" group may containing one or more O, S, S(O), or $S(O)_2$ atoms. Examples of "alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

As used herein, "cycloalkyl" refers to a alicyclic hydrocarbon group optionally possessing one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like.

As used herein, the term "cycloalkylene" refers to an non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and optionally possessing one or more degrees of unsaturation, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring optionally possessing one or more degrees of unsaturation, containing one or more heteroatomic substitutions selected from S, SO, SO_2, O, or N, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or

lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, piperazine, and the like.

As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical optionally having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO_2, O, or N, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, piperazine-1,4-dyil, and the like.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, -CH=CH-CO_2R_1, -C(O)R_1, -C(O)C(O)R_1, -C(O)C(O)OR_1, -C(O)C(O)NR_1R_2, alkyl ketones, ketoesters, keto amides, alkylene keto esters, alkylene ketoamides, carboxy esters, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, 1-anthracenyl, and the like.

As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, -CH=CH-CO_2R_1, -C(O)R_1, -C(O)C(O)R_1, -C(O)C(O)OR_1, -C(O)C(O)NR_1R_2, alkyl ketones, ketoesters, keto

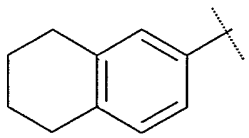
amides, alkylene keto esters, alkylene ketoamides, carboxy esters, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, quinazoline, benzofuran, benzothiophene, indole, and indazole, and the like.

As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of

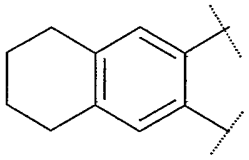
"heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "fused cycloalkylaryl" refers to a cycloalkyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused cycloalkylaryl" used herein include 5-indanyl, 5,6,7,8-tetrahydro-2-naphthyl,



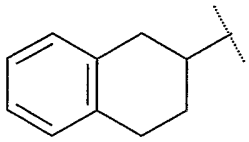
, and the like.

As used herein, the term "fused cycloalkylarylene" refers to a fused cycloalkylaryl, wherein the aryl group is divalent. Examples include



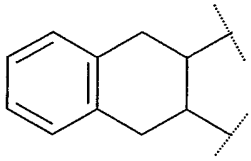
, and the like.

As used herein, the term "fused arylcycloalkyl" refers to an aryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused arylcycloalkyl" used herein include 1-indanyl, 2-indanyl, 1-(1,2,3,4-tetrahydronaphthyl),



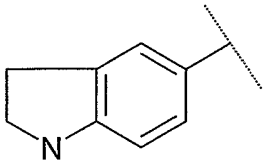
, and the like.

As used herein, the term "fused arylcycloalkylene" refers to a fused arylcycloalkyl, wherein the cycloalkyl group is divalent. Examples include



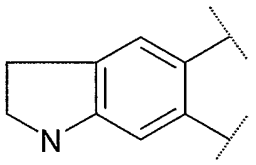
, and the like.

As used herein, the term "fused heterocyclylaryl" refers to a heterocyclyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused heterocyclylaryl" used herein include 3,4-methylenedioxy-1-phenyl,



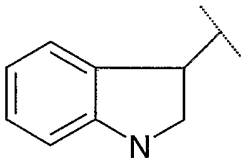
, and the like

As used herein, the term "fused heterocyclylarylene" refers to a fused heterocyclylaryl, wherein the aryl group is divalent. Examples include



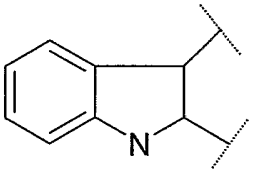
, and the like.

As used herein, the term "fused arylheterocyclyl" refers to an aryl group fused to a heterocyclyl group, the two having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of "fused arylheterocyclyl" used herein include 2-(1,3-benzodioxolyl),



, and the like.

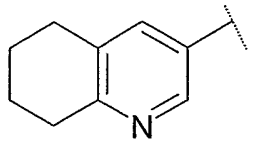
As used herein, the term "fused arylheterocyclylene" refers to a fused arylheterocyclyl, wherein the heterocyclyl group is divalent. Examples include



, and the like.

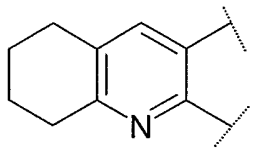
As used herein, the term "fused cycloalkylheteroaryl" refers to a cycloalkyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused cycloalkylheteroaryl" used herein

include 5-aza-6-indanyl,



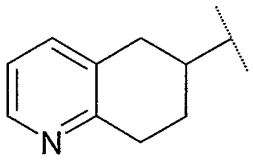
, and the like.

As used herein, the term "fused cycloalkylheteroarylene" refers to a fused cycloalkylheteroaryl, wherein the heteroaryl group is divalent. Examples include



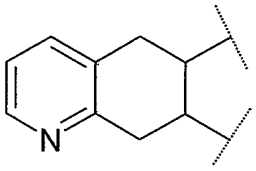
, and the like.

As used herein, the term "fused heteroarylcycloalkyl" refers to a heteroaryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused heteroarylcycloalkyl" used herein include 5-aza-1-indanyl,



and the like.

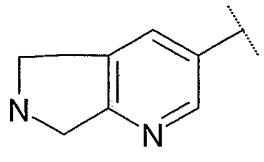
As used herein, the term "fused heteroarylcycloalkylene" refers to a fused heteroarylcycloalkyl, wherein the cycloalkyl group is divalent. Examples include



, and the like.

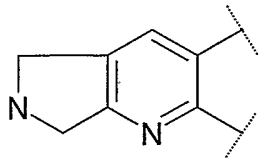
As used herein, the term "fused heterocyclylheteroaryl" refers to a heterocyclyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused heterocyclylheteroaryl" used herein

include 1,2,3,4-tetrahydro-beta-carbolin-8-yl,



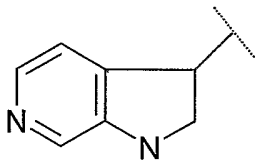
and the like.

As used herein, the term "fused heterocyclylheteroarylene" refers to a fused heterocyclylheteroaryl, wherein the heteroaryl group is divalent. Examples include



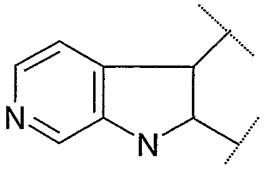
, and the like.

As used herein, the term "fused heteroarylheterocyclyl" refers to a heteroaryl group fused to a heterocyclyl group, the two having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of "fused heteroarylheterocyclyl" used herein include –5-aza-2,3-dihydrobenzofuran-2-yl,



, and the like.

As used herein, the term "fused heteroarylheterocyclylene" refers to a fused heteroarylheterocyclyl, wherein the heterocyclyl group is divalent. Examples include



, and the like.

As used herein, the term "acid isostere" refers to a substituent group that can ionize at physiological pH to bear a net negative charge. Examples of such "acid isosteres" include but are not limited to heteroaryl groups such as, but not limited to, isoxazol-3-ol-5-yl, 1H-tetrazole-5-yl, or 2H-tetrazole-5-yl. Such acid isosteres include but are not limited to heterocyclyl groups such as, but not limited to, imidazolidine-2,4-dione-5-yl, imidazolidine-2,4-dione-1-yl, 1,3-thiazolidine-2,4-dione-5-yl, or 5-hydroxy-4H-pyran-4-on-2-yl.

As used herein, the term "ester isostere" refers to a substituent group that can be metabolically stable and can retain the selectivity and affinity of a corresponding ester toward a target protein. Examples of such "ester isosteres" include, but are not limited to, heteroaryl groups such as, but not limited to, 1,3-oxazole-5-yl, 1,3-oxazole-2-yl, 1,2,3-oxadiazole-5-yl, 1,2,4-oxadiazole-5-yl, 1,3,4-oxadiazole-5-yl, 1,2,3-thiadiazole-5-yl, 1,2,4-thiadiazole-5-yl, 1,3,4-thiadiazole-5-yl, 5-alkyl-1,3-oxazole-2-yl, 2-alkyl-1,3-oxazole-5-yl, 4-alkyl-1,2,3-oxadiazole-5-yl, 3-alkyl-1,2,4-oxadiazole-5-yl, 2-alkyl-1,3,4-oxadiazole-5-yl, 4-alkyl-1,2,3-thiadiazole-5-yl, 3-alkyl-1,2,4-thiadiazole-5-yl, 2-alkyl-1,3,4-thiadiazole-5-yl, 1,2,4-triazole-1-yl, 3-alkyl-1,2,4-triazole-1-yl, tetrazole-1-yl, and 1-alkyl-tetrazole-5-yl; aryl groups such as, but not limited to, 3,5-difluoro-4-alkoxyphenyl; and heterocyclyl groups such as, but not limited to, 1-alkyl-imidazolidine-2,4-dione-5-yl, imidazolidine-2,4-dione-1-yl, 3-alkyl-1,3-thiazolidine-2,4-dione-5-yl, and 5-alkoxy-4H-pyran-4-on-2-yl. The alkyl groups in the heterocyclyl, aryl, and heteroaryl groups of the ester isosteres may be replaced with a phenyl or alkylphenyl group.

As used herein, the term "direct bond", where part of a structural variable specification, refers to the direct joining of the substituents flanking (preceding and succeeding) the variable taken as a "direct bond".

As used herein, the term "alkoxy" refers to the group R_aO-, where R_a is alkyl.

As used herein, the term "alkenyloxy" refers to the group R_aO-, where R_a is alkenyl.

As used herein, the term "alkynyloxy" refers to the group R_aO-, where R_a is alkynyl.

As used herein, the term "alkylsulfanyl" refers to the group R_aS-, where R_a is alkyl.

As used herein, the term "alkenylsulfanyl" refers to the group R_aS-, where R_a is alkenyl.

As used herein, the term "alkynylsulfanyl" refers to the group R_aS-, where R_a is alkynyl.

As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)$-, where R_a is alkyl.

As used herein, the term "alkenylsulfenyl" refers to the group $R_aS(O)$-, where R_a is alkenyl.

As used herein, the term "alkynylsulfenyl" refers to the group $R_aS(O)$-, where R_a is alkynyl.

As used herein, the term "alkylsulfonyl" refers to the group R_aSO_2-, where R_a is alkyl.

As used herein, the term "alkenylsulfonyl" refers to the group R_aSO_2-, where R_a is alkenyl.

As used herein, the term "alkynylsulfonyl" refers to the group R_aSO_2-, where R_a is alkynyl.

As used herein, the term "acyl" refers to the group $R_aC(O)$- , where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyl" refers to the group $R_aC(O)$- , where R_a is aryl.

As used herein, the term "heteroaroyl" refers to the group $R_aC(O)$- , where R_a is heteroaryl.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)$-, where R_a is alkyl.

As used herein, the term "acyloxy" refers to the group $R_aC(O)O$- , where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O$- , where R_a is aryl.

As used herein, the term "heteroaroyloxy" refers to the group $R_aC(O)O$- , where R_a is heteroaryl.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the terms "contain" or "containing" can refer to in-line substitutions at any position along the above defined alkyl, alkenyl, alkynyl or cycloalkyl substituents with one or more of any of O, S, SO, SO_2, N, or N-alkyl, including, for example, -CH_2-O-CH_2-, -CH_2-SO_2-CH_2-, -CH_2-NH-CH_3 and so forth.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "aryl". Designated numbers of carbon atoms (*e.g.* C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl, alkenyl or alkynyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which the term "alkyl" appears as its prefix root.

As used herein, the term "oxo" shall refer to the substituent =O.

As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" shall refer to the substituent -SH.

As used herein, the term "carboxy" shall refer to the substituent -COOH.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the term "aminosulfonyl" shall refer to the substituent $-SO_2NH_2$.

As used herein, the term "carbamoyl" shall refer to the substituent $-C(O)NH_2$.

As used herein, the term "sulfanyl" shall refer to the substituent -S-.

As used herein, the term "sulfenyl" shall refer to the substituent -S(O)-.

As used herein, the term "sulfonyl" shall refer to the substituent $-S(O)_2-$.

As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I)) and a solvent. Such solvents for the purpose of the invention may not sunstantially interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

As used herein, the term "biohydrolyzable ester" is an ester of a drug substance (in this invention, a compound of formula (I)) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable ester is orally absorbed from the gut and is transformed to Formula (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters (e.g., C_1-C_4), lower acyloxyalkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein, the term "biohydrolyzable amide" is an amide of a drug substance (in this invention, a compound of general formula (I)) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable amide is orally absorbed from the gut and is transformed to Formula (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl amides, .alpha-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

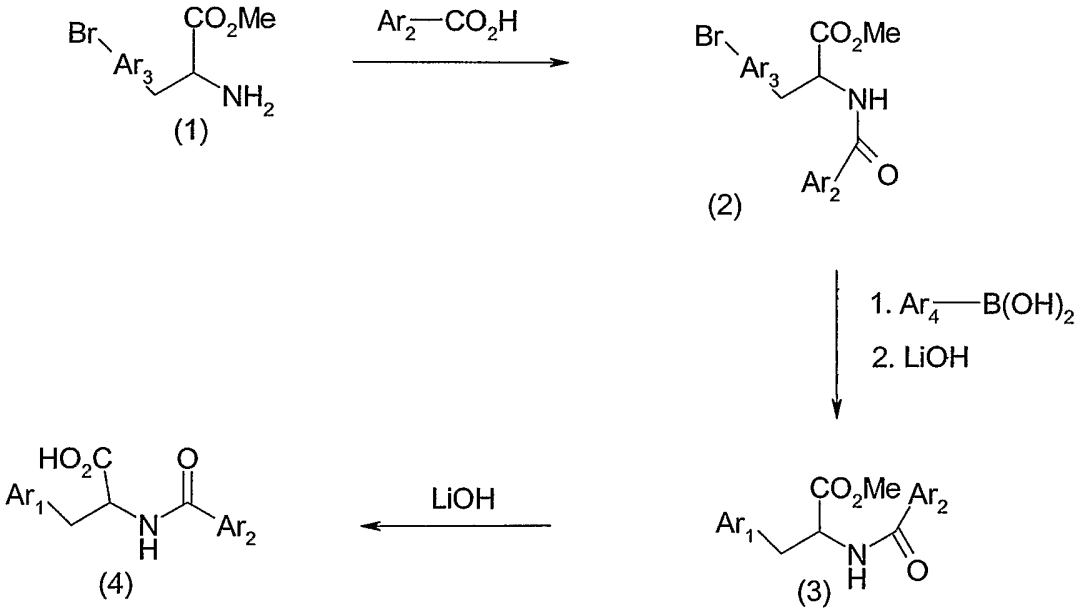
As used herein, the term "prodrug" includes biohydrolyzable amides and biohydrolyzable esters and encompasses a) compounds in which the biohydrolyzable functionality in such a prodrug is encompassed in the compound of formula (I) and b) compounds which may be oxidized or reduced biologically at a given functional group to

yield drug substances of formula (I). Examples of these functional groups include, but are not limited to, 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of Formula (I) along with methods for the preparation of compounds of Formula (I). The compounds can be prepared according to the following reaction Schemes and procedures in which variables are as defined. In these reactions, it is also possible to make use of variants that are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

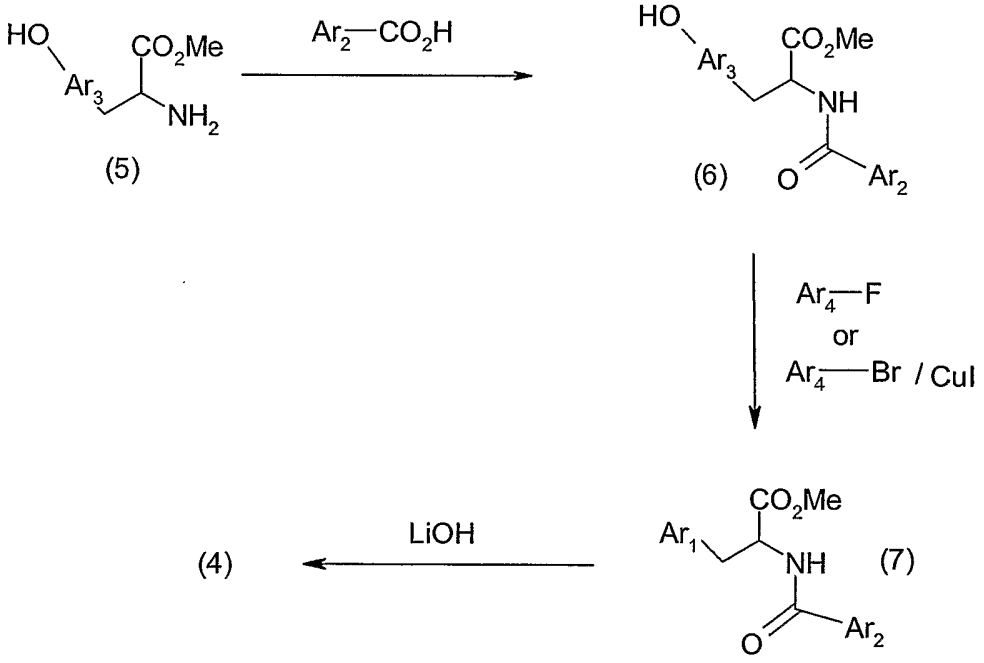
Scheme I describes the synthesis of an intermediate of structure (4). Ar_3 and Ar_4 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme I, in one embodiment, bromo- or iodo- substituted aryl alanine methyl ester (or amino acid esterified in linkage to Wang resin) (1) is treated with a carboxylic acid in the presence of a coupling reagent, such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (2). The resulting amide is then subjected to coupling with an arylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium (0), in the presence of base such as, but not limited to, sodium carbonate to form compound (3). The methyl ester (3) is hydrolyzed using a base such as, but not limited to, LiOH to provide the free carboxylic acid (4), where Ar_1 and Ar_2 are as defined for Formula (I).

Scheme I



Scheme II describes the preparation of a compound of structure (4). Ar_3 and Ar_4 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme II, in another embodiment, an aryl hydroxy amino acid methyl ester (or amino acid esterified in linkage to Wang resin) (5) is treated with a carboxylic acid Ar_2-CO_2H in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (6). The resulting amide is then subjected to: 1) nucleophilic substitutions with an optionally substituted electron – deficient fluoroaromatic or fluoroheteroaromatic in the presence of base such as, but not limited to, potassium carbonate; or 2) coupling with an aryl bromide, or heteroaryl bromide, and copper iodide in the presence of a base including, but not limited to, cesium carbonate to form compound (7). The methyl ester in (7) is hydrolyzed using a base such as LiOH to provide the free carboxylic acid (4), where Ar_1 and Ar_2 are as defined for Formula (I)

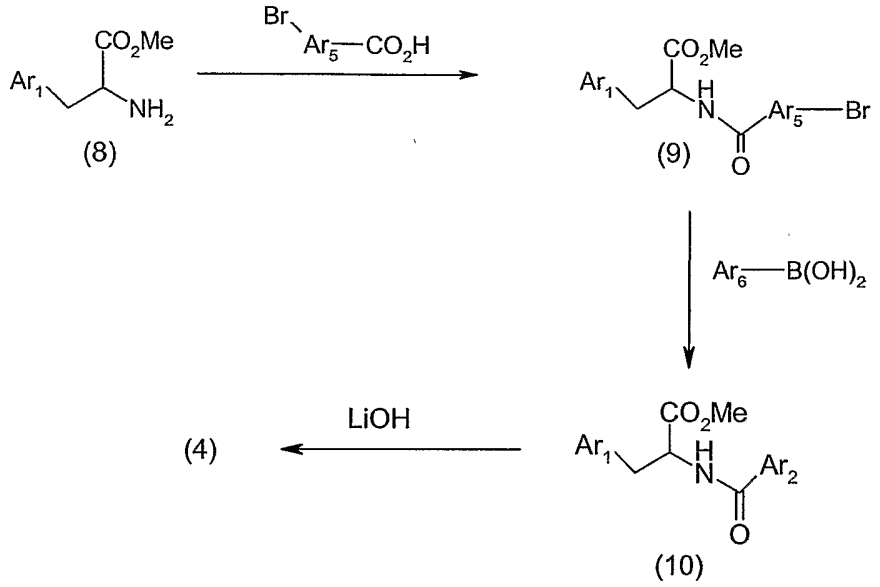
Scheme II



Scheme III describes the preparation of a compouind of formula (4). Ar_5 and Ar_6 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme III, in another embodiment, an amino acid methyl ester (or, alternately, an amino acid esterified in linkage to Wang resin) (8) is treated with a bromo-substituted aryl carboxylic acid in the presence of a coupling reagent such as, but not limited to, diisopropyl

carbodiimide (DIC) to form the amide (9). The resulting amide then is subjected to coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form compound (10). The methyl ester (10) is hydrolyzed using a base such as, but not limited to, LiOH to provide the free carboxylic acid (4), where Ar_1 and Ar_2 are as defined for Formula (I).

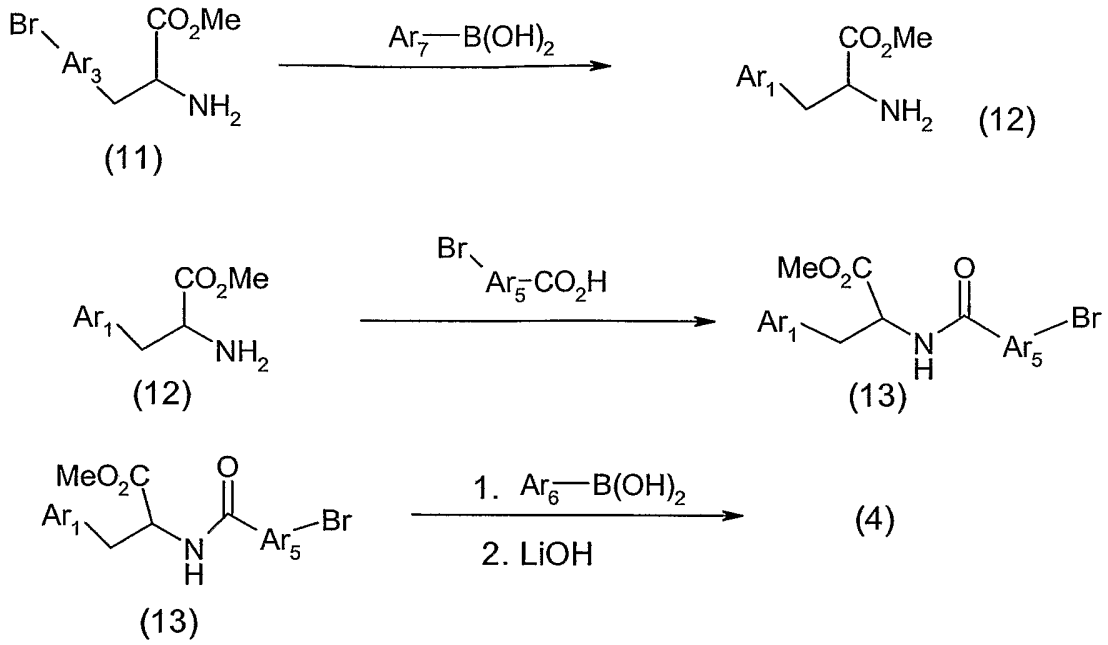
Scheme III



Scheme IV describes the synthesis of a compound of formula (4). Ar_3, Ar_7, Ar_5 and Ar_6 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme IV, in another embodiment, a bromo or iodo aryl alanine methyl ester (or amino acid esterified in linkage to Wang resin) (11) is subjected to coupling with an arylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form compound (12). The resulting compound is treated with a bromo- or iodo-substituted aryl carboxylic acid in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (13). The resulting amide is then subjected to coupling with a arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate, and the product methyl ester is

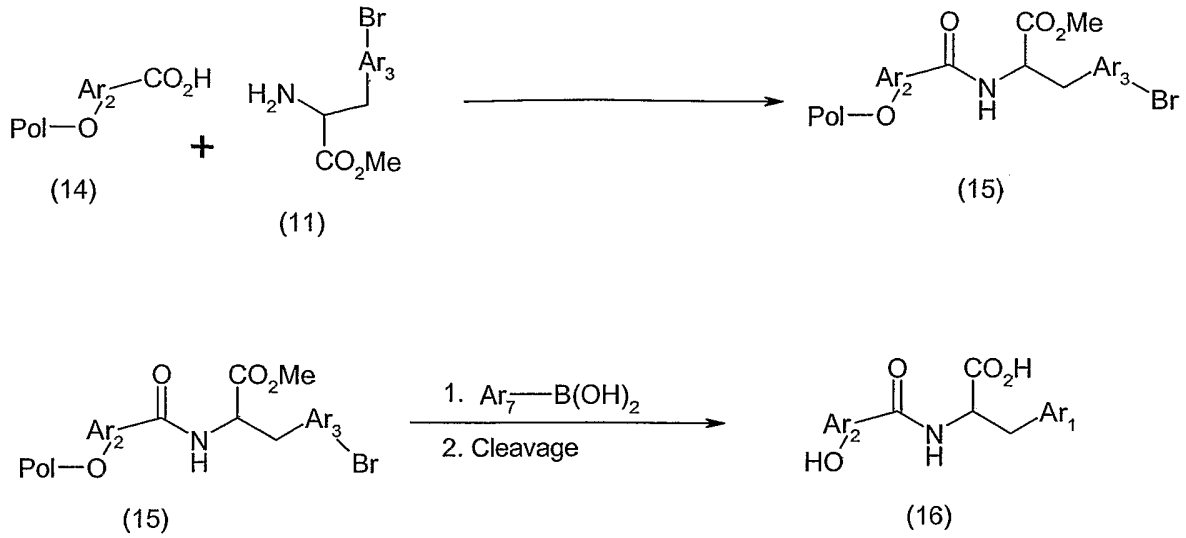
hydrolyzed using a base such as LiOH to provide the free carboxylic acid (4), where Ar_1 and Ar_2 are as defined for Formula (I).

Scheme IV



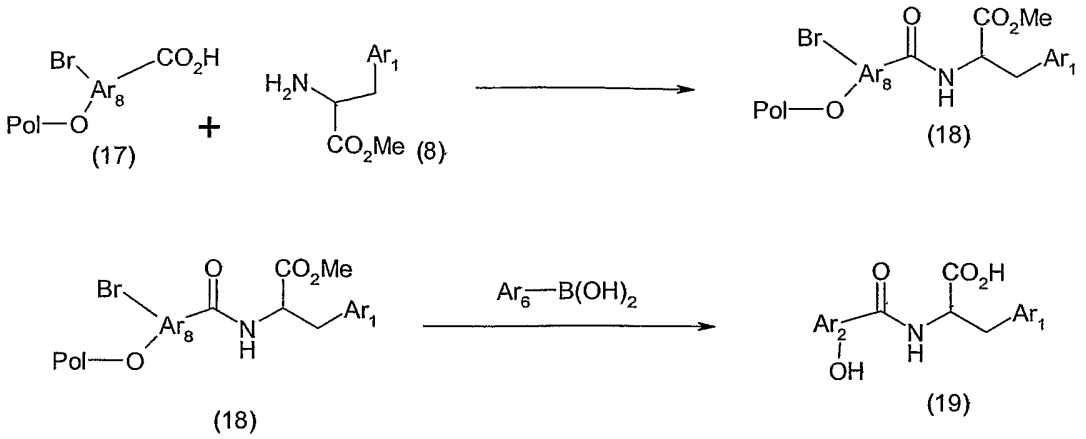
Scheme V describes the preparation of a compound of formula (16). Ar_3 and Ar_7 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. Pol is a functionalized polymeric support, such as, but not limited to, Wang Resin. As shown in Scheme V, in another embodiment, a hydroxy aryl ester loaded onto the Wang Bromo resin or Merrifield resin using base such as, but not limited to, sodium methoxide in DMA, and hydrolyzed to give (14), is coupled with a bromo- or iodo-subsituted aryl amino acid methyl ester (11) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (15). The resulting amide (15) is then subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate followed by cleavage from the resin with TMSBr/TFA/DCM (1:1:1) or a similar suitable cleavage cocktail to yield the desired product (16), where Ar_1 and Ar_2 are as defined for Formula (I).

Scheme V



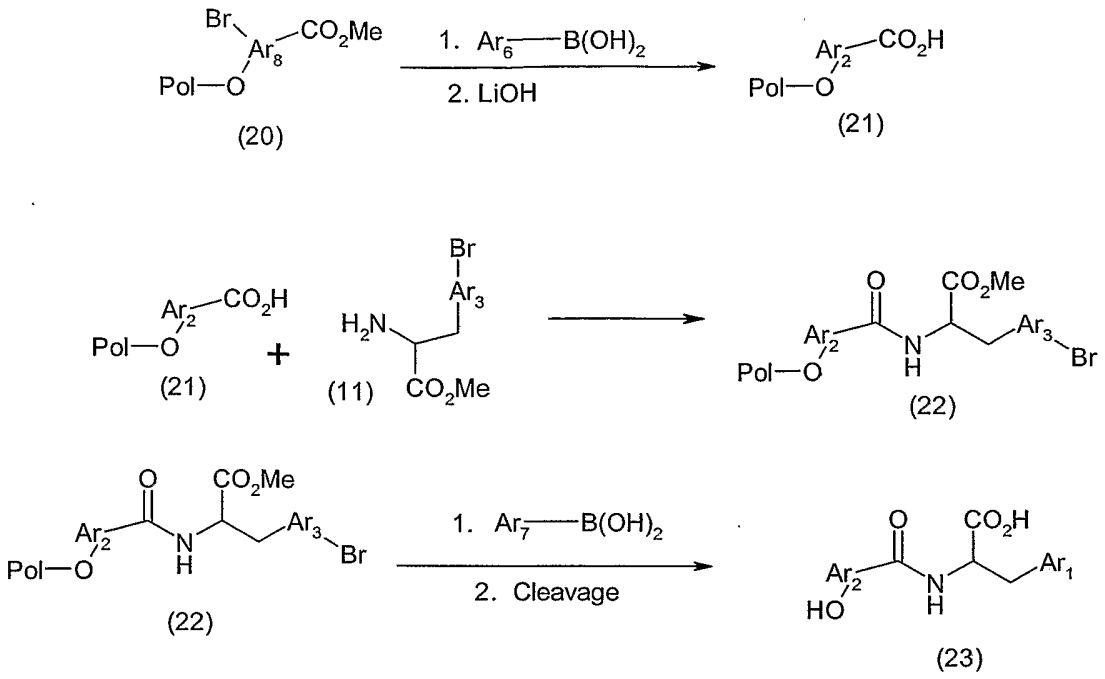
Scheme VI describes the preparation of a compound of formula (19). Ar_6 and Ar_8 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. Pol is a functionalized polymeric support, such as, but not limited to, Wang Resin. As shown in Scheme VI, in another embodiment, a hydroxy aryl ester loaded onto the Wang Bromo resin, Merrifiend resin, or other suitable support using base such as, but not limited to, sodium methoxide in DMA, is hydrolyzed to give (17), and is coupled with an amino acid methyl ester (8) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (18). The resulting amide (18) is then subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate, and is then cleaved from the resin with TMSBr/TFA/DCM (1:1:1) or a similar suitable cleavage cocktail to yield the desired product (19), where Ar_1 and Ar_2 are as defined for Formula (I).

Scheme VI



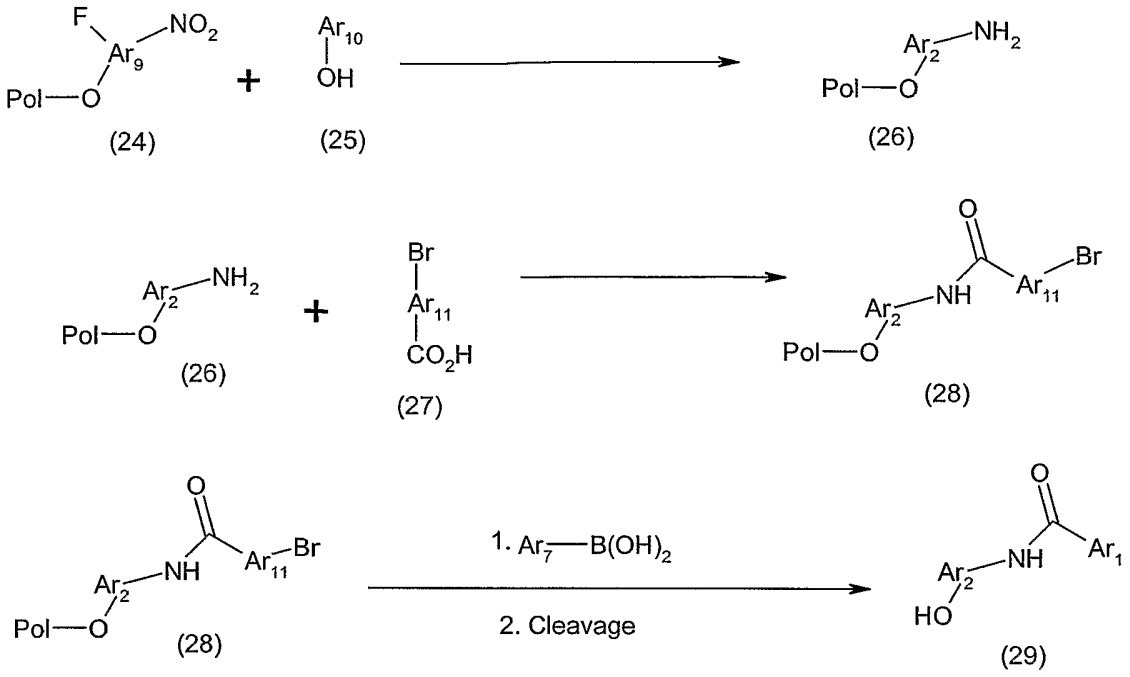
Scheme VII describes the synthesis of a compound of formula (23). Ar_6, Ar_7, and Ar_8 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. Pol is a functionalized polymeric support, such as, but not limited to, Wang Resin. As shown in Scheme VII, in another embodiment, a bromo hydroxy aryl ester (20) loaded onto Wang Bromo resin, Merrifield resin, or other suitable support using base such as, but not limited to, sodium methoxide in DMF, is then subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)plladium(0), in the presence of base such as, but not limited to, sodium carbonate, followed by hydrolysis of the product ester to yield the acid (21). The resulting carboxylic acid (21) is then subjected to coupling with a bromo- or iodo-substituted aryl amino acid methyl ester (11) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (22). The resulting amide (22) is then subjected to a coupling with an arylboronic acid or heteroaryl boronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate followed by cleavage from the resin with TMSBr/TFA/DCM (1:1:1) or a similar cleavage cocktail to yield the desired product (23), where Ar_1 and Ar_2 are as defined for Formula (I).

Scheme VII



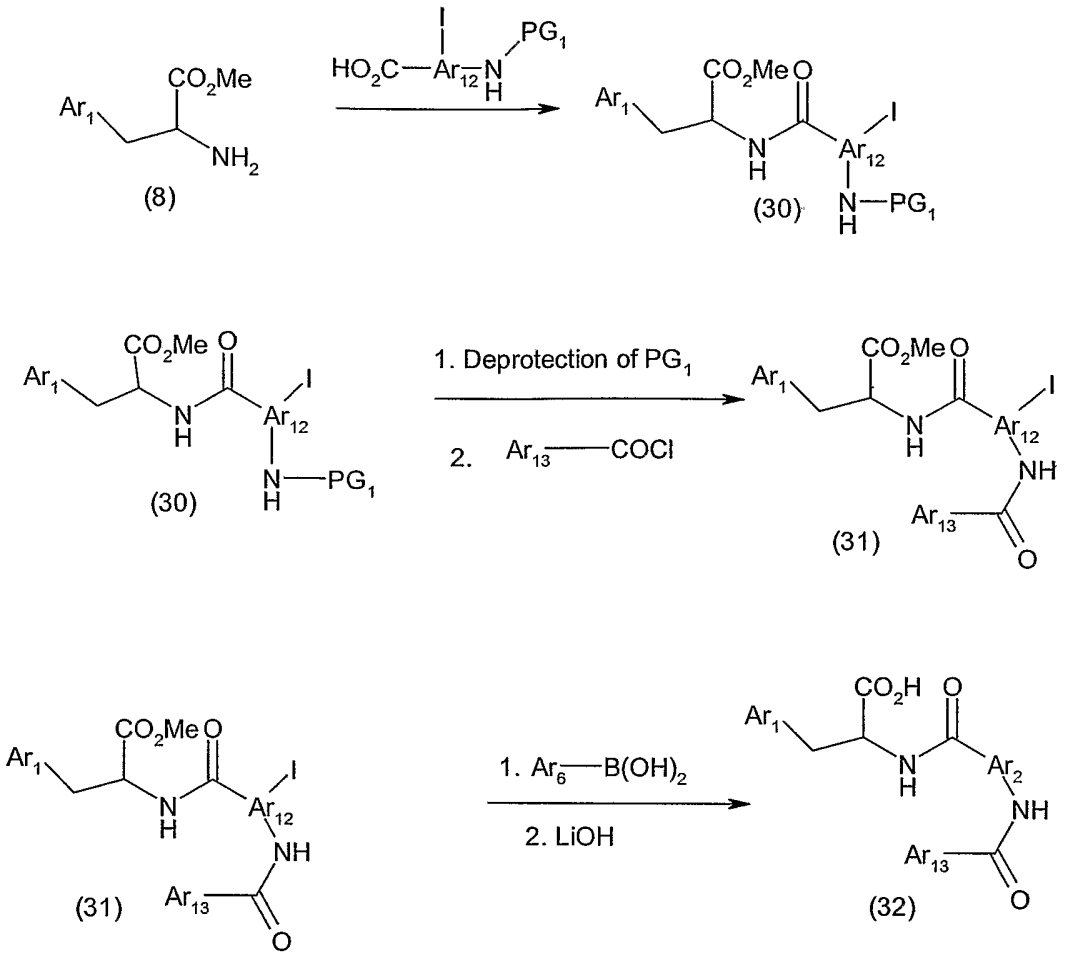
Scheme VIII describes the preparation of a compound of formula (29). Ar_7, Ar_9, Ar_{10}, and Ar_{11} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme VIII, in another embodiment, a fluoro nitro phenol (24) loaded onto a polymer such as Wang Bromo resin using base such as, but not limited to, sodium methoxide in DMA, is then treated with a hydroxy aryl compound (25) in the presence of base, followed by reduction of the nitro group to give the free amine (26). The resulting amine (26) is then subjected to coupling with a bromo- or iodo-substituted aryl acid (27) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (28). The resulting amide (28) is then subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate followed by cleavage from the resin with TMSBr/TFA/DCM (1:1:1) or a similar suitable cleavage cocktail to yield the desired product (29), where Ar_1 and Ar_2 are as defined for Formula (I).

Scheme VIII



Scheme IX describes the preparation of a compound of formula (32). Ar_6, Ar_{12}, and Ar_{13} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. PG_1 is an amino protecting group such as allyloxycarbonyl or tert-butoxycarbonyl. As shown in Scheme IX, in another embodiment, an aryl amino acid methyl ester (8) is reacted with an iodo-subsituted aryl amino carboxylic acid (the amino group of which may be protected with an amino protecting group PG_1 in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) giving the amide (30). The amino group of the amide (30) may be then deprotected, if desired, by treatment with, in the case of PG_1 as tert-butoxycarbonyl, TFA, and is then treated with an aroyl chloride in the presence of a base such as pyridine or TEA to give the iodo amide (31). The amide (31) is subjected to coupling with an arylboronic acid or heteroaryl boronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate. Hydrolysis of the product methyl ester with an alkaline reagent such as LiOH provides compound (32), where Ar_1 and Ar_2 are as defined for Formula (I).

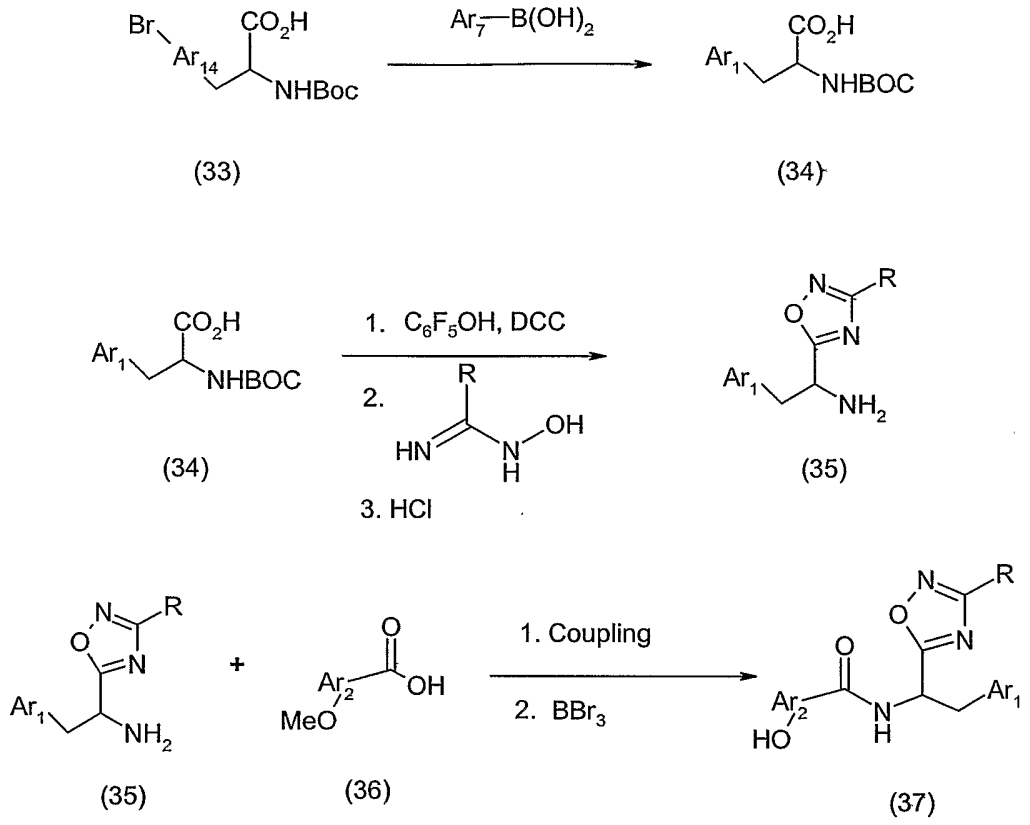
Scheme IX



Scheme X describes the preparation of a compound of formula (37). Ar_{14} and Ar_7 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. R is a group such as methyl, trifluromethyl, t-butyl, alkylene-sulfonyl alkyl or alkylene sulfonyl aryl, aryl, heterocyclyl. As shown in Scheme X, in another embodiment, a bromo or iodo aryl alanine t-butylcarbamate (or amino acid esterified in linkage to Wang resin) (33) is subjected to coupling with an arylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form compound (34). The resulting acid is subjected to esterification with pentafluorophenol in the presence of a coupling reagent such as, but not limited to, DCC to form the ester, which is then treated with hydroxyamidine to yield oxadiazole. The resulting BOC oxadiazole is deprotected using HCl to provide the free amino oxadiazole (35). The amine is then coupled with the methoxy substituted aryl carboxylic acid (36) in the presence of a coupling reagent such as, but not limited to, HBTU,

to form the amide. The resulting amide-methyl ether is hydrolyzed using agent such as, but not limited to, BBr_3 to provide free phenol (37), where Ar_1 and Ar_2 are as defined for formula(I).

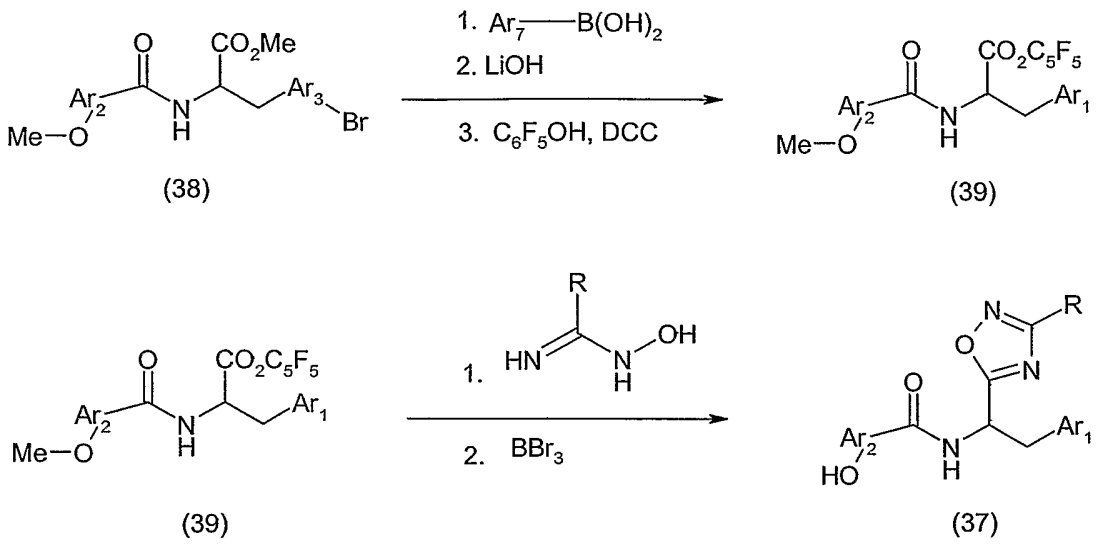
Scheme X



Scheme XI describes the preparation of a compound of formula (37). Ar_3 and Ar_7 are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. R is a group such as methyl, trifluromethyl, t-butyl, alkylene-sulfonyl alkyl or alkylene sulfonyl aryl, aryl, heterocyclyl. As shown in Scheme XI, in another embodiment, a bromo or Iodo methoxy ester (38) (as shown in Scheme VII, but starting from bromomethoxy arylcarboxy ester) is subjected to coupling with an arylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form the bisaryl ester which is hydrolyzed to the corresponding acid with LiOH. The resulting acid is then esterified using pentaflurophenol and in the presence of coupling reagent such as, but not limited to, DCC to provide methoxyester (39). The ester (39) is converted to oxadiazole using hydroxylamidine and the

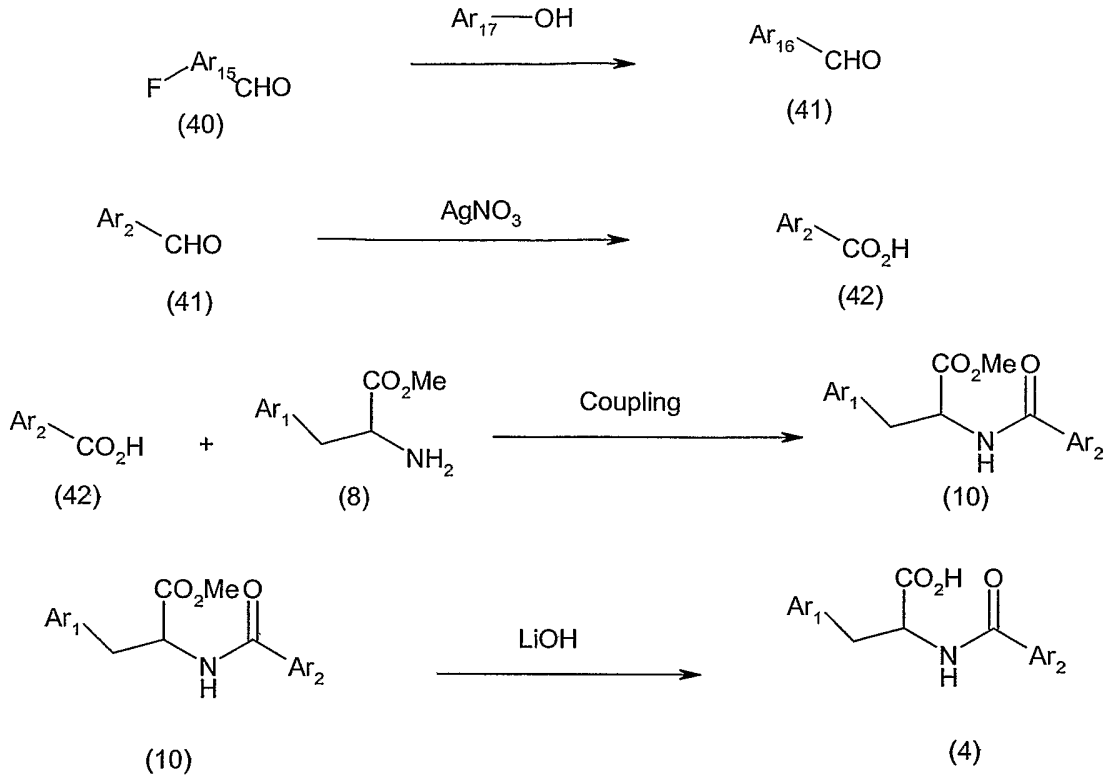
resulting methoxy oxadiazole is hydrolyzed with BBr_3 to obtain the free phenol (37), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XI



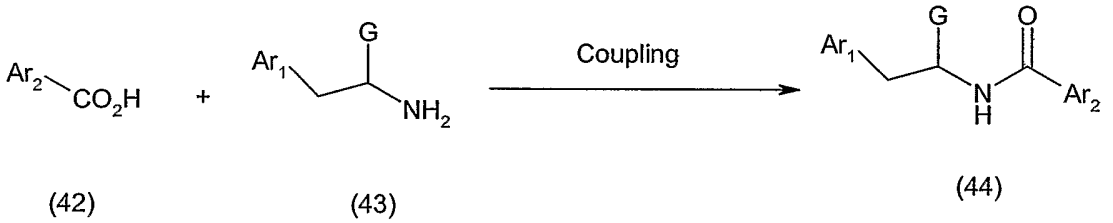
Scheme XII describes the preparation of a compound of formula (4). Ar_{15}, Ar_{16}, and Ar_{17} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme XII, in another embodiment, a fluoro aryl aldehyde (40) is treated with a hydroxy aryl compound in the presence of base, such as, but not limited to, sodium methoxide in DMA, to afford aryloxyaryl aldehyde (41) which is then oxidized with oxidation agent such as, but not limited to, silver nitrate to provide aryl carboxylic acid (42). The acid (42) is subjected to a coupling reaction with amine (8) using coupling reagent diisopropyl carbodimide (DIC) to give the amide (10). The resulting ester-amide(10) is hydrolyzed with LiOH to yield free carboxylic acid (4), where Ar_1 and Ar_2 are as defined for formula(I).

Scheme XII



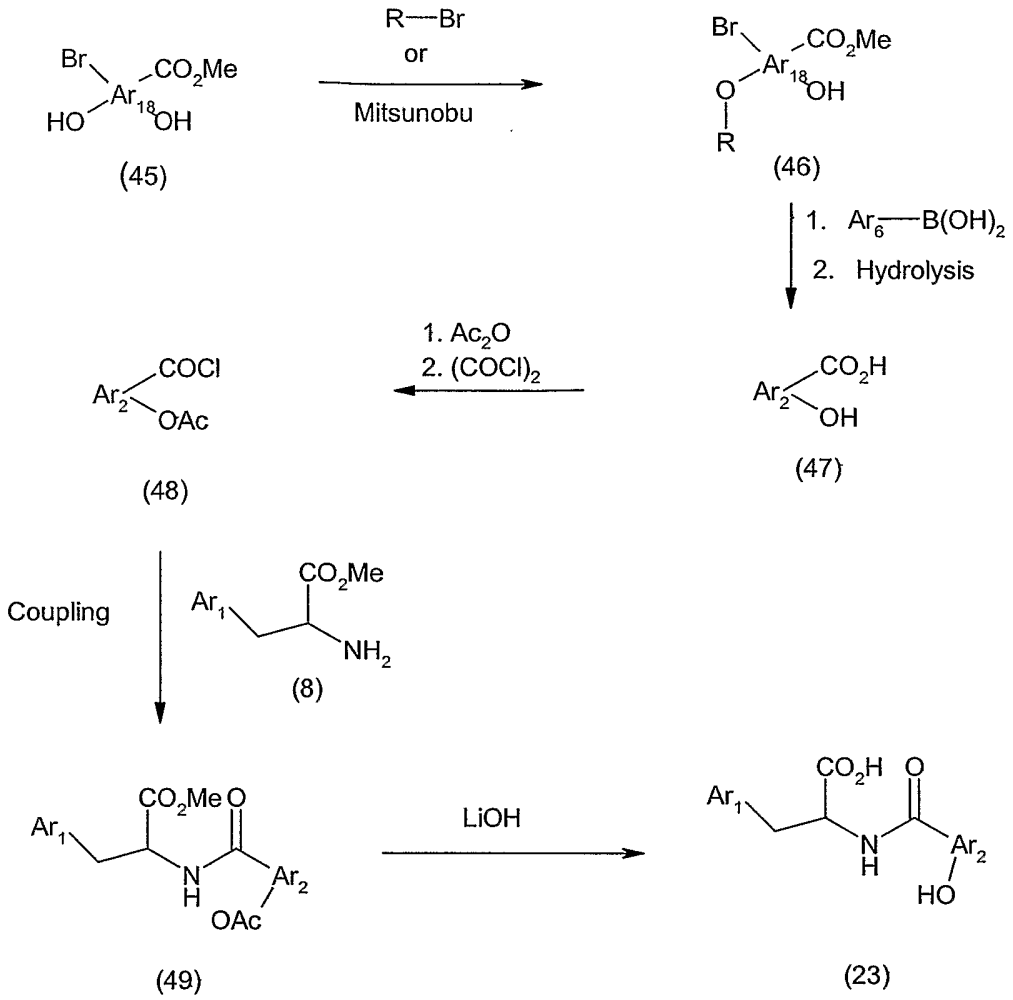
Scheme XIIa describes the preparation of a compound of formula (44). As shown in scheme XIIa, the acid (42) is coupled with an amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, or an ester isostere, such as, but not limited to, oxadiazole or oxazole, using a coupling reagent such as, but not limited to, DCC to give the amide (44), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XIIa



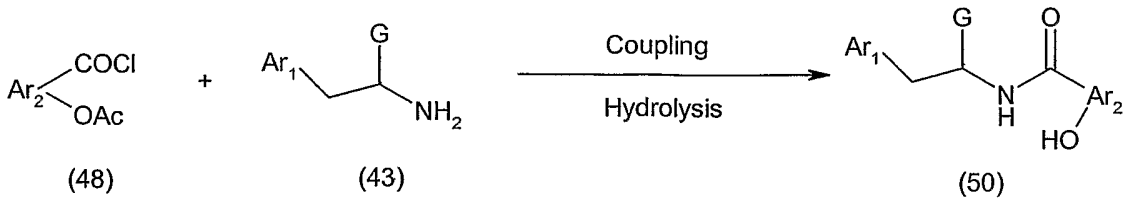
Scheme XIII describes the preparation of a compound of formula (23). Ar_6 and Ar_{18} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme XIII, in another embodiment, a bromo or iododihydroxyaryl ester (45) is converted to monohydroxyaryl ester (46) using alkylation method with alkyl halide (RBr) in the presence of base such as but not limited to, Cs_2CO_3 or Mitsunobu method using alkyl alcohol in the presence of diethylazadicarboxylate (DEAD). The resulting bromohydroxy ester (46) is subjected to coupling with an arylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form the bisaryl ester which is hydrolysed to the corresponding acid (47) with LiOH. The hydroxyl acid (47) is then subjected to acetylation followed by acid chloride formation using acetic anhydride and oxalyl chloride, respectively, to provide the acid choride (48). Treatment of the acid chloride with the amine (8) in the presence of a base such as but not limited to, diisopropylethylamine, yields the amide (49), which then hydrolyzed using LiOH to provide the free acid (23), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XIII



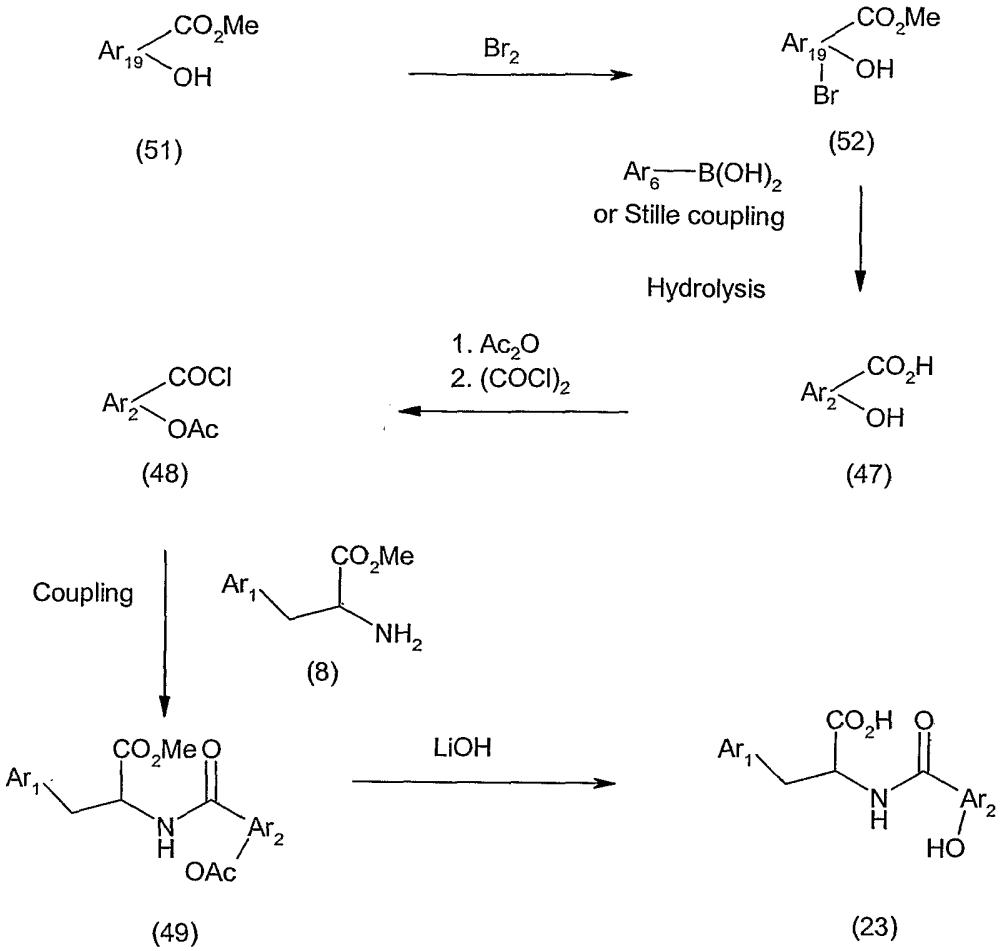
Scheme XIIIa describes the preparation of a compound of formula (50). As shown in Scheme XIIIa, the acid chloride (48) is coupled with the amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, or an ester isostere such as, but not limited to, oxadiazole and oxazole in the presence of base such as, but not limited to DIEA to give the acetate-amide, which is then hydrolyzed using base such as but not limited to, LiOH to provide the free phenol (50), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XIIIa



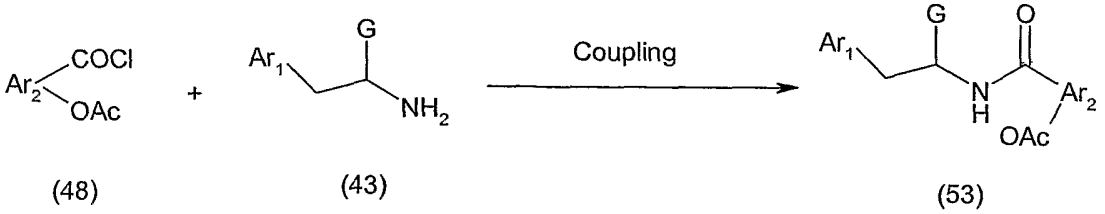
Scheme XIV describes the preparation of a compound of formula (23). Ar_6 and Ar_{19} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme XIV, in another embodiment, hydroxylaryl ester (51) is brominated using brominating agent such as bromine but not limited to, to provide bromo ester (52). The bromohydroxy ester (52) is subjected to either Suzuki coupling with an arylboronic acid in the presence of a catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate or Stille coupling with alkyl or aryl stananes in the presence of a catalyst such as but not limited to, tetrakis(triphenylphosphine)palladium(0) to form the hydroxy ester which is hydrolyzed to the corresponding acid (47) with LiOH. The hydroxyl acid (47) is then subjected to acetylation followed by acid chloride formation using acetic anhydride and oxalyl chloride, respectively, to provide the acid choride (48). Treatment of the acid chloride (48) with the amine (8) in the presence of a base such as but not limited to, diisopropylethylamine, to yield the amide (49), which then hydrolyzed using LiOH to provide the free acid (23), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XIV



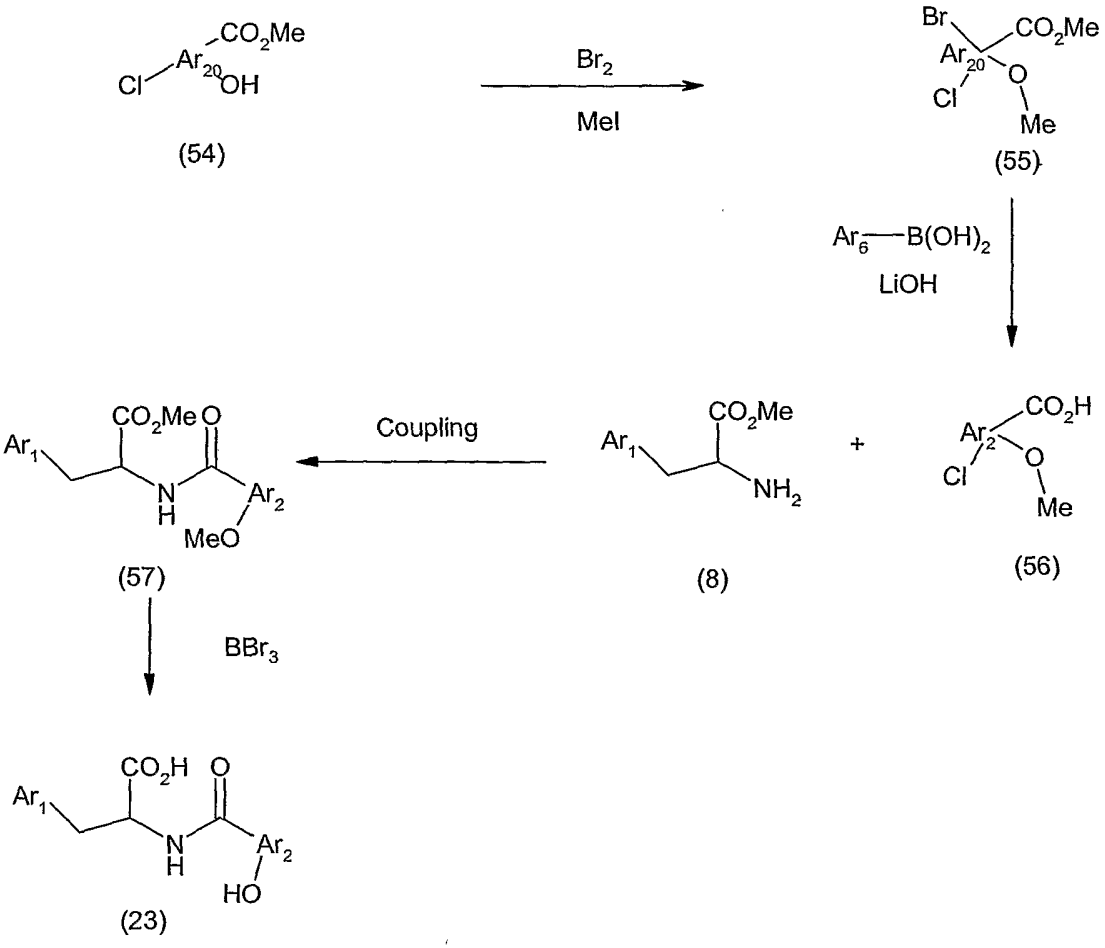
Scheme XIVa describes the preparation of a compound of formula (53). As shown in scheme XIVa, the acid chloride (48) is coupled with the amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, and an ester isostere, (such as, but not limited to, oxadiazole and oxazole) in the presence of a base such as, but not limited to, DIEA to give the acetate-amide, which is then hydrolyzed using base such as, but not limited to, LiOH to provide the free phenol (53), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XIVa



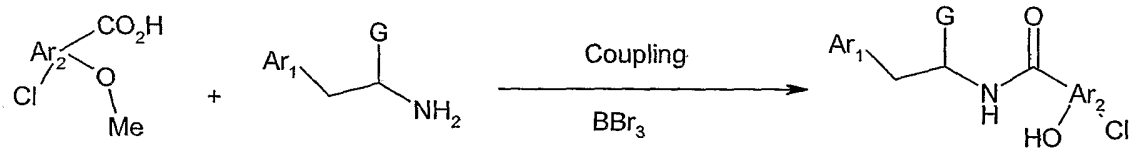
Scheme XV describes the preparation of a compound of formula (23). Ar_6 and Ar_{20} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme XV, in another embodiment, chlorohydroxylaryl ester (54) is brominated using brominating agent such as bromine but not limited to, to provide bromo ester which was then alkylated with MeI in the presence of base such as but not limited to, potassium carbonate to provide dihalomethoxy ester (55). The bromomethoxy ester (55) is subjected to Suzuki coupling with an arylboronic acid in the presence of a catalyst such as but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form the methoxy ester which is hydrolyzed to the corresponding acid (56) with LiOH. The methoxy acid (56) is then coupled with the amine (8) using a coupling agent such as, but not limited to, HBTU to form the amide (57). The methyl ether (57) is then hydrolyzed using BBr_3 to yield the hydroxy acid (23), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XV



Scheme XVa describes the preparation of a compound of formula (58). As shown in scheme XVa, the methoxy acid (56) is coupled with a amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, and an ester isostere, (such as, but not limited to, oxadiazole and oxazole) using a coupling reagent such as, but not limited to HBTU to give the methoxyamide, which is then hydrolyzed using an agent such as but not limited to, BBr_3 to provide the free phenol (58), where Ar_1 and Ar_2 are as defined for formula(I).

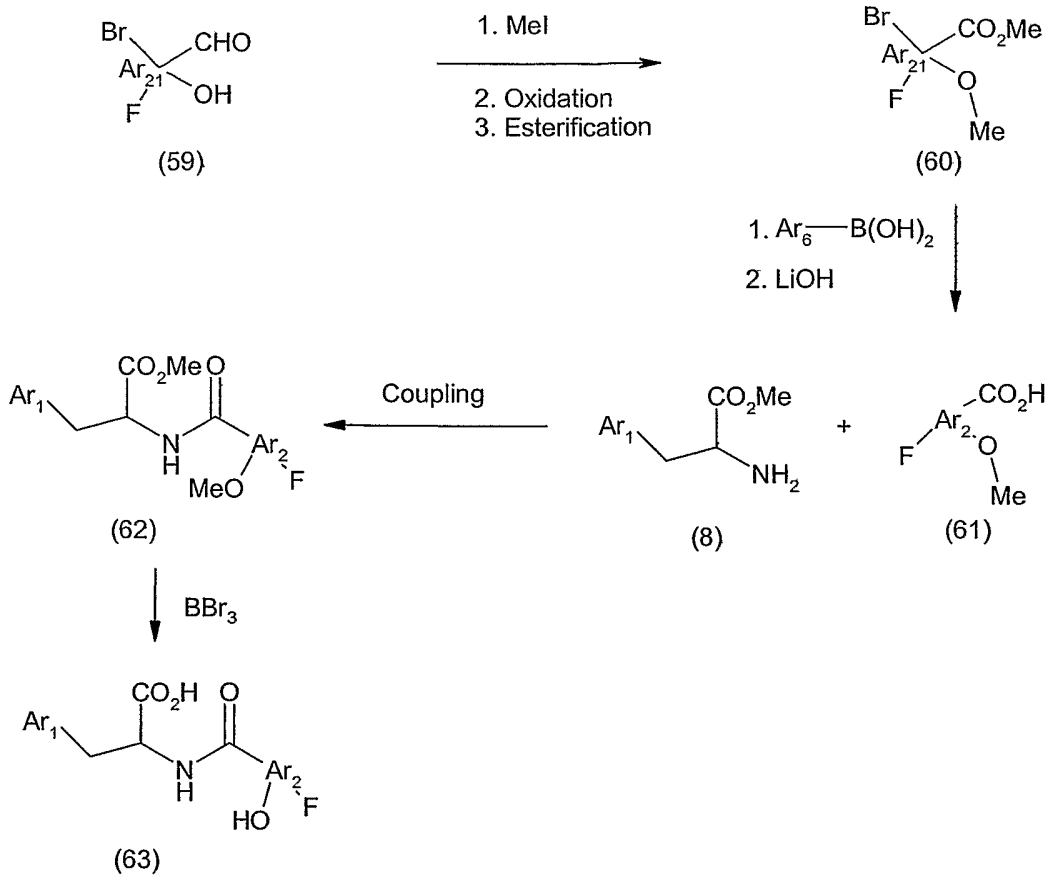
Scheme XVa



(56) (43) (58)

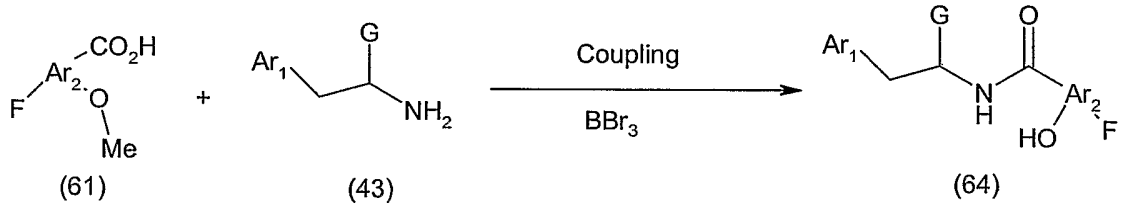
Scheme XVI describes the preparation of a compound of formula (63). Ar_6 and Ar_{21} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme XVI, in another embodiment, fluorobromoarylaldehyde (59) is subjected to alkylation with MeI using a base such as but not limited to, potassium carbonate followed by oxidation using reagent such, as but not limited to, pyridinium dichromate (PDC) to provide methoxy acid which is then coverted to the ester using esterification methods such as, but not limited to, methanolic HCl to obtain methoxyester (60). The dihalomethoxy ester (60) is subjected to Suzuki coupling with an arylboronic acid in the presence of a catalyst such as but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form the methoxy ester which is hydrolyzed to the corresponding acid (61) with LiOH. The methoxy acid (61) is then coupled with the amine (8) using coupling agent such as, but not limited, to HBTU to form the amide (62). The methyl ether (62) is then hydrolyzed using BBr_3 to yield the hydroxyl ester(63), which is hydrolyzed with LiOH to provide hydroxy acid (63), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XVI



Scheme XVIa describes the preparation of a compound of formula (64). As shown in scheme XVIa, the methoxy acid (61) is coupled with a amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, and an ester isostere, (such as, but not limited to, oxadiazole and oxazole) using a coupling reagent such as, but not limited to, DCC to give the methoxyamide, which is then hydrolyzed using an agent such as, but not limited to, BBr_3 to provide the free phenol (64), where Ar_1 and Ar_2 are as defined for formula (I).

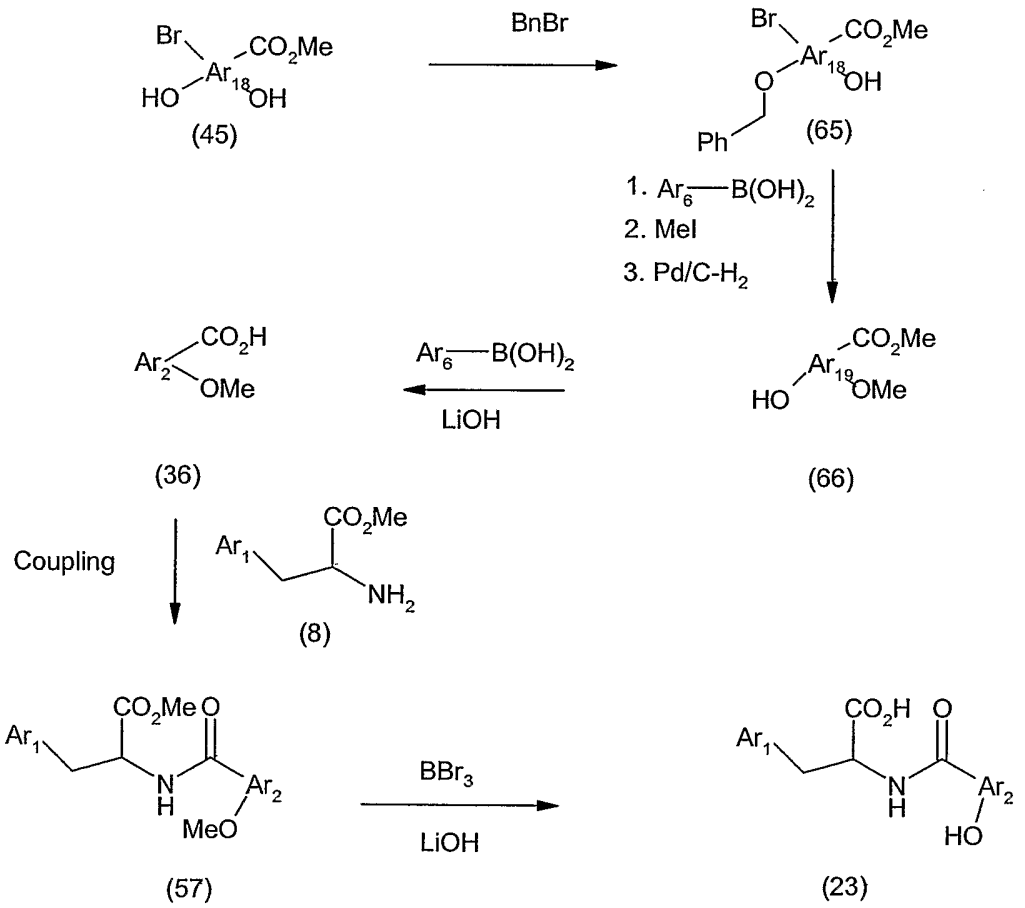
Scheme XVIa



Scheme XVII describes the preparation of a compound of formula (23). Ar_6 and Ar_{18} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system.

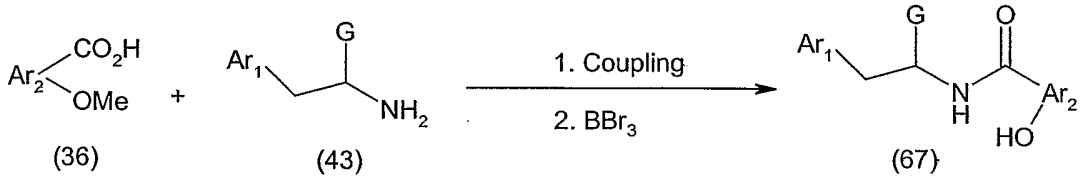
As shown in Scheme XVII, in another embodiment, a bromo or iododihydroxyaryl ester (45) is converted to monohydroxyaryl ester (65) using alkylation method with benzyl bromide in the presence of base such as but not limited to, Cs_2CO_3. The bromoester (65) is then subjected to Suzuki coupling with an arylboronic acid in the presence of a catalyst such as but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form the hydroxy ester which is alkylated using MeI. The methoxy ester is reduced using Pd/C in the presence of hydrogen gas to obtain the hydroxyl ester (66). The hydroxyl ester is then subjected to oxidative coupling using aryl boronic acid in the presence of copper acetate to obtain aryloxy arylester which is then hydrolyzed with LiOH to provide methoxy acid (36). The methoxy acid (36) is then coupled with the amine (8) using coupling agent such as, but not limited to, HBTU to form the amide (57). The methyl ether (57) is then subjected to hydrolysis using BBr_3 and subsequent ester hydrolysis with LiOH to yield the hydroxyl acid (23), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XVII



Scheme XVIIa describes the preparation of a compound of formula (64). As shown in scheme XVIIa, the methoxy acid (36) is coupled with a amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, and an ester isostere, (such as, but not limited to, oxadiazole and oxazole) using a coupling reagent such as, but not limited to, HBTU to give the methoxyamide, which is then hydrolyzed using an agent such as, but not limited to, BBr_3 to provide the free phenol (67), where Ar_1 and Ar_2 are as defined for formula (I).

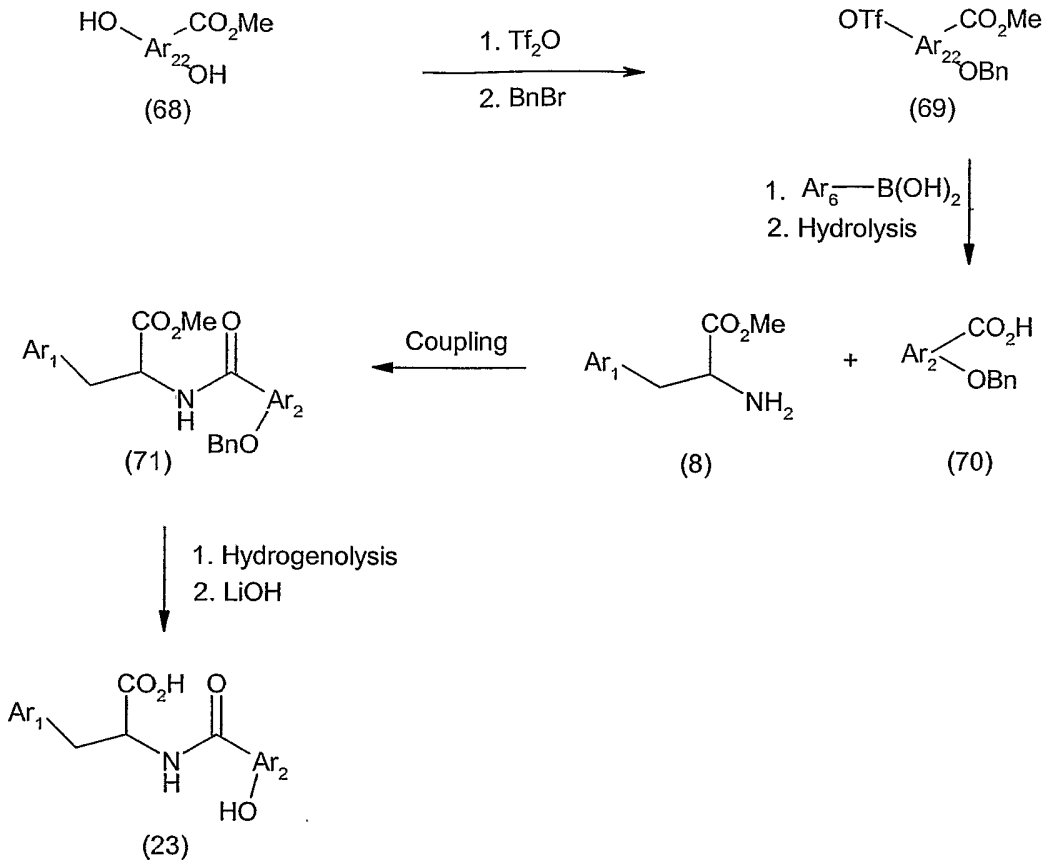
Scheme XVIIa



(36) (43) (67)

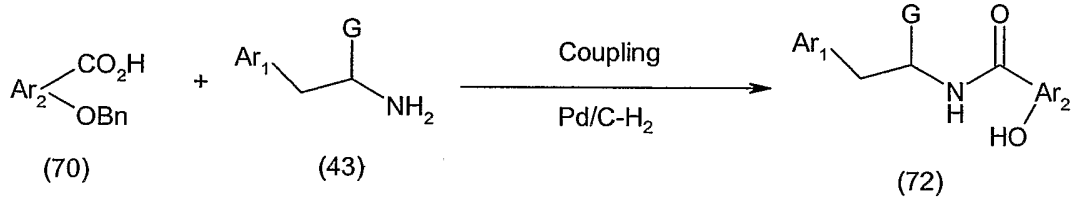
Scheme XVIII describes the preparation of a compound of formula (23). Ar_6 and Ar_{22} are, independently, groups such as, but not limited to, a heteroaryl or aryl ring system. As shown in Scheme XVIII, in another embodiment, a bromo or dihydroxyaryl ester (68) is treated with triflic anhydride to obtain the hydroxy triflate which is then alkylated with benzyl bromide to get benzyloxy ester (69). The benzyloxyester (69) is then subjected to Suzuki coupling with an arylboronic acid in the presence of a catalyst such as but not limited to, tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form the hydroxy ester which is hydrolyzed to the corresponding acid (70) with LiOH. The benzyloxy acid (70) is then coupled with the amine (8) using coupling agent such as, but not limited to, HBTU to form the amide (71). The benzyl ether (71) is then subjected to hydrogenolysis and hydrolysis using Pd/C catalyst in the presence of hydrogen and LiOH, respectively, to obtain the free acid (23), where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XVIII



Scheme XVIIIa describes the preparation of a compound of formula (72). As shown in scheme XVIIIa, the benzyloxy acid (70) is coupled with a amine (43), wherein G is an acid isostere such as, but not limited to, tetrazole, and an ester isostere, (such as, but not limited to, oxadiazole and oxazole) using a coupling reagent such as, but not limited to, HBTU to give the methoxyamide, which is then subjected to hydrogenolysis using Pd/C in the presence of hydrogen to provide the free phenol (72), where Ar_1 and Ar_2 are as defined for formula (I).

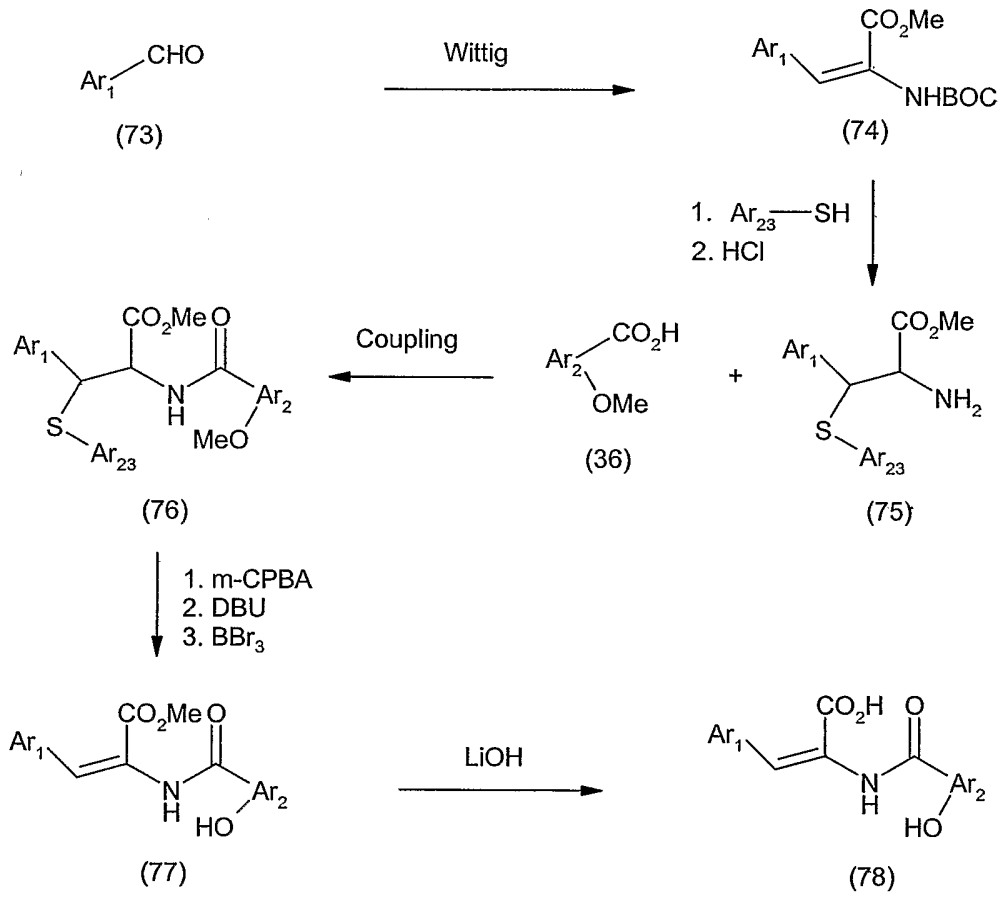
Scheme XVIIIa



Scheme XIX describes the preparation of a compound of formula (78). Ar_{23} is a group such as, but not limited to, a heteroaryl, aryl, alkylene-aryl, or alkyl group. As shown

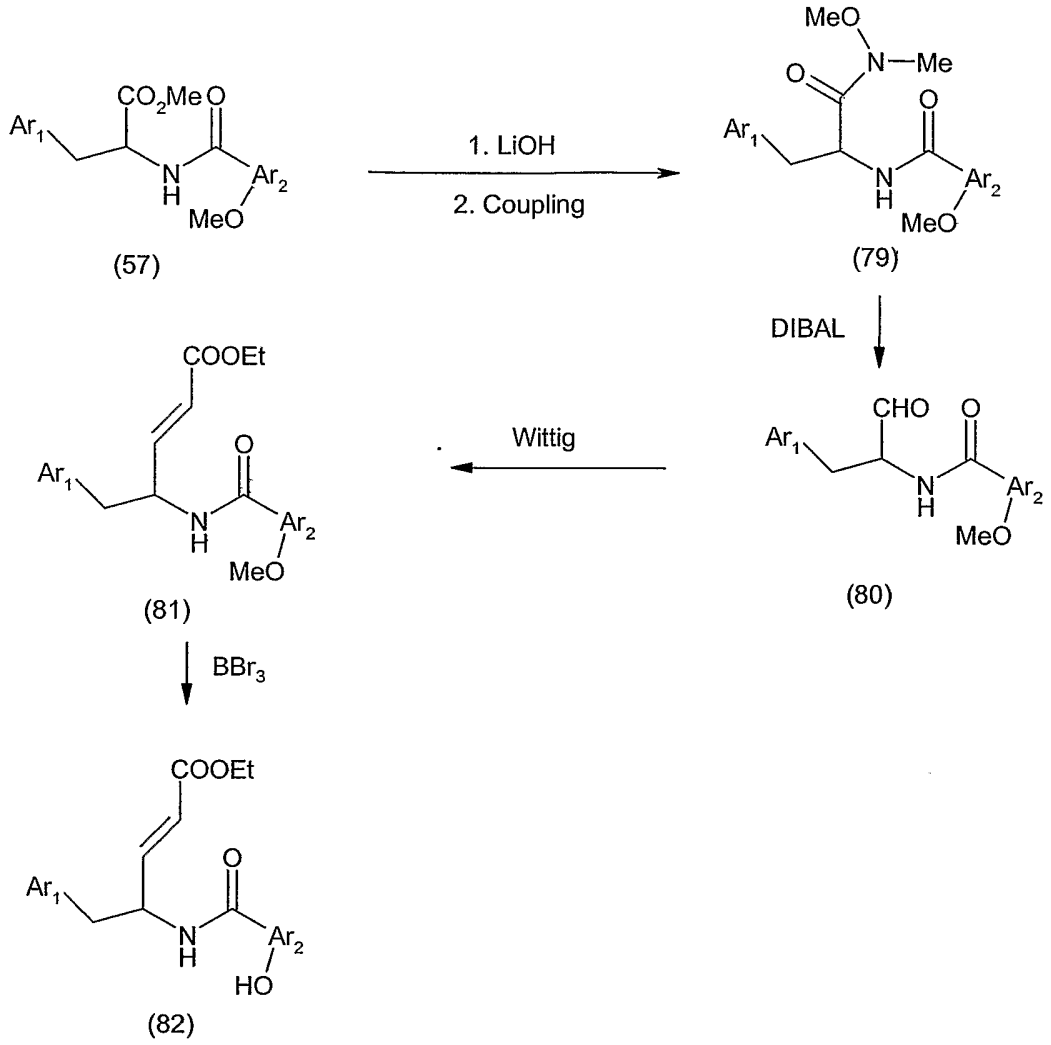
in Scheme XIX, in another embodiment, an arylaldehyde (73) is subjected to Wittig reaction to obtain the dehydroaminoester (74). The dehydroaminoester is then treated with $Ar_{23}SH$, followed by the hydrolysis using HCl to obtain the aminoester (75). The amino ester is then coupled with methoxy acid (36) using a coupling agent such as, but not limited to, HBTU, to provide the amide (76). The amide is subjected to oxidation with metachloroperbenzoic acid and the resulting sulfone is treated with DBU to obtain methoxy ester and the methyl ether is hydrolyzed with BBr_3 to provide the free phenol (77). The hydroxyester is hydrolyzed to free carboxylic acid (78) using LiOH, where Ar_1 and Ar_2 are as defined for formula (I).

Scheme XIX



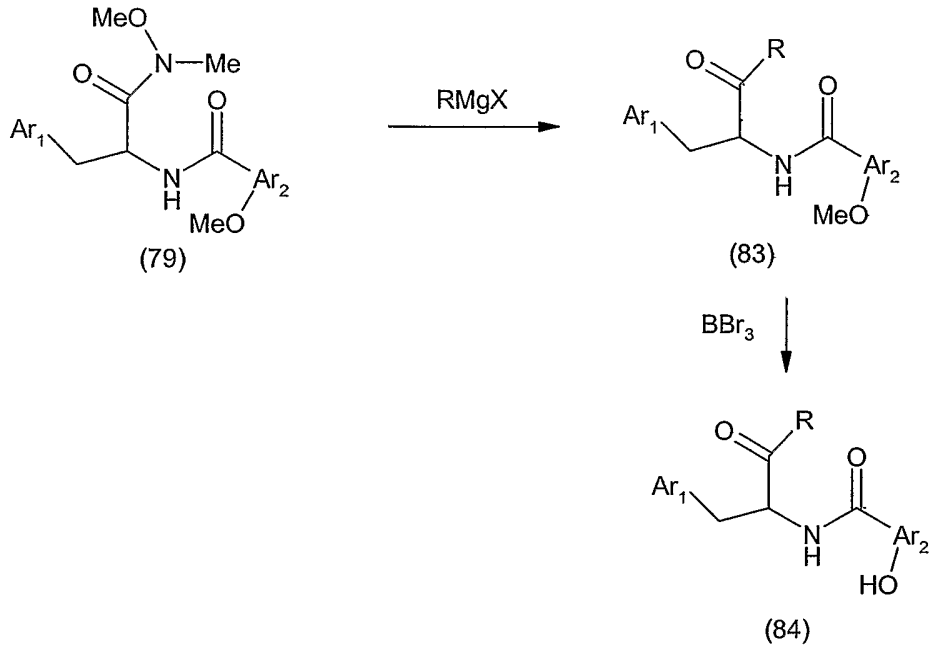
Scheme XX describes the preparation of a compound of formula (82). As shown in Scheme XX, in another embodiment, the methoxy methyl ester (57) is hydrolyzed with LiOH and then coupled with N,O-dimethylhydroxylamine using HBTU to obtain the Weinreb amide (79). The amide (79) is then reduced with DIBAL to get the aldehyde (80). The aldehyde (80) is then subjected to Wittig reaction to provide the alpha,beta-unsaturated ester (81). The methyl ether (81) is then hydrolyzed with BBr_3 to obtain the free phenol (82).

Scheme XX



Scheme XXI describes the preparation of a compound of formula (84). As shown in Scheme XXI, in another embodiment, the Weinreb amide (79) is treated with Grignard reagent (RMgX, where R is alkyl, aryl, heteroaryl and X is a halogen) to obtain the ketone (83). The methyl ether (83) is hydrolyzed with BBr_3 to get the free phenol (84).

Scheme XXI



The term "amino protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include the formyl group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxy-carbonyl, 2-(4-xenyl)iso-propoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("FMOC"), t-butoxycarbonyl ("BOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-

(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; the benzoylmethylsulfonyl group, the 2-(nitro)phenylsulfenyl group, the diphenylphosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the compound of Formula (I) and can be removed at the desired point without disrupting the remainder of the molecule. Examples of commonly used amino-protecting groups are the allyloxycarbonyl, the t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, and the trityl groups. Similar amino-protecting groups used in the cephalosporin, penicillin and peptide art are also embraced by the above terms. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected amino" or "protected amino group" defines an amino group substituted with an amino-protecting group discussed above.

The term "hydroxyl protecting group" as used herein refers to substituents of the alcohol group commonly employed to block or protect the alcohol functionality while reacting other functional groups on the compound. Examples of such alcohol -protecting groups include the 2-tetrahydropyranyl group, 2-ethoxyethyl group, the trityl group, the trichloroacetyl group, urethane-type blocking groups such as benzyloxycarbonyl, and the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyldimethylsilyl, phenyldimethylsilyl, triiospropylsilyl and thexyldimethylsilyl. The choice of of alcohol-protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected hydroxyl" or "protected alcohol" defines a hydroxyl group substituted with a hydroxyl - protecting group as discussed above.

The term "carboxyl protecting group" as used herein refers to substituents of the carboxyl group commonly employed to block or protect the -OH functionality while reacting other functional groups on the compound. Examples of such alcohol -protecting groups include the 2-tetrahydropyranyl group, 2-ethoxyethyl group, the trityl group, the allyl group, the trimethylsilylethoxymethyl group, the 2,2,2-trichloroethyl group, the benzyl group, and

the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyldimethylsilyl, phenyldimethylsilyl, triiospropylsilyl and thexyldimethylsilyl. The choice of carboxyl protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected carboxyl" defines a carboxyl group substituted with a carboxyl -protecting group as discussed above.

The invention also provides pharmaceutical compositions comprising the antiviral active compounds of the invention. Thus, in another embodiment, the present invention comprises a pharmaceutical composition comprising the compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents. The term "pharmaceutical composition" is used herein to denote a composition that may be administered to a mammalian host, *e.g.*, orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or by infusion techniques.

The compounds and compositions of the present invention may be administered to a subject in a therapeutically effective amount. The term "therapeutically effective amount" is used herein to denote that amount of a drug or pharmaceutical agent that will elicit the therapeutic response of an animal or human that is being sought.

The pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically -acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid;

binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; or dispersing or wetting agents, such as a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alchol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectible aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions of suspensions, etc., containing the compounds of the invention are contemplated. For the purpose of this application, topical applications shall include eyedrops, mouth washes and gargles.

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

Also provided by the present invention are prodrugs of the invention.

Pharmaceutically-acceptable salts of the compounds of the present invention, where a basic or acidic group is present in the structure, are also included within the scope of the invention. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrocloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Methanesulfonate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. When an acidic substituent is present, such as–COOH, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxlate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethanesulfonate, picrate and the like, and include acids related to the pharmaceutically-acceptable salts listed in the Journal of Pharmaceutical Science, 66, 2 (1977) p. 1-19.

Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the invention and these form a further aspect of the invention.

In addition, some of the compounds of Formula (I) may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the invention.

Thus, in another embodiment of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug therof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. In an embodiment of the

pharmaceutical composition, the compound of Formula (I) is an inhibitor of smallpox virus. Thus, in one embodiment, a therapeutically effective amount of the compounds of Formula (I) is an amount sufficient to reduce viral load in a subject. In an embodiment, the virus is an orthopox virus. For example, the compounds of the present invention may be used to inhibit smallpox infection.

In yet another embodiment, the present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), and one or more pharmaceutically acceptable carriers, excipients, or diluents, further comprising one or more additional therapeutic agents. Additional therapeutic agents may be those as described below, or may include other therapeutic agents as may be known in the art.

The present invention also comprises a method of administering a compound of Formula (I) to a subject. In one embodiment of the method, the compound of Formula (I) is administered in an amount sufficient to substantially reduce the viral load in a subject. In another embodiment, the compound of Formula (I) is administered in an amount sufficient to partially reduce the viral load in said subject.

The compounds of the present invention may be effective antiviral agents preventing, ameliorating or treating a virus infection. Embodiments of the present invention may therefore comprise methods for the inhibition of a virus comprising administering to a subject in need thereof a compound of Formula (I), wherein said compound of Formula (I) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents. In one embodiment, a therapeutically effective amount of the compound of Formula (I) may inhibit an orthopox virus such as smallpox virus. Thus, in one example embodiment, the present invention provides a method for the inhibition of the smallpox virus comprising administering to a subject in need thereof a compound of Formula (I), wherein the compound of Formula (I) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein a therapeutically effective amount of the compound of Formula (I) comprises an amount for treatment or prevention of orthopox-mediated diseases or prevention of opportunistic infections. In alternate embodiments, other types of viral infectons may be targeted by the compounds of the present invention.

The dosage at which the compounds of Formula (I) are used may be varied depending upon the condition being treated, the size of the individual, pharmacokinetic parameters, and the individual compound. In one embodiment, the compound of Formula (I) may comprise a dosage such that the concentration of the compound of Formula (I) at the surface of a virus infected cell is about 100 micromolar (μM) or less. In another embodiment, the compound of Formula (I) may comprise a dosage such that the concentration of compound at the surface of a virus infected cell is about 50 micromolar (μM) or less. In yet another embodiment, the compound of Formula (I) may comprise a dosage such that the concentration of compound at the surface of a virus infected cell is about 10 micromolar (μM) or less.

In another embodiment, a therapeutically effective amount of the compound of Formula (I) comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially inhibit the virus growth. In alternate embodiments, the sustained blood level comprises a concentration ranging from about 0.01 μM to 200 μM, more preferably from about 1 μM to 50 μM, and even more preferably from about 10 μM to about 25 μM. In another embodiment of the method, the pharmaceutical composition further comprises one or more therapeutic agents.

The pharmaceutical compositions of the present invention may be administered in the form of an oral dosage, a parenteral dosage unit, or by other routes. For example, in various embodiments, the compound of Formula (I) may be administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day, or as a dose in a range from about 0.1 to 100 mg/kg of body weight per day, or as a dose in a range from about 0.5 to 10 mg/kg of body weight per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 1 mg to 2 grams of a compound of Formula (I) with an appropriate and convenient amount of carrier material that may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500 mg of active ingredient. The dosage may be individualized by the clinician based on the specific clinical condition of the subject being treated. Thus, it will be understood that the specific dosage level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

As used herein, the term "subject" includes mammalian subjects such as, but not limited not, humans, cows, horses, and other agricultural live stock, and birds. In an embodiment, a subject may include one that either suffers from one or more aforesaid diseases, disease states, or viral infections, or one that is at risk for contracting one or more aforesaid diseases, disease states, or viral infections. Accordingly, in the context of the method of treatment comprising administration of a compound of Formula (I) or a pharmaceutical composition comprising a compound of Formula (I) to a subject prophylactically, or prior to the onset of or diagnosis of such diseases, disease states, or viral infections.

The term "treatment" as used herein, refers to the full spectrum of treatments for a given disorder from which the patient is suffering, including alleviation of one, most of all symptoms resulting from that disorder, to an outright cure for the particular disorder or prevention of the onset of the disorder.

As used herein, the terms "virus", "viral", or "viral infection" includes DNA and RNA viruses

As described above, the compound of Formula (I) may be used alone, or to replace or supplement compounds that inhibit viruses. Additionally, the compound of Formula I may be used in conjuction with other therapeutic agents. The following is a non-exhaustive listing of adjuvants and additional therapeutic agents that may be used in combination with the viral inhibitor of the present invention:

1. Analgesics: Aspirin
2. NSAIDs (Nonsteroidal anti-inflammatory drugs): Ibuprofen, Naproxen, Diclofenac
3. DMARDs (Disease-Modifying Antirheumatic drugs): Methotrexate, gold preparations, hydroxychloroquine, sulfasalazine
4. Biologic Response Modifiers, DMARDs: Etanercept, Infliximab
5. Glucocorticoids
6. Immunosuppresants and immunomodulators

Pharmacologic classifications of treatment for bacterial or viral infection

1. gyrase inhibitors; ciprofloxacin
2. beta lactam antibiotics; cefuroxime, amoxicillin, cephalexin, ceclor, meropenem, aztreonam
3. miscellaneous antibiotics; linezolid, erythromycin, streptomycin, vancomycin, doxycycline, rifampin, isoniazid

4. antifungal agents; terbinafine, fluconazole, ketoconazole, amphotericin B, griseofulvin
5. antiviral agents
    a. Antiviral agents for AIDS treatment; AZT, abacavir, ddC, ddI, d4T, 3TC, ZDV, tenofovir, nevirapine, pentafuside, amprenavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquanivir
    b. Antiviral agents (general); lamivudine, foscarnet, acyclovir, cidofovir, ganciclovir, valaciclovir

The present invention therefore provides a method of treating or preventing viral mediated diseases including comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) alone or in combination with therapeutic agents selected from the group consisting of antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, immunosuppressants, immunomodulators, thrombolytic agents, antidepressants, gyrase inhibitors, beta lactam antibiotics, antifungal agents, and antiviral agents (as described above). In one embodiment, the virus targeted using the compositions of the present invention (comprising compounds of Formula (I) alone or in combination with other agents) may comprise a pox virus. In another embodiment, the virus may comprise smallpox.

EXAMPLES

The present invention may be further understood by reference to the following non-limiting examples. Examples of compounds of the present invention and procedures that may be used in to prepare and identify useful compounds of the present invention are described below.

General Experimental:

LC-MS data was obtained using gradient elution on a Waters 600 controller equipped with a 2487 dual wavelength detector and a Leap Technologies HTS PAL Autosampler using an YMC Combiscreen ODS-A 50x4.6 mm column. A three minute gradient was run from 25% B (97.5%acetonitrile, 2.5% water, 0.05% TFA) and 75% A (97.5% water, 2.5% acetonitrile, 0.05% TFA) to 100% B. The mass spectrometer used was a Micromass ZMD instrument. All data was obtained in the positive mode unless otherwise noted. ^{1}H NMR data was obtained on a Varian 400 MHz spectrometer.

Common names and definitions for resin reagents used in the disclosure are;

Merrifield	p-Chloromethyl polystyrene
Hydroxy-Merrifield	p-Hydroxymethyl polystyrene
Wang	(4-Hydroxymethyl)phenoxymethyl polystyrene
Wang carbonate	4-(p-nitrophenyl carbonate) phenoxymethyl polystyrene
Rink Resin	4-(2',4'-Dimethoxyphenyl-Fmco-aminomethyl)-phenoxy polystyrene resin
Wang Bromo Resin	(4-Bromomethyl)phenoxymethyl polystyrene
THP Resin	3,4-Dihydro-2H-pyran-2-ylmethoxymethyl polystyrene

Aldehyde resin can refer to the following:

4-Benzyloxybenzaldehyde polystyrene

3-Benzyloxybenzaldehyde polystyrene

4-(4-Formyl-3-methoxyphenoxy)butyryl-aminomethyl polystyrene

2-(4-Formyl-3-methoxyphenoxy)ethyl polystyrene

2-(3,5-dimethoxy-4-formylphenoxy)ethoxy-methyl polystyrene

2-(3,5-dimethoxy-4-formylphenoxy)ethoxy polystyrene

(3-Formylindolyl)acetamidomethyl polystyrene

(4-Formyl-3-methoxyphenoxy) grafted (polyethyleneglycol)-polystyrene; or

(4-Formyl-3-methoxyphenoxy)methylpolystyrene.

Abbreviations used in the Examples are as follows:

APCI = atmospheric pressure chemical ionization

BOC = tert-butoxycarbonyl

BOP= (1-benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate

d = day

DIAD = diisopropyl azodicarboxylate

DCC = dicyclohexylcarbodiimide

DCM = dichloromethane

DCE = dichloroethane

DIC = diisopropylcarbodiimide

DIEA = diisopropylethylamine

DMA = N, N-dimethylacetamide

DMAP = dimethylaminopyridine

DME = 1,2 dimethoxyethane

DMF = N, N-dimethylformamide

DMPU= 1,3-dimethypropylene urea

DMSO= dimethylsulfoxide

EDC =1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride

EDTA = ethylenediamine tetraacetic acid

ELISA= enzyme - linked immunosorbent assay

ESI = electrospray ionization

ether = diethyl ether

EtOAc = ethyl acetate

FBS = fetal bovine serum

g = gram

h = hour

HBTU= O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate

HMPA= hexamethylphosphoric triamide

HOBt =1-hydroxybenzotriazole

Hz = hertz

i.v. = intravenous

kD = kiloDalton

L = liter

LAH = lithium aluminum hydride

LDA = lithium diisopropylamide

LPS = lipopolysaccharide

M = molar

m/z = mass to charge ratio

mbar = millibar

MeOH = methanol

mg = milligram

min = minute

mL = milliliter

mM = millimolar

mmol = millimole

mol = mole

mp = melting point

MS = mass spectrometry

N = normal

NMM = N-methylmorpholine, 4-methylmorpholine

NMR = nuclear magnetic resonance spectroscopy

p.o. = per oral

PBS = phosphate buffered saline solution

PMA = phorbol myristate acetate

ppm = parts per million

psi = pounds per square inch

R_f = relative TLC mobility

rt = room temperature

s.c. = subcutaneous

SPA = scintillation proximity assay

TEA = triethylamine

TFA = trifluoroacetic acid

THF = tetrahydrofuran

THP = tetrahydropyranyl

TLC = thin layer chromatography

TMSBr= bromotrimethylsilane, trimethylsilylbromide

T_r = retention time

Thus, in an embodiment, the following compounds were synthesized according to the Schemes described herein.

General procedure A:

To a solution of a carboxylic acid (1.0-1.5 mmol) in DMF (6 mL) was added an amino acid methyl ester (1.0-1.5 mmol), HBTU (1.0-1.5 mmol), and DIEA (2.0-3.0 mmol) and the mixture was stirred overnight. After completion of the reaction, sufficient amount of water was added and the mixture was extracted with ethyl acetate (3x15 ml). The combined organic layer was washed with water and brine, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the amide, which was used for further usage without further purification or purified by flash chromatography.

General procedure B:

To a mixture of phenol and the aryl fluoride (2 eq) in DMF was added solid potassium carbonate or sodium methoxide (10 eq), and the mixture was heated at 80 °C for 12 h. After completion of the reaction, sufficient amount of water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate. The solvent was removed in vacuum and the crude material obtained was purified by flash chromatography to afford the desired aryl ethers.

General procedure C:

To a solution of ester in THF, CH_3OH (4:1), 2N-lithium hydroxide solution (5 eq) was added, and the resulting reaction mixture was stirred at 0 ^{0}C for 30 minutes and then warmed to room temperature. After completion of the reaction, 2N HCl was used to neutralize the base, extracted with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed in vacuum to afford the product in pure form.

General procedure D:

To a solution of phenyl bromide in DME were added corresponding boronic acid (5 eq), Pd $(PPh_3)_4$ (0.5 % eq), 2N Na_2CO_3 solution (5 eq). The mixture was heated at 75 °C for 12 h. After completion of the reaction, solvent was evaporated *in vacuo*. During the reaction, most of the ester was hydrolyzed to the corresponding acid. The crude product so obtained was re-esterfied by dissolving it in CH_3OH containing 1% of HCl. The mixture was refluxed for 6h and after the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica, CH_2Cl_2) to provide the desired ester. The resulting ester was hydrolyzed as described in procedure C yielding the pure acid.

General procedure E:

To a solution of an aniline (1.0 mmol) in DCM (10 mL) was added a sulfonyl chloride (1.0 mmol), and pyridine (10.0 mmol) and the mixture was stirred overnight. After completion of the reaction, 50 mL of DCM was added and the organic layer was washed with 1N HCl, saturated sodium bicarbonate solution and brine, and then dried over sodium sulfate.

The solvent was removed in vacuum to afford the sulfonamide, which was purified by flash chromatography.

General procedure F:

A flask was charged with phenol or aniline (1.0 equiv), Cu $(OAc)_2$ (1.0 equiv), arylboronic acid (1.0-3.0), and powdered 4 A^0 molecular sieves. The reaction mixture was diluted with CH_2Cl_2 to yield a solution approximately 0.1M in phenol or aniline, and the Et_3N (5.0 equiv) was added. After stirring the colored heterogeneous reaction mixture for 24 h at 25 ^0C under ambient atmosphere, the resulting slurry was filtered and the diaryl ether or diaryl amine is isolated from the organic filtrate by flash chromatography.

General procedure G:

To a solution of a phenol (1.0 mmol) in DMF (5 mL) was added an alkyl halide (1.2 mmol) (a catalytic amount of NaI is added for alkyl chloirdes), and potassium carbonate (2.5 mmol) and the mixture heated at 70 °C overnight. After completion of the reaction, 5 mL of ethyl acetate and 5 mL of water was added. The organic layer was washed with water, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the ether, which was purified by flash chromatography.

General procedure H:

Approximately, 10 ml of DMF per gram of resin was suspended in a round bottomed flask. In a separate flask, 2.5 eqivalents (relative to the resin) of the carboxylic acid was dissolved in a minimum amount of DMF. Next, the same equivalent of HOBT and 0.1 equivalent of DMAP(relative to the acid) was added. The mixture was stirred until the acid and HOBT dissolved, and then the solution was added to the resin. Next, 1.0 equivalent (relative to the acid) of DIC was added to the resin mixture. The flask was equipped with a drying tube and the mixture agitated on shaker overnight. The resin was filtered in a sintered glass funnel and washed 3 times with DMF, 3 times with methanol, and finally 3 times with DCM. The resin was in vacuo to a constant weight.

General procedure I:

DIAD or DEAD was added dropwise to a mixture of a phenol, a primary or secondary alcohol (1.5 eq.), and triphenylphosphine (1.5 eq.) dissolved in anhydrous THF, at –20 °C

under a nitrogen atmosphere. The mixture was stirred for 1-2 hours while allowing to gradually warm to r.t. The solvent was removed and the residue purified by flash column chromatography to afford the desired alkyl aryl ether.

General procedure J:

To 1.0 g (2.5 mmol) of resin-bound naphthoic acid was added a mixture of 1.5 g (7.5 mmol) of 4-Bromophenethylamine, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound *N*-2-(4-Bromophenyl)ethyl-3-hydroxyl-2-naphthamide.

General procedure K:

To the aryl acid (5.0 mmol) solution in DCM (20 ml) and pyridine (20.0 mmol) was added acetyl chloride (20.0 mmol) at –10 ^{0}C and the reaction mixture was stirred and allowed to warm up to r.t. The reaction mixture was then poured in to icy water (50 ml) and extracted with DCM (3x50 mL), organic extracts were combined, dried (Na_2SO_4), and concentrated in *vacuo* to furnish the desired acid.

General procedure L:

To a solution of 2-acetoxyaryl acid (10.0 mmol) solution in DCM (50 ml) was added oxalyl chloride (25.0 mmol) at –10 ^{0}C and the reaction mixture was allowed to warm up to r.t. and stirred for 2 hours. Then the reaction mixture concentrated in *vacuo* to furnish the desired acid chloride.

General procedure M:

To a solution of 2-acetoxyaryl acid chloride (5.0 mmol) solution in DCE (20 ml) was added desired amine (5.0 mmol) and 4-methyl morpholine (10.0 mmol). The reaction mixture was stirred at r.t. for 2 hours. The reaction mixture was then concentrated in *vacuo* and poured into water (20 mL), and extracted with ethyl acetate (3x25 mL). Organic extracts were combined and concentrated in *vacuo*. The crude product was then purified with silica gel column chromatography by using ethyl acetate:hexanes (5:95 to 20:80) as eluent system to afford desired amides.

General procedure N:

To a solution of *N*-Boc-protected amino acids (5.0 mmol) in methanol (20 mL) was added hydrochloric acid (5 mL, 4.0 solution in dioxane) and refluxed for 1h. The reaction mixture was concentrated in *vacuo* to give the desired amino ester. Deprotection of Boc groups and esterification of non-amino acids are also performed using this method.

General procedure O:

To a solution of *N*-Boc-amino acid (1.0 mmol) in THF (10 mL) was added polymer-supported DCC (2.4 g, 2.0 mmol, as a suspension in chloroform (30 mL)). This mixture was placed to a shaker and was shaken for 10 min. Then pentafluorophenol (300 mg, 1.5 mmol, 5 mL solution in THF) was added to the reaction mixture and placed to the shaker for 16 hours at r.t. The reaction mixture was then filtered through with celite and concentrated in *vacuo* to give the pentafluoroohenyl ester. This ester was then subjected to further manipulations without purification.

To a solution of above pentafluorophenyl ester (300 mg, 0.5 mmol) was added desired alkylamideoxime (1.0 mmol) and molecular sieves (100 mg) in dry chlorobenzene (20 mL). The reaction mixture was then heated at 120 ^{0}C for 4-5 hours and concentrated in *vacuo* to remove most of chlorobenzene. To this slurry was added DCM (50 mL) and filtered through with a plug of silica gel, again concentrated in *vacuo*. This crude product was then purified with ethyl acetate:hexanes 5:95 to 10:90 to give the desired oxadiazoles.

The intermediate alkyloxyaryl oxadiazole was then deprotected using hydrochloric acid (1 mL, 4.0 M solution in dioxane) following by general procedure N to give free amine. This free amine was then subjected to general procedure A to give the desired amides in a quantitative yield.

General procedure P:

To a solution of alkylphenyl ether (0.2 mmol) in anhydrous DCM (10 mL) was added boron tribromide (0.5 mmol, 1.0 M solution in DCM or neat) at –78 °C and the reaction mixture stirred at –78 °C for 3 hours and allowed to warm up to the ambient temperature. After the reaction was completed, the reaction mixture was slowly quenched with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with DCM (3x 20 mL). The reaction mixture was concentrated in *vacuo* to give the crude product. This crude product was

then purified by silica gel chromatography with hexanes:ethyl acetate (from 95:5 to 80-20) as an eluent system to obtain desired phenols.

General procedure Q:

To the phosphonate ester (1.0 mmol) in DCM was added DBU (1.0 mmol) and the mixture was stirred for 10 min, then the aldehyde (0.9 mmol) was added to the mixture and stirred for another 2 h. Aqueous citric acid was then added and the mixture was extracted with ethyl acetate (3x25 mL). Organic extracts were combined and concentrated in *vacuo*. The crude product was then purified on a silica gel column chromatography by using ethyl acetate:hexanes as eluent system to afford desired alkenes.

General procedure R:

To a solution of an aniline (1.0 mmol) in DCE (10 mL) was added an aldehyde (2.0-2.2 mmol), acetic acid (3.0 mmol), and sodium triacetoxyborohydride (2.5 mmol) and the mixture was stirred overnight. After completion of the reaction, 50 mL of DCM was added and the organic layer was washed with 1N HCl, saturated sodium bicarbonate solution and brine, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the amine, which was purified by flash chromatography.

The above general methods are for illustration only. Alternative conditions that may optionally be used include: use of alternative solvents, alternative stoichiometries of reagents, alternative reagents, alternative reaction conditions, including temperatures and alternative methods of purification.

Synthesis of Amino acids:

Synthesis of 4'-Trifluoromethyl-biphenyl-4-carboxylic acid

The title compound was prepared following procedure D using 4-bromo benzoic acid (10g, 50 mmol), 4-trifluoromethyl boronic acid (14.1g, 75 mmol), palladium tetrakis-triphenylphosphine (6.0, 10 mol%) and 2N Na_2CO_3 aq.solution (150 ml, 140 mmol) in 500 ml of toluene. 9.9 g of title compound was isolated after usual work up.

(*2S*)-Amino-3- (2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

The title compound was prepared following procedure D using (L)-4-bromophenylalanine (8.55g, 35.0 mmol), 2-phenoxyphenyl boronic acid (10.00g, 46.73 mmol), palladium tetrakis-triphenylphosphine (4.0 g, 10% mmol)) and 2*N* Na_2CO_3 aq.

solution (70 mL, 140 mmol) in 140 ml of DME. After removal of solvents, the solid was washed with ether to afford the tile compound in HCl salt form (10.0 g, 26.20 mmol).

Example 1

3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-4 -hydroxy- biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

To 40 g (200 mmol) of 5-bromo-2-hydroxy-benzoic acid methyl ester, 11.0 g (220 mmol) of sodium methoxide in 500 mL of anhydrous DMA was added 13.30 g (71 mmol) of Merrifield resin. The mixture was heated at 110 °C overnight. The resin was washed with H_2O, DMF, MeOH, DCM three times of each, and dried.

To 1.0 g (2.5 mmol) of resin-bound 5-bromo-2-hydroxy-benzoic acid was added 1.92 g (7.5 mmol) of (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester following general procedure A to give resin-bound 3-(biphenyl-4-yl)-(2S)-(5-bromo-4-hydroxy-benzoylamino)-propionic acid methyl ester .

The resin-bound 3-(biphenyl-4-yl)-(2S)-(5-bromo-4-hydroxy-benzoylamino)-propionic acid methyl ester (50 mg, 0.3 mmol) was reacted with 3-chloro-4-fluorophenylboronic acid (240 mg, 1.5 mmol) following general procedure D, cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography to give 35 mg of title compound.

^{1}H-NMR(400 MHz, $CDCl_3$): 3.33 (t, 2H), 3.83 (s, 3H), 5.10 (m, 1H), 6.83 (d, 1H), 7.35 (m, 2H), 7.22 (d, 2H), 7.29 (m, 1H), 7.35 (m, 2H), 7.43 (m, 2H), 7.48 (dd, 1H), 7.55 (m, 5H); LC/MS (*m/z*): 504 $(M+1)^+$.

Example 2

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid biphenyl-4-yl-1(S)-formyl-ethyl)-amide; compound with methoxymethane

The resin-bound 3-(biphenyl-4-yl)-(2S)-(5-bromo-4-hydroxy-benzoyl-amino)-propionic acid methyl ester (30 mg, 0.09 mmol) obtained as in Example 1 was reacted with 4-trifluoromethyl-phenyl boronic acid (86 mg, 0.45 mmol) as described in the general procedure D to provide the title compound (25 mg).

^{1}H-NMR(400 MHz, $CDCl_3$): 3.35 (m, 2H), 3.84 (s, 3H), 5.10 (m, 1H), 6.79 (d, 1H), 7.09 (d, 1H), 7.21 (d, 2H), 7.37 (m, 1H), 7.43 (m, 3H), 7.56 (m, 8H), 7.64 (dd, 1H); LC/MS (*m/z*): 520 $(M+1)^+$.

Example 3

2-(S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)propionic acid methyl ester

The resin-bound 3-(4-bromo-phenyl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (30 mg, 0.09 mmol) prepared as described in Example 1 was reacted with 4-trifluoromethyl-phenyl boronic acid (86 mg, 0.45 mmol) by following procedure D to give the title compound (24 mg).

^{1}H NMR (400 MHz, $CDCl_3$): 3.30-3.42 (m, 2H), 3.84 (s, 3H), 5.11 (dd, 1H, J = 12.8, 5.2 Hz), 6.82 (d, 1H, J = 7.2 Hz), 7.10 (d, 1H, J = 8.8 Hz), 7.43-7.45 (m, 2H), 7.53-7.57 (m, 5H), 7.60-7.70 (m, 7H); LC/MS (*m/z*): 588 $(M+1)^+$.

By analogous methods to those described above, the following compounds were synthesized.

EX.	NAME	LC/MS (m/z)
4	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	499
5	3-Biphenyl-4-yl-2-(S)-[(4-hydroxy-4'-trifluoromethoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	536
6	3-Biphenyl-4-yl-2-(S)-[(4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	470
7	3-Biphenyl-4-yl-2-(2S)-[(3'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	470
8	3-Biphenyl-4-yl-2-(2S)-[(4-hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	588
9	3-Biphenyl-4-yl-2-(2S)-[(3',5'-difluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	488
10	2-(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	572
11	2-(2S)-(5-Benzo[1,3]dioxol-5-yl-2-hydroxy-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester	496

12	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(2S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	572
13	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	640
14	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(2S)-[(3'chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)amino]-propionic acid methyl ester	656
15	2-(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid	558
16	2-(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester	604
17	2-(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588
18	3-Biphenyl-4-yl-2-(S)-[(4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	452
19	2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester	588
20	2-(S)-[(4-Hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588
21	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	556
22	2-(S)-[(4-Hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester	542
23	2-(S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588

24	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	572
25	3-Biphenyl-4-yl-2-(S)-[(4-hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	520
26	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	656
27	2-(S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588

Example 28

2-(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-nitro-biphenyl-4-yl)-propionic acid methyl ester

To 2.50 g (5.0 mmol) of resin-bound methyl 5-bromo-2-hydroxy-benzoate obtained by a similar procedure as in Example 1 in 30 mL of DME was added 2.90 g (15 mmol) of 4-(trifluoromethyl)phenylboronic acid, 1.12 g (1.0 mmol) of $Pd(PPh_3)_4$, and 15 mL (30.0 mmol) of 2*N* Na_2CO_3 solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H_2O, DMF, MeOH, and DCM (three times of each), and was hydrolyzed by LiOH/H_2O/THF/ethanol at rt for 3 days to give the resin-bound 4'-trifluoromethyl-4-hydroxy-biphenyl-3-carboxylic acid.

To 1.5 g (2.5 mmol) of above resin-bound 4'-trifluoromethyl-4-hydroxy-biphenyl-3-carboxylic acid was added 1.95 g (7.5 mmol) of 4-(S)-bromophenylalanine methyl ester, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, and DCM (three times of each) to give resin-bound 3-(4-bromo-phenyl)-2-(S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester.

To 0.05 g (0.1 mmol) of above resin-bound 3-(4-bromo-phenyl)-2-(S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester in 2.0 mL of DME was added 50.1 mg (0.3 mmol) of 4-nitrophenylboronic acid, 30 mg (0.03 mmol) of $Pd(PPh_3)_4$, and 0.3 mL (0.6 mmol) of 2*N* Na_2CO_3 solution. The mixture was

heated at 80 °C for 12 h. The resin was washed with H_2O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (100% DCM) to give 28.2 mg of the title compound. LC/MS (*m/z*): 565 $(M+1)^+$.

By analogous methods to those described above the following compounds were synthesized

EX.	NAME	LC/MS (m/z)
29	3-(3',4'-Difluoro-biphenyl-4-yl)-2-(S)(2-hydroxy-5-pyridin-3-yl-benzoylamino)-propionic acid methyl ester	489
30	2-(S)-[(4'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-biphenyl-4yl-propionic acid methyl ester	467

Example 31

3-Biphenyl-4-yl-2-(2S)-{2-hydroxy-5-[2-(4'-trifluoromethyl-biphenyl-3-yl)-acetylamino]-benzoylamino] propionic acid methyl ester

The resin-bound 2-hydroxy-5-nitro-benzoic acid (500 mg, 0.5 mmol) obtained by a similar procedure as in Example 1 was reacted with 2-S-amino-3-biphenyl-4-yl-propionic acid methyl ester (385mg, 1.5 mmol) as described in general procedure A. The resulting resin was reduced by $SnCl_2$ hydrate in NMP at rt for 4h to give the resin-bound 3-biphenyl-4-yl-2-(S)-(5-amino-2-hydroxy-phenyl)carbonylamino-propionic acid methyl ester. The above resin (120 mg, 0.1 mmol) was reacted with 110 mg (0.5 mmol) of 4-bromophenylacetyl chloride, followed by 58 mg (0.3 mmol) of 4-trifluormethyl-phenyl boronic acid, 30 mg (0.03 mmol) of $Pd(PPh_3)_4$, and 0.3 mL (0.6 mmol) of 2*N* Na_2CO_3 solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H_2O, DMF, MeOH, and DCM (three times of each) and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (100% methylene chloride) to afford 25 mg of title compound.

LC/MS (*m/z*) 653 $(M+1)^+$.

Example 32

3-Biphenyl-4-yl-2-S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

3-Chloro-4-fluoro-phenylboronic acid (3.2g, 18.4 mmol), 5-bromo-2-hydroxy-benzoic acid (4.0 g, 18.4 mmol), and Pd (PPh_3)$_4$ (1.67 g, 1.84 mmol) were dissolved in 250 mL of DME, a 1M Na_2CO_3 solution (46 mL, 46.0 mmol) added and the mixture heated to 80 °C for 20 h. The reaction mixture was filtered, partially evaporated and EtOAc (200 mL) and 1N HCl (100 mL) added. The organic layer washed with 1N HCl and saturated sodium bicarbonate, dried over sodium sulfate, and evaporated. The crude material was filtered through a silica plug (THF) to give 3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (2.15 g).

3-Biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (51 mg) was prepared from 3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (300 mg, 1.1 mmol) and 2-(S)-amino-3-biphenyl-4-yl-propionic acid methyl ester-hydrochloride (330 mg, 1.1 mmol) as described in general procedure A, except for an adapted work-up. After reaction completion, the reaction mixture was poured onto 100 mL of 1N HCl and 100 mL of EtOAc. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, dried over sodium sulfate and evaporated. The crude material was purified over silica gel (8:2, DCM-hexanes).
LC/MS (*m/z*): 504 $(M+1)^+$.

Example 33

3-biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid

3-Biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester, example 32 (20 mg, 0.040 mmol) was dissolved in 5 mL of THF-MeOH (4-1), cooled to 0 °C and 1.1 equiv of 2 N LiOH added. After 45 minutes, 2.2 additional equiv of 2N LiOH was added and the reaction stirred for 60 minutes. The reaction was worked up according to general procedure C to give 3-(S)-biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid (10 mg).
LC/MS (*m/z*): 490 $(M+1)^+$.

Example 34

2-(S)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

5-Chloro-salicylic acid (2.16 g, 10 mmol) was first transformed into 2-acetyl-5-chloro-salicylic acid (252 g) with acetyl chloride (2.34 g, 30 mmol) and pyridine (3.95 g, 50 mmol) in DCM. The above acid (1.29 g, 5.0 mmol) was converted into acid chloride by using oxayl chloride (1.97 g, 15 mmol) and catalytic amount of DMF in DCM, then (*2S*)-Amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (1.45 g, 5.0 mmol) and DIEA (0.77 g, 6.0 mmol) were added to the acid chloride to form (*2S*)-[5-Chloro-2-hydroxybenzoylamine]-3-(2'-phenoxybiphenyl-4-yl)-propionic acid methyl ester (1.92 g).
LC/MS: 502

Example 35

2-(S)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

To a solution of the preceeding compound, 2-(S)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid (10mg, 18μmol) inTHF/MeOH was added aqueous LiOH, as described in General procedure C which, after work-up afforded the title compound(10 mg) LCMS for $C_{28}H_{22}BrNO_5$: 531, 533.

Example 36

2-(S)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

The preparation of the title compound proceeds via the same protocol as in the synthesis of (2*S*)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (*vide supra*) with the one exception that the Suzuki coupling (General procedure D) uses 4-phenoxy-phenylboronic acid instead of 2-phenoxy phenylboronic acid. LCMS for $C_{29}H_{24}BrNO_5$: 546, 548. ^{1}H NMR (400MHz, $CDCl_3$) 11.98 (s, 1H), 7.30-7.65 (m, 8H), 7.03-7.25 (m, 7H), 6.87 (d, 1H), 6.83 (d,1H), 5.07 (dt, 1H), 3.83 (s,3H), 3.29 (qd,2H).

Example 37

2-(S)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid

To a solution of the preceding compound, (2*S*)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (10mg, 18μmol) inTHF/MeOH was added aqueous LiOH, as described in General procedure C which, after work-up afforded the

title compound, (2*S*)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid (10 mg) LCMS for $C_{28}H_{22}BrNO_5$: 531, 533.

Example 38

5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

N-Bromosuccinimide (2.38g, 13.38 mmol) was added to a solution of 3-chlorosalicylic acid (2.1g, 12.16 mmol) in CH_3CN (10mL) solution and stirred for 1h. The reaction mixture was diluted with water (25mL), solids were filtered and washed with water and dried to get 5-bromo-3-chloro-2-hydroxy-benzoic acid (2.87g).

Methyl Iodide (3.83g, 27.04mmol) was added to a solution of 5-Bromo-3-chloro-2-hydroxy-benzoic acid (1.7 g, 6.76mmol) and Cs_2CO_3 (4.83g, 14.86mmol) in DMF (10mL) and heated at 50°C for 12h. The reaction mixture was diluted with EtOAc (30mL) and filtered over celite pad. Filtrate was washed with water, brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silicagel column chromagography to get pure 5-Bromo-3-chloro-2-methoxy-benzoic acid methyl ester (1.56g)

4-Trifluorophenylboronic acid (0.815g, 4.29mmol) was added to a solution of 5-Bromo-3-chloro-2-methoxy-benzoic acid methyl ester (1.0g, 3.57mmol) , $Pd(PPh_3)_4$ (0.2g, 0.178 mmol) and CsF (1.08g, 7.15mmol) in DME (10mL)and heated at 85°C for 10h. The reaction was diluted with EtOAc (20mL) and filtered, filtrate was washed water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the silica gel column chromatography gave pure 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (0.94g).

5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.62g) was prepared from 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (0.7g, 2.03mmol) following the procedure C.

2-(R)-tert-Butoxycarbonylamino-3-(3'-chloro-4'-fluoro-biphenyl-3-yl)-propionic acid (0.93g) was prepared from (R)-N-Boc-3-bromophenylalanine (1.0g, 2.9mmol) and 3-chloro-4-fluorophenylboronic acid (1.0g, 5.8mmol) following general procedure D.

[2-(3'-Chloro-4'-fluoro-biphenyl-3-yl)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butylester (0.7g)was prepared from 2-tert-Butoxycarbonylamino-3-(3'-chloro-4'-fluoro-biphenyl-3-yl)-propionic acid (0.9g, 2.2mmol) following general procedure O.

5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.087) was prepared using the general procedure A, from 2-(3'-Chloro-4'-fluoro-biphenyl-3-yl)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride salt (0.077g, 0.21 mmol, prepared from [2-(3'-Chloro-4'-fluoro-biphenyl-3-yl)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butylester following general procedure N) and 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.07g, 0.21mmol).

The title compound (0.022g) was prepared from 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.04g, 0.062mmol), using the general procedure P. ^{1}HNMR (400MHz, $CDCl_3$): 2.40 (s, 3H), 3.40 (m, 2H), 5.87 (m, 1H), 7.05-7.21 (m, 4H), 7.29 (m, 1H), 7.37 (t, 1H), 7.41-7.48 (m, 3H), 7.53 (d, 2H), 7.67 (d, 2H), 7.76 (d, 1H), 12.04 (br s, 1H).

Example 39

5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluorophenoxy)-phenyl]-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

2-tert-Butoxycarbonylamino-3-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-propionic acid (0.87g) was prepared from Boc-D-tyrosine methyl ester (1.0g, 3.38mmol) 3-chloro-4-fluorophenylboronic acid (1.76g, 10.15mmol) as described in general procedure F.

[2-[4-(3-Chloro-4-fluoro-phenoxy)-phenyl]-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (0.57g) was prepared from 2-tert-Butoxycarbonylamino-3-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-propionic acid [0.73g, 1.78mmol, [which was prepared from 2-tert-Butoxycarbonylamino-3-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-propionic acid methyl ester following general procedure C] by following general procedure O.

5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.07g) was prepared from 2-[4-(3-Chloro-4-fluoro-phenoxy)-phenyl]-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride [0.07g, 0.182mmol, which was prepared from [2-[4-(3-Chloro-4-fluoro-phenoxy)-phenyl]-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester by the hydrolysis of BOC group using the general procedure N] and 5-Chloro 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (as in example 42) (0.053g, 0.18mmol) following general procedure A. 5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-

3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (20 mg) was obtained upon methyl ether hydrolysis using the general procedure P. ^{1}HNMR (400MHz, $CDCl_3$): 2.40 (s, 3H), 3.39 (m, 2H), 5.79 (dd, 1H), 6.84 (m, 1H), 6.90 (d, 2H), 7.02 (1H), 7.04-7.17 (m, 4H), 7.50 (d, 1H), 7.61 (d, 2H), 7.71 (d, 2H), 7.78 (d, 1H), 12.03 (s, 1H).

Example 40

3-(4'-Chloro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

3-(4'-Chloro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester was synthesized from 3-(4-bromo-phenyl)-2-(S)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (300 mg, 0.56 mmol, obtained from the coupling of 4-bromophenylalanine and 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid using general procedure A) and 4-chlorophenyl boronic acid (156 mg, 1.0 mmol) following general procedure D. (250 mg).
LC/MS (*m/z*): 568 $(M+1)^+$.

Example 41

3-(4'-Chloro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid

The title compound was prepared from 3-(4'-chloro-biphenyl-4-yl)-2-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (250 mg, 0.44 mmol) following general procedure C. (190 mg).
LC/MS (*m/z*): 554 $(M+1)^+$.

Example 42

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-biphenyl-4-yl)-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

The title compound was prepared from 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (160 mg, 0.27 mmol obtained using protocol similar to example 44) following general procedure O. (78 mg).
^{1}H-NMR(400 MHz, $CDCl_3$): 2.41 (s, 3H), 3.47 (d, 2H), 5.83 (m, 1H), 6.86 (d, 1H), 7.14 (m, 3H), 7.38 (m, 4H), 7.55 (m, 5H), 7.65 (m, 3H); LC/MS (*m/z*): 578 $(M+1)^+$.

By analogous methods to those described above the following compounds were synthesized

EX.	NAME	LC/MS (m/z)
43	4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-chloro-biphenyl-4-yl)-1(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide	578
44	4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1(R)-(3-trifluoromethyl[1,2,4]oxadiazol-5-yl)-ethyl]-amide	650
45	4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1(R)-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-ethyl]-amide	638

Example 46

5-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-4-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3(R)-carbonyl) amino]-pent-2-enoic acid ethyl ester

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl) –2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (223 mg) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (141 mg, 0.5 mmol) and-2-(R)-amino-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester (155 mg, 0.5 mmol) following the general procedure A.

LC-MS (*m/z*): 586 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 3.24-3.38 (m, 2H), 3.76 (m, 1H), 3.80 (s, 3H), 3.90 (s, 3H), 5.14 (q, 1H), 6.68 (d, 1H), 7.06 (q, 1H), 7.18 (q, 1H), 7.24 (m, 3H), 7.44 (m, 2H), 7.52-7.60 (m, 2H), 7.68-7.72 (m, 3H) and 8.16 (dd, 1H).

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid was obtained from the hydrolysis of the above ester using the general procedure C.

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(methoxy-methyl-carbamoyl)-ethyl]-amide (0.078g) was prepared from 3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-

carbonyl)-amino]-propionic acid (0.1g, 0.179 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.017g, 0.179mmol) following general procedure A

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-formyl-ethyl]-amide was synthesized by the following procedure: To 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(methoxy-methyl-carbamoyl)-ethyl]-amide (85 mg, 0.14 mmol) in THF (2 mL) was added DIBAL-H (0.64 mL, 0.64 mmol, 1.0 M in DCM) at –78 °C and the mixture was stirred at –78 °C for 2 h. After that potassium sodium tartrate was added and the mixture was stirred overnight, then the mixture was extracted with ethyl acetate (3x25 mL). Organic extracts were combined and concentrated in *vacuo*. The crude product was then purified with silica gel column chromatography by using ethyl acetate:hexanes (2:1) to afford the aldehyde intermediate(45 mg).

^{1}H-NMR(300 MHz, $CDCl_3$): 3.30 (m, 2H), 3.98 (s, 3H), 4.95 (m, 1H), 7.15 (m, 2H), 7.50 (m, 12H), 8.50 (s, 1H), 9.75 (s, 1H); LC/MS (*m/z*): 556 $(M+1)^+$.

5-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-4-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-(R)-carbonyl)-amino]-pent-2-enoic acid ethyl ester (Isomer I28 mg) and its geometrical isomer (Isomer II, 15 mg) were prepared from the above, 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-formyl-ethyl]-amide (40 mg, 0.072 mmol) and (diethoxy-phosphoryl)-acetic acid ethyl ester (32 mg, 0.14 mmol) following general procedure Q.

Isomer I: ^{1}H-NMR(300 MHz, $CDCl_3$): 1.27 (t, 3H), 3.18 (d, 2H), 3.83 (s, 3H), 4.18 (m, 2H), 5.50 (t, 1H), 1.27 (t, 3H), 3.18 (d, 2H), 3.83 (s, 3H), 4.18 (m, 2H), 5.50 (t, 1H), 7.03 (d, 1H), 7.18 (m, 1H), 7.40 (m, 6H), 7.60 (m, 1H), 7.69 (m, 5H), 8.46 (d, 1H), 9.08 (s, 1H); LC/MS (*m/z*): 626 (M+1)

Isomer II: ^{1}H-NMR(300 MHz, $CDCl_3$): 1.27 (s, 3H), 3,11 (d, 2H), 3.91 (s, 3H), 4.20 (m, 2H), 5.30 (m, 1H), 5.94 (dd, 1H), 7.07 (m, 2H), 7.20 (m, 1H), 7.32 (m ,3H), 7.46 (m, 2H), 7.60 (m, 1H), 7.69 (m, 4H), 8.00 (d, 1H), 8.48 (d, 1H); LC/MS (*m/z*): 626 $(M+1)^+$.

The title compound (example 50) was prepared from 5-(3'-chloro-4'-fluoro-biphenyl-4-yl)-4-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-(R)-carbonyl)-amino]-pent-2-enoic acid ethyl ester (Isomer II, 15 mg, 0.024 mmol) following general procedure P (2.5 mg).

Example 47

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-6-methoxy-biphenyl-3-yl)-ethyl]-amide

The resin-bound 4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (20 mg, 0.06 mmol) obtained as in Example 1 was reacted with 3-bromo-4-methoxy-phenethyl amine (57 mg, 0.25 mmol) following general procedure A to give resin bound 4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-3-bromo-4-methoxy-phenyl)-ethyl]-amide(18 mg, 0.05 mmol). The above resin bound amide was treated with 3-chloro-4-fluoro-phenyl boronic acid (43 mg, 0.25 mmol) as described in the general procedure D to provide the title compound (8.0mg,).

^{1}H-NMR(400 MHz, $CDCl_3$): 2.95 (t, 2H), 3.73 (dd, 2H), 3.80 (s, 3H), 6.94 (d, 1H), 7.11 (m, 3H), 7.21 (dd, 1H), 7.31 (m, 1H), 7.37 (d, 1H), 7.52 (m, 4H), 7.64 (m, 3H); LC/MS (*m/z*): 544 $(M+1)^+$.

Example 48

2-(S)-[(4-Amino-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester

4-Amino-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (3.0 g) was prepared from 2-amino-5-bromobenzoic acid methyl ester (4.58 g, 20 mmol) and 4-trifluoromethylphenyl boronic acid (4.75 g, 25 mmol) following general procedure D, then hydrolyzed following general procedure C. The above acid (281 mg, 1.0 mmol) was reacted with 2(S)-amino-3-(3'chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester (343 mg, 1.0 mmol) as described in general procedure A to give the title compound. (300 mg)

^{1}H NMR (400 MHz, $CDCl_3$): 3.34 (m, 2H), 3.83 (s, 3H), 5.06 (m, 1H), 6.77 (d, 1H), 7.42-7.80 (m, 11H), 7.84 (d, 2H), 8.32 (m, 1H); LC/MS (*m/z*): 571 $(M+1)^+$.

Example 49

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-methanesulfonyl amino-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]propionic acid methyl ester

2(S)-[(4-Amino-4'trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester (30 mg, 0.053 mmol) was reacted with methanesulfonyl chloride (12 mg, 0.11 mmol) following general procedure E to give the title compound. (21 mg)

^{1}H NMR (400 MHz, $CDCl_3$): 3.05 (s, 3H), 3.28, 3.36 (ABX, 2H), 3.85 (s, 3H), 5.07 (dd, 1H), 6.72 (d, 1H), 7.21 (m, 3H), 7.38 (m, 1H), 7.46-7.62 (m, 8H), 7.71 (dd, 1H), 7.82 (d, 1H); LC/MS (*m/z*): 649 $(M+1)^+$.

Example 50

3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (2-biphenyl-4-yl-1(S)-methylcarbamoyl-ethyl)-amide

Resin bound 3-(Biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid (30 mg, 0.09 mmol) prepared from resin bound 3-(Biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester following general procedure C, was reacted with methyl amine in THF(0.45 mmol) as described in general procedure A, then cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography to give the title compound. (36 mg). LC/MS (*m/z*): 503 $(M+1)^+$.

By analogous methods to those described above the following compounds were synthesized.

EX.	NAME	LC/MS (M+1)
51	3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid {2-biphenyl-4-yl-1-(S)-[2-(4-chloro-phenyl)-ethylcarbamoyl]-ethyl}-amide	627
52	3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (1-(S)-allylcarbamoyl-2-biphenyl-4-yl-ethyl)-amide	529
53	2-(S)-{3-Biphenyl-4-yl-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)amino]propionylamino}-3-methyl-butyric acid	589
54	3-(S)-{3-Biphenyl-4-yl-2-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]propionylamino}-propionic acid	561
55	3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(S)-(2-methoxy-ethylcarbamoyl)-ethyl]-amide	547

Example 56

2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-hexanoic acid

5-Bromomsalicylic acid (12.4 g, 57.3 mmol), 3-chloro-4-fluorophenylboronic acid (10.0 g, 57.3 mmol), and palladium tetrakistriphenylphosphine (5.2 g, 5.73 mmol) were dissolved in 200 mL DME and a 2N sodium carbonate (143.4 mL, 143.4 mmol) solution added. The reaction mixture was stirred overnight at 75°C. The solvent was removed and 10 mL concentrated HCl was added, followed by 100 mL THF. Additional HCl was added until the solution was neutralized and the mixture was filtered through a silica gel plug to remove the catalyst. DCM was added to the solution until the layers separated and the organic layer was dried over magnesium sulfate and evaporated. The solid was stirred with DCM for 2 hours, filtered, washed 2x with hexanes and dried (9.1g).

The 3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid (4.56 g, 17.1 mmol), 2-(S)-amino-3-(4-bromo-phenyl)-propionic acid methyl ester (5.0 g, 17.1 mmol) and HBTU (6.48 g, 17.1 mmol) were dissolved in 100 mL DMF. DIEA (5.96 mL, 34.2 mmol) was added and the mixture was stirred overnight. Ethyl acetate (200 mL) and 1N HCl (200 mL) were added to the mixture and the organic layer was washed with 10% sodium carbonate, dried over sodium sulfate and evaporated. The product was purified over silica (hexanes/ethyl acetate) (5.6 g). LC/MS (*m/z*): 508 $[(M+1)^+]$.

3-(4-bromo-phenyl)-2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (4.3 g, 8.49 mmol), 3-trifluoromethylphenylboronic acid (3.22 g, 16.98 mmol), and palladium tetrakistriphenylphosphine (1.54 g, 1.70 mmol) were dissolved in 200 mL DME and a 2N sodium carbonate (21.23 mL, 21.23 mmol) solution added. The reaction mixture was stirred overnight at 75°C. The solvent was removed and 5 mL concentrated HCl was added, followed by 100 mL THF. Additional HCl was added until solution was neutralized and the mixture was filtered through a silica gel plug to remove the catalyst. DCM was added to the solution until the layers separated and the organic layer was dried over magnesium sulfate and evaporated. The solid was stirred with DCM for 2 hours, filtered, washed 2x with hexanes and dried (3.0 g). LC/MS (*m/z*): 572 $[(M+1)^+]$.

2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester (3.0 g, 5.2 mmol) was dissolved in 100 mL of THF-methanol (4-1), cooled to 0°C and 20 mL 2N LiOH added. The reaction was stirred at 0°C for 1 hour. Ethyl acetate (100 mL) and 1N HCl (100 mL) were added to the mixture and the organic washed with brine, dried and evaporated to give 2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid (2.8 g). LC/MS (*m/z*): 558 $[(M+1)^+]$.

Resin-bound fmoc-norleucine (0.08 mmol) was deprotected with 20% piperidine in DMF (25 mL) for 2 hours. The reaction mixture was drained and washed 3x with DMF, methanol and DCM (3x 15 mL each solvent).

To the resin-bound norleucine (0.08 mmol), a solution of 2-(S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid (0.118 g, 0.20 mmol) in DMF (0.2 mL), HOBt (0.027 g, 0.20 mmol) in DMF (0.2 mL) and DIC (0.025 g, 0.2 mmol) in DMF (0.2 mL) were added and the mixture was shaken overnight. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 150mL each solvent).

Resin-bound 2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-3-phenyl-propionic acid was treated with 20% TFA in DCM (2mL) for 1 hour. The filtrate was collected and evaporated to give 2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-3-phenyl-propionic acid. The product was purified via prep TLC (ethyl acetate/methanol/acetic acid). LC/MS (*m/z*): 671 [$(M+1)^+$].

By analogous methods to those described above the following compounds were synthesized.

EX.	NAME	LC/MS (M+1)
57	1-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionyl]-pyrrolidine-2-(S)-carboxylic acid	655
58	2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-4-methylpentanoic acid	504
59	{[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionyl]-methyl-amino}-acetic acid	504
60	[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-2-(S)-phenyl-acetic acid	490
61	2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-	721

	propionylamino]-3-(4-hydroxy-phenyl)-propionic acid	
62	2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-propionic acid	629
63	2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-3-methyl-butyric acid	657
64	2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-pentanedioic acid	687
65	2-(S)-[2-(S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-succinic acid	673

Example 66

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(R)-(4-methyl-piperazin-1-yl)-2-oxo-1-(4'-trifluoromethyl-biphenyl-4-ylmethyl)-ethyl]-amide

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(R)-(4-methyl-piperazin-1-yl)-2-oxo-1-(4'-trifluoromethyl-biphenyl-4-ylmethyl)-ethyl]-amide (83 mg) was prepared from 2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid (96 mg, 0.0.16 mmol), N-methyl piperazine (22 μL, 0.19 mmol), HBTU (68 mg, 0.18 mmol) and DIEA (43 μL, 0.24 mmol) similar to general procedure A. Silica gel chromatography using 25% EtOAc in hexanes afforded the title compound.

LC-MS (*m/z*): 670 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.30-2.36 (m, 4H), 3.13-3.21 (m, 2H), 3.42 (m, 2H), 3.62 (m, 2H), 3.82 (s, 3H), 5.36 (q, 1H), 7.09 (d, 1H), 7.20 (t, 1H), 7.28 (d, 2H), 7.39-7.42 (m, 1H), 7.46 (d, 3H), 7.57 (d, 1H), 7.59 (m, 2H), 7.63 (m, 2H), 7.66 (m, 2H), and 12.14 (s, 1H).

Example 67

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(S)-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(S)-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide (46 mg) was prepared from 3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)--2-(S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid (55 mg, 0.1 mmol) and N-methyl piperazine following the general procedure A.

LC-MS (*m/z*): 640 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.30-2.36 (m, 4H), 3.13-3.21 (m, 2H), 3.42 (m, 2H), 3.62 (m, 2H), 5.36 (q, 1H), 7.09 (d, 1H), 7.20 (t, 1H), 7.28 (d, 2H), 7.39-7.42 (m, 1H), 7.46 (d, 3H), 7.57 (d, 1H), 7.59 (m, 2H), 7.63 (m, 2H), 7.66 (m, 2H), and 12.14 (br, 1H).

Example 68

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid {2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-[(2-dimethylamino-ethyl)-methyl-carbamoyl]-ethyl}-amide

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid {2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-[(2-dimethylamino-ethyl)-methyl-carbamoyl]-ethyl}-amide (49 mg, 76%) was prepared from 3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(R)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid (55 mg, 0.1 mmol) following the general procedure A.

LC-MS (*m/z*): 643 $(M+3)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.12 (s, 6H), 2.28 (m, 1H), 2.42 (m, 1H), 3.24 (t, 2H), 3.38 (m, 2H), 4.74 (q, 1H), 7.10 (dd, 1H), 7.18 (t, 2H), 7.36 (m, 2H), 7.44 (dd, 2H), 7.49 (d, 2H), 7.56 (m, 1H), 7.68 (d, 2H), 7.72 (d, 2H), 7.78 (t, 1H), and 12.12 (br, 1H).

Example 69

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-oxo-propyl]-amide

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(methoxy-methyl-carbamoyl)-ethyl]-amide (0.13g) was prepared from the 3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(R)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid (0.16g, 0.28mmol) and N,O-dimethylhydroxylamine hydrochloride (0.027, 0.28mmol) according to the general procedure A.

To a solution of 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(methoxy-methyl-carbamoyl)-ethyl]-amide (0.1g,

0.162mmol)in anhydrous THF (2mL) was added methyl magnesium bromide [0.35ml , 1.4M solution in Toluene/THF (75:25)] at 0°C and allowed to come to room temperature and stirred for 6h. Reaction was quenched with aq NH_4Cl and extracted with EtOAc. Organic layer was washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by silicagel column chromatography to get pure 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-oxo-propyl]-amide (0.055g)

LC/MS (*m/z*): 570.2 $(M+1)^+$.

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-oxo-propyl]-amide, example 73 (0.028g) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-oxo-propyl]-amide (0.05g, 0.087mmol) following general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.30 (s, 3H), 3.27 (dd, 1H), 3.37 (dd, 1H), 5.10 (s, 1H) 7.08-7.30 (m, 5H) 7.38 (m, 1H), 7.44-7.52 (m, 3H), 7.54-7.70 (m, 6H), 12.15 (s, 1H)

LC/MS (*m/z*): 556.9 $(M+1)^+$.

Example 70

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

[2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (96 mg,) was prepared from 2-(R)-tert-butoxycarbonylamino-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid pentafluorophenyl ester (140 mg, 0.25 mmol) and N-hydroxy-acetamidine (37 mg, 0.5 mmol) following the general procedure O.

2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (33 mg) was prepared from [2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (43 mg, 0.1 mmol) and hydrochloric acid (0.5 mL, 4.0 M. solution in dioxane) following the typical Boc deprotection procedure N.

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (55 mg) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl chloride (31 mg, 0.1 mmol) and 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (40 mg, 0.12 mmol) following the general procedure M.

LC-MS (*m/z*): 610 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.59 (t, 2H), 3.91 (s, 3H), 5.87 (q, 1H), 7.08 (d, 1H), 7.20 (dd, 2H), 7.38 (m, 1H), 7.46 (d, 3H), 7.58 (dd, 1H), 7.64-7.72 (m, 4H), 7.74 (d, 1H), 7.82 (dd, 1H), and 12.16 (br, 1H).

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (94 mg) was prepared from 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (122 mg, 0.20 mmol) and boron tribromide (0.5 mL, 0.5 mmol, 1.0 M solution in DCM) following the general procedure P.

LC-MS (*m/z*): 596 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.45 (d, 2H), 3.98 (m, 1H), 5.84 (q, 1H), 6.98 (d, 1H), 7.10 (d, 1H), 7.16-7.20 (m, 2H), 7.36 (m, 1H), 7.44 (d, 2H), 7.48 (d, 1H), 7.58 (m, 2H), 7.62-7.68 (m, 4H), and 11.85 (br, 1H).

By analogous methods to those described above the following compounds were synthesized.

EX.	NAME	LC/MS (M+1)
71	4-Hydroxy-4'-methanesulfonyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide	631.7
72	4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide	689.6
73	3',4'-Difluoro-4-hydroxy-biphenyl-3-carboxylic acid [2-(3',4'-difluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide	547.5
74	4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-(4'-trifluoromethyl-biphenyl-4-yl)-ethyl]-amide	611.5

Example 75

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

4-Ethoxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (57 mg) was prepared from 2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (33 mg, 0.10 mmol) and 4-Ethoxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid (37 mg, 0.1 mmol) following the general procedure A.

LC-MS (*m/z*): 693 $(M+2)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, 3H), 2.41 (s, 3H), 3.47 (d, 2H), 4.09 (q, 2H), 5.85 (q, 1H), 7.03 (d, 1H), 7.19 (m, 2H), 7.38 (m, 1H), 7.42 (d, 4H), 7.52 (dd, 1H), 7.58 (d, 1H), 7.64 (dd, 1H), 7.81 (s, 2H), and 7.88 (s, 1H).

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (48 mg) was prepared from 4-Ethoxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amid e (69 mg, 0.10 mmol) and boron tribromide (0.25 mL, 0.25 mmol, 1.0 M solution in DCM) following the general procedure P.

LC-MS (*m/z*): 665 $(M+2)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.45 (d, 2H), 5.84 (q, 1H), 7.08 (d, 1H), 7.18 (m, 2H), 7.38 (m, 1H), 7.44 (d, 4H), 7.54 (dd, 1H), 7.60 (d, 1H), 7.66 (dd, 1H), 7.83 (s, 2H), 7.90 (s, 1H), and 11.91 (br, 1H).

Example 76

Acetic acid 3-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-4'-trifluoromethyl-biphenyl-4-yl ester

Acetic acid 3-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-4'-trifluoromethyl-biphenyl-4-yl ester (45 mg) was prepared from 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (33 mg, 0.1 mmol) and acetic acid 3-chlorocarbonyl-4'-trifluoromethyl-biphenyl-4-yl ester (34 mg, 0.1 mmol) following the general procedure M.

LC-MS (*m/z*): 582 $(M+2)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.39 (s, 3H), 3.42 (dd, 1H), 3.50 (dd, 1H), 5.85 (q, 1H), 7.06 (d, 1H), 7.24 (dd, 2H), 7.38 (m, 1H), 7.42 (d, 2H), 7.48 (d, 1H), 7.58 (dd, 1H), 7.69 (m, 4H), 7.74 (d, 2H), and 8.18 (d, 1H).

Example 77

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-benzyloxy-3'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [(4'-benzyloxy-3'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (58 mg) was prepared from acetic acid 3-chlorocarbonyl-4'-trifluoromethyl-biphenyl-4-yl ester (1.96 mL, 0.1 M CH_2Cl_2), 2-(4'-benzyloxy-3'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride (90 mg, 0.178 mmol) and DIEA (95 μL, 0.55 mmol) analogous to procedure M. The crude reaction mixture was concentrated and redissolved in THF (3 mL) and MeOH (1 mL). 1N $NaHCO_3$ (200 μL) and 1N Na_2CO_3 (50 μL) were added and the hydrolysis was followed by TLC and LCMS. Once complete, the reaction was diluted with EtOAc and the layers were separated. After extraction and drying the combined organics over $MgSO_4$, the crude mixture was concentrated onto silica gel and purified by chromatography using 15% EtOAc in hexanes.

LC-MS (*m/z*): 668 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.43 (d, 2H), 5.20 (s, 2H), 5.82 (q, 1H), 7.02-7.22 (m, 5H), 7.27-7.41(m, 2H), 7.42-7.44 (m, 6H), 7.50-7.68 (m, 6H), 11.83 (s, 1H).

Example 78

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (49 mg) was prepared from acetic acid 3-chlorocarbonyl-4'-trifluoromethyl-biphenyl-4-yl ester (1.93 mL, 0.1 M CH_2Cl_2) and 2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride (80 mg, 0.175 mmol) and DIEA (92 μL, 0.525 mmol) using standard procedure M. The crude reaction mixture was concentrated and redissolved in THF (3 mL) and MeOH (1 mL). 1N $NaHCO_3$ (200 μL) and 1N Na_2CO_3 (50 μL) were added and the hydrolysis was followed by TLC and LCMS. Once complete, the reaction was diluted with EtOAc and the layers were separated. After extraction and drying the combined organics over $MgSO_4$, the crude mixture was concentrated onto silica gel and purified by chromatography using 15% EtOAc in hexanes.

LC-MS (*m/z*): 622 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.09 (s, 3H), 3.46 (d, 2H), 5.86 (q, 1H), 7.09-7.19 (m, 3H), 7.23 (d, 2H), 7.52-7.73 (m, 8H), 7.99 (d, 2H), 11.80 (s, 1H).

Example 79

4-Hydroxy-4'-nitro-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

4-Hydroxy-4'-nitro-biphenyl-3-carboxylic acid (1.98) was prepared from 5-bromosalicylic acid (2.6g, 11.9mmol) and 4-nitrophenylboronic acid (3.0g, 17.9) following general procedure D

To a solution of 4-Hydroxy-4'-nitro-biphenyl-3-carboxylic acid (2.0g, 7.71mmol) in acetone was added K_2CO_3(2.34g, 16.9mmol) and MeI (4.3g, 30.8mmol) and refluxed for 12h. Reaction mixture was diluted with EtOAc and filtered, filtrate was washed with water brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and silicagel column chromatography gave pure 4-Methoxy-4'-nitro-biphenyl-3-carboxylic acid methyl ester (1.9g).

To a solution of 4-Methoxy-4'-nitro-biphenyl-3-carboxylic acid methyl ester (0.15g, 0.52mmol) in THF-MeOH (3:1) was added LiOH (1.04mL of 1N solution) and heated at 65°C for 12h. Reaction mixture was acidified with HCl (1N, 1.04mL) and diluted with EtOAc, and washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the product 4-Methoxy-4'-nitro-biphenyl-3-carboxylic acid (0.12g) was used in the next reaction without further purification.

4-Methoxy-4'-nitro-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.045g) was prepared from 4-Methoxy-4'-nitro-biphenyl-3-carboxylic acid (0.03g, 0.11mmol) and 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride salt (0.04g, 0.11mmol) following general procedure A

LC/MS (*m/z*): 587.9 $(M+1)^+$.

4-Hydroxy-4'-nitro-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.017g) was prepared from 4-Methoxy-4'-nitro-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.03g, 0.05mmol) following general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.42 (s, 3H), 3.46 (dd, 2H), 5.84 (m, 1H), 6.94 (d, 1H), 7.10-7.24 (m, 4H), 7.38 (m, 1H), 7.45 (d, 2H), 7.51 (d, 1H), 7.56 (dd, 1H), 7.64 (m, 2H), 7.70 (m, 1H) 8.26 (d, 2H), 11.90 (s, 1H).
LC/MS (*m/z*): 573.8 $(M+1)^+$.

Example 80

6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

To a solution of 5-Bromo-2,4-dihydroxy-benzoic acid methyl ester (1.0g, 4.04mmol) in DMF (7mL) was added Cs_2CO_3 (1.58g, 4.85mmol) and benzylbromide (0.69g, 4.04mmol) and heated at 70°C for 6h. Reaction mixture was diluted with EtOAc (10mL) and filtered, filtrate was washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and silicagel column chromatography (EtOAc:Hex , 1:3) gave pure 4-benzyloxy-5-bromo-2-hydroxy-benzoic acid methyl ester (0.62g).

To a solution of 4-benzyloxy-5-bromo-2-hydroxy-benzoic acid methyl ester (0.5g, 1.48mmol) in toluene (5mL) was added 4-trifluorophenylboronic acid (0.56g, 2.96mmol), tetrakistriphenylphosphine (0.17g, 0.14mmol), Na_2CO_3 (2.96ml, 1N solution) and stirred the reaction mixture at 80°C for 12h. Reaction mixture was diluted with EtOAc (10mL) and washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and silicagel column chromatography (20:80 EtOAc:hexane) gave pure 6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (0.39g).

6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.13g,) was prepared from 6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (0.16g, 0.39mmol) following general procedure C.

To a solution of 6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (52mg, 0.13mmol) in THF:DCE (1:1, 2mL) was added PS-Carbodiimide resin (0.14g, 1.3mmol/g) and 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (0.03g, 0.09mmol) and stirred for 12h, resin was filtered and washed with EtOAc (5mL), filtrate was concentrated and silicagel chromatography of the residue gave pure 6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.013g).
^{1}HNMR (400MHz, $CDCl_3$): 2.39 (s, 3H), 3.42 (dd, 2H), 5.13 (s, 2H), 5.80 (m 1H), 6.63 (s, 1H), 6.68 (d, 1H), 7.10-7.24 (m, 4H), 7.27-7.40 (m, 6H), 7.42 (d, 2H), 7.54-7.64 (m, 5H), 12.2 (s, 1H); LC/MS (*m/z*): 703.0 $(M+1)^+$.

Example 81

5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

N-Bromosuccinimide (2.38g, 13.38mmol) was added to a solution of 3-chlorosalicylic acid (2.1g, 12.16mmol) in CH_3CN (10mL) solution and stirred for 1h, reaction mixture was diluted with water (25mL), solids were filtered and washed with water and dried to get 5-Bromo-3-chloro-2-hydroxy-benzoic acid (2.87g).

Methyl Iodide (3.83g, 27.04mmol) was added to a solution of 5-Bromo-3-chloro-2-hydroxy-benzoic acid (1.7 g, 6.76mmol) and Cs_2CO_3 (4.83g, 14.86mmol) in DMF (10mL) and heated at 50°C for 12h. The reaction mixture was diluted with EtOAc (30mL) and filtered over celite pad. Filtrate was washed with water, brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silicagel column chromagography to get pure 5-Bromo-3-chloro-2-methoxy-benzoic acid methyl ester (1.56g).

4-Trifluoromethylphenylboronic acid (0.815g, 4.29mmol) was added to a solution of 5-Bromo-3-chloro-2-methoxy-benzoic acid methyl ester (1.0g, 3.57mmol) , $Pd(PPh_3)_4$ (0.2g, 0.178 mmol) and CsF (1.08g, 7.15mmol) in DME (10mL)and heated at 85°C for 10h. The reaction was diluted with EtOAc (20mL) and filtered, filtrate was washed water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the silicagel column chromatography gave pure 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (0.94g).

5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.62g) was prepared from 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (0.7g, 2.03mmol) following the procedure C.

5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.5g) was prepared from 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.4g, 1.2mmol) and 2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (0.4g, 1.2mmol) according to the general procedure A.
LC/MS (*m/z*): 644.0 $(M+1)^+$.

5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.22g) was prepared from 5-Chloro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-

chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.4g, 0.62mmol) following general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.41 (s, 3H), 3.46 (m, 2H), 5.83 (dd, 1H), 7.06-7.23 (m, 4H), 7.35-7.70 (m, 10H), 7.77 (d, 1H)

LC/MS (*m/z*): 630.5 $(M+1)^+$.

Example 82

Acetic acid 5'-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl) ethylcarbamoyl]-4-trifluoromethyl[1,1';3',1"]terphenyl-4'-yl ester

To a solution of 5-Bromo-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid methylester (0.3g, 0.8mmol) in toluene (5mL) was added phenylboronic acid (0.19g, 1.6mmol), tetrakistriphenylphosphine (0.0.09g, 0.08mmol), Na_2CO_3 (2.4ml, 1N solution) and stirred the reaction mixture at 80°C for 10h. The reaction mixture was diluted with EtOAc (10mL) and washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and silicagel column chromatography (20:80 EtOAc:hexane) gave pure 4'-Hydroxy-4-trifluoromethyl-[1,1';3',1"]terphenyl-5'-carboxylic acid methyl ester (0.21g).

4'-Hydroxy-4-trifluoromethyl-[1,1';3',1"]terphenyl-5'-carboxylic acid (0.17g) was prepared from 4'-Hydroxy-4-trifluoromethyl-[1,1';3',1"]terphenyl-5'-carboxylic acid methyl ester (0.2g, 0.53mmol) following general procedure C.

Acetic acid 5'-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-4-trifluoromethyl-[1,1';3',1"]terphenyl-4'-yl ester (0.04g) was prepared from Acetic acid 5'-chlorocarbonyl-4-trifluoromethyl-[1,1';3',1"]terphenyl-4'-yl ester (0.06g, 0.14mmol) [prepared from 4'-Hydroxy-4-trifluoromethyl-[1,1';3',1"]terphenyl-5'-carboxylic acid following general procedures K & L.] and 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (0.047g,0.14mmol) following general procedure M.

^{1}HNMR (400MHz, $CDCl_3$): 1.85 (s, 3H), 2.39 (s, 3H), 3.37 (dd, 1H), 3.53 (dd, 1H), 5.84 (m, 1H), 7.09-7.24 (m, 4H), 7.33-7.50 (m, 8H), 7.55 (dd, 1H), 7.64-7.73 (m, 5H), 7.99 (d, 1H),

LC/MS (*m/z*): 744.9 $(M+1)^+$.

Example 83

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4-benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

Example 105

2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4-naphthalen-2-ylphenyl)-propionic acid methyl ester

To 1.0 g (2.5 mmol) of resin-bound naphthoic acid obtained using the procedure described in example 1, was added 1.95 g (7.5 mmol) of (S)-4-hydroxyphenylalanine methyl ester, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound 2-(3-Hydroxy-naphthalene-2-carbonyl)-amino-3-(4-hydroxy-phenyl)-propionic acid methyl ester.

To 0.05 g (0.1 mmol) of resin-bound 2-(S)-(3-Hydroxy-naphthalene-2-carbonyl)-amino-3-(4-hydroxy-phenyl)-propionic acid methyl ester was reacted with 2-(4-chloro-phenyl)-ethanol (156 mg, 1.0 mmol), DIAD (1.0 mmol), Ph_3P (1.0 mmol) in THF at rt overnight.

The resin was washed and cleaved as described in Example 28 to give the title compound (25 mg). LC/MS (*m/z*) 504 $(M+1)^+$.

Example 106

3-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester

0.05 g (0.1 mmol) of resin-bound 2-(S)-(3-Hydroxy-naphthalene-2-carbonyl)-amino-3-(4-hydroxy-phenyl)-propionic acid methyl ester obtained in Example 105 was reacted with 2-(4-chloro-phenyl)-ethanol (156 mg, 1.0 mmol), DIAD (1.0 mmol), Ph_3P (1.0 mmol) in THF at rt overnight. The resulting resin was hydrolyzed according to general procedure C. The resin was then washed and cleaved as described in Example 28 to give the title compound (20 mg). LC/MS (*m/z*) 490 $(M+1)^+$.

Example 107

2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-[4-(4-nitro-phenoxy)-phenyl]propionic acid methyl ester

To 0.05 g (0.1 mmol) of the above resin-bound 2-(S)-(3-Hydroxy-naphthalene-2-carbonyl)-amino-3-phenyl-propionic acid methyl ester as obtained in Example 105 was reacted with 4-nitro-fluorobenzene (42 mg, 0.30 mmol) as described in general procedure B.

The resin was washed with H_2O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent

[2-(4-Benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (2.75g) was prepared from N-boc-O-benzyl tyrosine (2.6g, 7.00mmol) following general procedure G.

2-(4-Benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride salt (1.27g) was prepared from the [2-(4-Benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (1.5g, 3.67mmol) following general procedure N.

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4-benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide was prepared from Acetic acid 3-chlorocarbonyl-4'-trifluoromethyl-biphenyl-4-yl ester (0.32g, 0.93mmol) and 2-(4-Benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride salt (0.32g, 0.93mmol) following the general procedure M. followed by the hydrolysis of the resulting acetate using K_2CO_3.

^{1}HNMR (400MHz, $CDCl_3$): 2.39 (s, 3H), 3.35 (d, 2H), 5.01 (s, 2H), 5.75 (, 1H), 6.85-6.93 (m, 3H), 6.97-7.21(m, 2H), 7.10 (d, 1H), 7.29-7.43 (m, 5H), 7.46 (d, 1H), 7.59 (d, 2H), 7.65 (dd, 1H), 7.70 (d, 2H).11.90 (s, 1H)

Example 84

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.018) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl [1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.03g, 0.052mmol) using the general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.41 (s, 3H), 3.46 (d, 2H), 5.82 (dd, 1H), 6.82 (br d, 1H), 7.08-7.19 (m, 2H), 7.42 (s, 1H), 7.46-7.68 (m, 9H), 11.80 (s, 1H)

Example 85

5-Fluoro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

To a solution of 5-Bromo-3-fluoro-2-hydroxy-benzaldehyde (2.0g, 9.13mmol), in DMF (10mL) was added Cs_2CO_3 (3.56g, 10.95 mmol) and iodomethane (2.59g, 18.26mmol) and heated at 70°C for 6h. Reaction mixture was diluted with EtOAc (25mL) and filtered,

filtrate was washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and silicagel column chromatography (EtOAc:Hex , 1:3) gave pure 5-Bromo-3-fluoro-2-methoxy-benzaldehyde (2.0g).

4-Trifluorophenylboronic acid (1.05g, 5.57mmol) was added to a solution of 5-Bromo-3-fluoro-2-methoxy-benzaldehyde (1.0g, 4.29mmol), $Pd(PPh_3)_4$ (0.24g, 0.21 mmol) and CsF (1.3g, 8.58mmol) in DME (10mL)and heated at 85°C for 10h. The reaction was diluted with EtOAc (20mL) and filtered, filtrate was washed water, brine and dried over Na2SO4. Solvent was removed under reduced pressure and the silicagel column chromatography gave pure 5-Fluoro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxaldehyde (0.91g).

Pyridinium dichromate (0.25g, 0.67 mmol) was added to a solution of 5-Fluoro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carbaldehyde (0.2g, 0.67mmol) DMF (2mL) and stirred for 12h, to complete the reaction more pyridinium dichromate (0.2g , 0.53mmol) was added and stirred for 12h. The reaction mixture was diluted with water (5mL) and extracted with EtOAc(10mL). Solvent was removed under reduced pressure to get 5-Fluoro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.12g).

5-Fluoro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide was prepared from 5-Fluoro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.06g, 0.19mmol) and 2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (0.063g, 0.19mmol) following general procedure A.

LC/MS (*m/z*): 628.0 $(M+1)^+$.

5-Fluoro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide was prepared from 5-Fluoro-4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide following general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.41 (s, 3H), 3.46 (m, 2H), 5.83 (dd, 1H), 7.00 (br d, 1H), 7.12-7.23 (3H), 7.30 (s, 1H), 7.38 (m, 1H), 7.43-7.60 (m, 6H), 7.66 (d, 2H).

Example 86

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl 1,2,4]oxadiazol-5-yl)-ethyl]-amide

2-(R)-tert-Butoxycarbonylamino-3-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-propionic acid (0.87g) was prepared from Boc-D-tyrosine methyl ester (1.0g, 3.38mmol) 3-chloro-4-fluorophenylboronic acid (1.76g, 10.15mmol) as described in the general procedure F.

[2-[4-(3-Chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester (0.57g) was prepared from 2-(R)-tert-Butoxycarbonylamino-3-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-propionic acid [0.73g, 1.78mmol, which was prepared from 2-(R)-tert-Butoxycarbonylamino-3-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-propionic acid methyl ester using the general procedure C] following the general procedure O.

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.07g) was prepared from 2-[4-(3-Chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride [0.07g, 0.182mmol, which was prepared from [2-[4-(3-Chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butyl ester following general procedure N] and 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.053g, 0.18mmol) following general procedure A.

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.022g) was prepared from 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.04g, 0.063 mmol) following general procedure P.^{1}HNMR (400MHz, $CDCl_3$): 2.40 (s, 3H), 3.39 (m, 2H), 5.78 (dd, 1H), 6.80-6.94 (m, 4H), 6.90-7.14 (m, 5H), 7.47 (s, 1H), 7.54-7.74 (m, 5H), 11.85 (s, 1H); LC/MS (*m/z*): $(M+1)^+$.

Example 87

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

2-(R)-tert-Butoxycarbonylamino-3-(3'-chloro-4'-fluoro-biphenyl-3-yl)-propionic acid (0.93g) was prepared from (R)-N-Boc-3-bromophenylalanine (1.0g, 2.9mmol) and 3-chloro-4-fluorophenylboronic acid (1.0g, 5.8mmol) following general procedure D.

[2-(3'-Chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butylester (0.7g)was prepared from 2-(R)-tert-Butoxycarbonylamino-3-(3'-chloro-4'-fluoro-biphenyl-3-yl)-propionic acid (0.9g, 2.2mmol) following general procedure O.

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.073g) was prepared from 2-(3'-Chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride salt [0.07g, 0.19mmol, prepared from [2-(3'-Chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butylester following general procedure N] and 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.056g, 0.19mmol) following general procedure A.

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.022g) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-3-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide(0.04g, 0.065mmol) follwing general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.41 (s, 3H), 3.47 (m, 1H), 4.86 (m, 1H), 6.90 (d, 1H), 7.07-7.15 (m, 4H), 7.20 (m, 1H), 7.29 (m, 1H), 7.37 (t, 1H), 7.42-7.46 (m, 3H), 7.52 (d, 2H), 7.66 (d, 3H)11.81 (s, 1H)

Example 88

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

[2-(3'-Chloro-4'-fluoro-biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-carbamic acid tert-butylester (0.72g) was prepared following general procedure O from 2-(R)-tert-Butoxycarbonylamino-2-(3'-chloro-4'-fluoro-biphenyl-2-yl)-propionic acid (1.0g, 2.54mmol) which was prepared from (D)-N-Boc-2-bromophenylalanine and 3-chloro-4-fluoro boronic acid, following general procedure D.

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.081g) was prepared from 2-(3'-Chloro-4'-fluoro-biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine hydrochloride salt (0.075g, 0.2mmol) which was prepared from 2-(R)-tert-Butoxycarbonylamino-2-(3'-chloro-4'-fluoro-biphenyl-2-yl)-propionic acid following general procedure N and 4-methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (0.06g, 0.2mmol) following general procedure A.

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.024) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-

biphenyl-2-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (0.04g, 0.065mmol) following general procedure P.

^{1}HNMR (400MHz, $CDCl_3$): 2.36 (s, 3H), 3.38 (dd, 1H), 3.47 (dd, 1H), 5.56 (dd, 1H), 6.74 (d, 1H), 7.04 (m, 3H), 7.14-7.37 (m, 5H), 7.40 (d, 1H), 7.60 (d, 2H), 7.66 (dd, 1H), 7.72 (d, 2H), 11.89 (s, 1H)

Example 89

5-Bromo-N-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-2-hydroxy-benzamide

The title compound (39 mg) was prepared from 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine (33 mg, 0.1 mmol) and 5-bromo-2-hydroxy-benzoic acid (21 mg, 0.1 mmol) following the general procedure A.

LC-MS (*m/z*): 532 $(M+2)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.42 (t, 2H), 5.79 (q, 1H), 6.82 (d, 1H), 6.90 (dd, 1H), 7.14 (d, 2H), 7.19 (t, 2H), 7.40 (m, 1H), 7.48 (m, 2H), 7.52 (dd, 1H), 7.58 (dd, 1H), and 11.82 (br, 1H).

Example 90

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (53 mg) was prepared from 4-benzyloxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide (70 mg, 0.1 mmol) and boron tribromide (0.25 mL, 0.25 mmol, 1.0 M solution in DCM) following the general procedure P.

LC-MS (*m/z*): 613 $(M+2)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.45 (d, 2H), 5.85 (q, 1H), 7.11 (dd, 1H), 7.17 (d, 2H), 7.34 (d, 1H), 7.38 (s, 1H), 7.41 (m, 2H), 7.49-7.53 (m, 3H), 7.56 (d, 1H), 7.63 (t, 1H), 7.67 (t, 1H), 7.83 (s, 1H), 7.91 (m, 2H), and 11.94 (br, 1H).

Example 91

Acetic acid 3-[2-(6-methoxy-4'-nitro-biphenyl-3-yl)-ethylcarbamoyl]-naphthalen-2-yl ester

3-Acetoxy-naphthalene-2-carboxylic acid (232 mg) was prepared from 3-hydroxy-naphthalene-2-carboxylic acid (188 mg, 1.0 mmol) following the general procedure K.

Acetic acid 3-[2-(6-methoxy-4'-nitro-biphenyl-3-yl)-ethylcarbamoyl]-naphthalen-2-yl ester (108 mg) was prepared from 3-Acetoxy-naphthalene-2-carboxylic acid (58 mg, 0.25 mmol) and 2-(6-Methoxy-4'-nitro-biphenyl-3-yl)-ethylamine (68 mg, 0.25 mmol following the general procedure A.

LC-MS (*m/z*): 485 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.95 (t, 2H), 3.74 (q, 2H), 3.82 (s, 3H), 6.36 (br, 1H), 6.98 (d, 1H), 7.22-7.32 (m, 2H), 7.46-7.58 (m, 4H), 7.66 (d, 2H), 7.82 (d, 2H), 8.14 (s, 1H), and 8.24 (d, 1H).

Example 92

3-Biphenyl-4-yl-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester

The title compound (26 mg) was prepared from 0.05 g (0.1 mmol) of resin-bound 3-(4-bromophenyl)ethyl-(2S)-[3-(hydroxy-napthalene-2-carbonyl)-amino]-propionic acid methyl ester and 36.0 mg (0.3 mmol) of phenyl boronic acid as described in the general procedure D followed by the cleavage described in example 28. LC/MS (*m/z*): 426 $(M+1)^+$.

Example 93

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester

To 1.0 g (2.5 mmol) of resin-bound naphthoic acid obtained using the procedure described in example 1, was added 1.95 g (7.5 mmol) of (S)-4-bromophenylalanine methyl ester, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound 3-(4-bromophenyl) ethyl-2-(S)-[3-(hydroxy-napthalene-2-carbonyl)amino]-propionic acid methyl ester.

To 0.05 g (0.1 mmol) of the above resin-bound 3-(4-bromophenyl)ethyl-(2S)-[3-(hydroxy-napthalene-2-carbonyl)-amino]-propionic acid methyl ester in 2.0 mL of DME were added 52.0 mg (0.3 mmol) of 3-chloro-4-fluorophenylboronic acid, 30 mg (0.03 mmol) of $Pd(PPh_3)_4$, and 0.3 mL (0.6 mmol) of 2*N* Na_2CO_3 solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H_2O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the

solvent was purified by chromatography (DCM) to give the title compound (30mg). LC/MS (*m/z*) 478 $(M+1)^+$.

By analogous methods to those described above the following compounds were synthesized.

EX.	NAME	LC/MS (m/z)
94	3-(4'-Fluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester	444
95	3-(3',4'-Difluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester	462
96	3-(4'-Chloro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester	460
97	2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester	510
98	2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	493
99	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester	562
100	3-(3',5'-Difluoro-biphenyl-4-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester	462
101	2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-[1,1';4',1"]terphenyl-4-yl-propionic acid methyl ester	502
102	3-(2'-Fluoro-[1,1';4',1"]terphenyl -4"-yl)-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester	507
103	3-(4'-tert-Butyl-biphenyl-4-yl)-2-[(3-hydroxy-naphthalene-2-(S)-carbonyl)-amino]-propionic acid methyl ester	482
104	2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4-naphthalen-2-yl-phenyl)-propionic acid methyl ester	476

was purified by chromatography (DCM) to give the title compound (28 mg). LC/MS (*m/z*) 487 $(M+1)^+$.

Example 108

2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-[4-(3-phenyl-propylamino)-phenyl]-propionic acid methyl ester

400 mg (1.0 mmol) of resin-bound naphthoic acid was reacted with 560 mg (2.5 mmol) of (2S)-Amino-3-(4-nitro-phenyl)-propionic acid methyl ester as described in Example 105 to give resin-bound 2-(S)-(3-Hydroxy-naphthalene-2-carbonyl)-amino-3-(4-nitro-phenyl)-propionic acid methyl ester.

To 0.10 g (0.2 mmol) of the above resin was reduced by excess $SnCl_2$ hydrate in NMP at RT for 6h, then reacted with 3-phenyl-propionaldehyde (134 mg, 1.0 mmol) as described in general procedure R. The resin was then washed and cleaved as described in Example 28 to give the title compound (48mg). LC/MS (*m/z*) 483 $(M+1)^+$.

Example 109

[2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionylamino]-acetic acid methyl ester

The resin-bound (2S)-[(3-Hydroxy-napthalene-2-carbonyl)-amino]-3-[(4'-trifluoromethyl)-biphenyl-4-yl]-propionylamino]-acetic acid methyl ester (29 mg) was prepared from 0.05 g (0.1 mmol) of resin-bound 3-(4-bromophenyl)ethyl-(2S)-[3-(hydroxy-napthalene-2-carbonyl)-amino]-propionic acid methyl ester and 58.0 mg (0.3 mmol) of 4-(trifluoromrthyl)phenylboronic acid as described in general procedure D LC/MS (*m/z*): 494 $(M+1)^+$.

The above methyl ester (100 mg, 0.1 mmol) was hydrolyzed according to general procedure C to afford the resin-bound (2S)-[(3-Hydroxy-napthalene-2-carbonyl)-amino]-3-[(4'-trifluoromethyl)-biphenyl-4-yl]-propionylamino]-acetic acid, which was reacted with glycine methyl ester (46 mg, 0.5 mmol) as described in general procedure A. The resin was cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (DCM) to give the title compound (20mg). LC/MS (*m/z*) 551 $(M+1)^+$.

Example 110

3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-methoxy-4'-nitro-biphenyl-3-yl)-ethyl]-amide

To 1.0 g (2.5 mmol) of resin-bound 3-hydroxy-2-naphthoic acid obtained using the procedure described in example 1, was added a mixture of 1.5 g (7.5 mmol) of 3-Bromo-6-methoxyphenethylamine, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound *N*-2-(3-bromo-6-methoxyphenyl)ethyl-3-hydroxyl-2-naphthamide.

To 0.05 g (0.1 mmol) of above resin-bound *N*-2-(3-bromo-6-methoxyphenyl)ethyl-3-hydroxyl-2-naphthamide in 2.0 mL of DME were added 36.6 mg (0.3 mmol) of 4-nitrophenylboronic acid, 30 mg (0.03 mmol) of $Pd(PPh_3)_4$, and 0.3 mL (0.6 mmol) of 2*N* Na_2CO_3 solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H_2O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (100% methylene chloride) to give 22 mg of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): 2.99 (t, 2H), 3.77 (dd, 2H), 3.83 (s, 3H), 6.62 (broad, 1H), 6.99 (d, 1H), 7.21 (s, 1H), 7.31-7.27 (m, 3H), 7.48 (t, 1H), 7.69-7.61 (m, 4H), 7.81 (s, 1H), 8.20 (d, 2H); LC/MS (*m/z*): 443$(M+1)^+$.

Example 111

3-Hydroxy-naphthalene-2-carboxylic acid [2-(6-methoxy-4'-nitro-biphenyl-3-yl)-ethyl]-amide

The title compound (27 mg) was prepared from 0.05 g (0.1 mmol) of resin-bound *N*-2-(3-bromo-4-methoxyphenyl)ethyl-3-hydroxyl-2-naphthamide and 50.0 mg (0.3 mmol) of 4-nitro-phenyl boronic acid as described in Example 110.

^{1}H NMR (400 MHz, $CDCl_3$): 3.11 (t, 2H), 3.78 (dd, 2H), 3.98 (s, 3H), 6.95 (broad, 1H), 7.03 (d, 1H), 7.29 (d, 2H), 7.49-7.44 (m, 2H), 7.54 (dd, 1H), 7.69-7.61 (m, 4H), 7.81 (s, 1H), 8.22 (d, 2H); LC/MS (*m/z*): 443 $(M+1)^+$.

Examples 112 and 113

3-Hydroxy-naphthalene-2-carboxylic acid [2-(4'-methanesulfonyl-4-methoxy-biphenyl-3-yl)-ethyl]-amide and 3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-hydroxy-4'-methanesulfonyl-biphenyl-3-yl)-ethyl]-amide

3-Methoxy-2-naphthoic acid 1g, (4.95 mmol) and 2-Methoxy-5-bromo-1-phenethylamine were coupled using the general procedure A, to obtain 450 mg of the coupled product.

The bromo dervative (414mg, 1mmol) was subjected to Sujuki coupling using 4-Methylsulfonyl-1 phenylboronic acid 300mg(1.5 mmol) using the general procedure D which afforded 300mg of the 3-Methoxy-naphthalene-2-carboxylic acid [2-(4'-methanesulfonyl-4-methoxy-biphenyl-3-yl)-ethyl]-amide.

The above methyl ether (250 mg) was then hydrolyzed with BBr_3 following the general procedure P which was purified on silica gel column to afford the 3-Hydroxy-naphthalene-2-carboxylic acid [2-(4'-methanesulfonyl-4-methoxy-biphenyl-3-yl)-ethyl]-amide 10 mg as well as the 3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-hydroxy-4'-methanesulfonyl-biphenyl-3-yl)-ethyl]-amide(25 mg).

LC/MS 476 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (s, 3H), 3.1(m, 2H), 3.75 (m, 2H), 3.85 (s, 3H), 7.0 (d, 1H), 7.25 (s, 1H), 7.5 (m, 3H), 7.62 (d, 1H), 7.7 (m, 2H), 7.8 (m, 3H), 7.86 (d, 2H), 8.1 (d, 1H).

3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-hydroxy-4'-methanesulfonyl-biphenyl-3-yl)-ethyl]-amide (Example 113)

LC/MS 462 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.1 (s, 3H), 3.15(m, 2H), 3.7 (m, 2H), 7.0 (d, 1H), 7.2 (m, 1H), 7.3 (s, 1H), 7.5 (m, 5H), 7.7 (m, 4H), 7.86 (d, 2H).

Example 114

(3-{2-[(3-Hydroxy-naphthalene-2-carbonyl)-amino]-ethyl}-4'-methanesulfonyl-biphenyl-4-yloxy)-acetic acid methyl ester

To a solution of the 3-Hydroxy-naphthalene-2-carboxylic acid [2-(4-hydroxy-4'-methanesulfonyl-biphenyl-3-yl)-ethyl]-amide (18 mg, 0.039 mmol) was in DMF were added ethylbromoacetate (0.039 mmol) and Cs_2CO_3 (0.039 mmol, 13 mg). The reaction mixture was for 12hr and the reaction mixture was diluted with ethylacetate and washed with water.

The organic layer was separated, dried and the crude obtained after removal of the solvent was purified on a silicagel column to afford the desired product 5 mg, and 5 mg of bis ester. LC/MS 548 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37(t, 3H), 3.05(s, 3H), 3.1(m, 2H), 3.65(m, 2H), 4.38(q, 2H), 4.82(s, 2H), 7.05(d, 1H), 7.15(s, 1H), 7.35 (s, 1H), 7.45 (m, 2H), 7.55 (m, 1H), 7.7 (m, 3H), 7.95(m, 3H), 8.9(s, 1H), 9.45(s, 1H), 9.5 (t, 1H).

Example 115

3-Hydroxy-naphthalene-2-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide

3-Methoxy-2-naphthoic acid 86mg (0.43 mmol) and the 2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylamine 100 mg (0.35 mmol) were coupled using the general procedure A. to afford the 3-Methoxy-naphthalene-2-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide 60 mg.

The resulting methyl ether was hydrolysed using BBr_3 following the general procedure P and provided the title compound (15mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.4(s, 3H), 3.45(d, 2H), 5.9(m, 1H), 7.05(d, 1H), 7.2(m, 3H), 7.3(m, 2H), 7.4(m, 2H), 7.5(m, 2H), 7.6(d, 1H), 7.7 (d, 1H), 7.75(d, 1H), 7.95(s, 1H), 11.15(s, 1H).

Example 116

2-(S)-[5-Bromo-2-(2-morpholin-4-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

A solution of (2S)-(5-bromo-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (25 mg, 46μmol, obtained by following similar procedure described for example 34), 2-morpholin-4-yl-ethanol (1.5 eq., 8.3 μL, 69 μmol) and triphenylphosphine (1.5 eq., 18mg, 69μmol) in anhydrous THF (1 mL) was treated with DIAD (1.5 eq., 13.5μl, 69μmol) as described in Procedure I. Flash column chromatography (4:1 hexanes:EtOAc) provided 13mg of the title compound. LCMS for $C_{35}H_{35}BrN_2O_6$: 659, 661.

By analogous methods to those described above, the following compounds were synthesized.

EX.	NAME	LC/MS M^+, and M+2 (m/z)
117	2-(S)-[5-Bromo-2-(3-pyridin-4-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	665, 667
118	2-(S)-{5-Bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	657, 659
119	2-(S)-[5-Bromo-2-(2-morpholin-4-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	642 644
120	2-(S)-[5-Bromo-2-(4,4,4-trifluoro-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	643, 645
121	2-(S)-[5-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	657, 659

Example 122

2-(S)-[(4-Butoxy-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino]-3-(3'-tri fluoromethyl-biphenyl-4-yl)-propionic acid

A mixture of 5-bromo-2-hydroxy-benzoic acid (2.21 g,10 mmol), butyl bromide (3.46 g, 25 mmol), potassium carbonate (2.76 g, 20 mmol) and DMF (20 mL) was heated at 100 °C for 1 h. The reaction mixture was partitioned between ether (120 mL) and brine (100 mL). Ether layer was separated and washed again with brine (100 mL), dried over $MgSO_4$. Purification by flash chromatography (ethyl acetate/hexanes 1:99, 1:19, 1:9) gave 5-Bromo-2-butoxy-benzoic acid butyl ester as yellow oil (1.648 g, 5.01 mmol).

The 4-Butoxy-3'-chloro-4'-fluoro-biphenyl-3-carboxylic acid butyl ester was prepared following General Procedure D using 5-bromo-2-butoxy-benzoic acid butyl ester (1.648 g, 5.01 mmol), 3-chloro-4-fluoro-benzene boronic acid (1.31 g, 7.5 mmol), palladium tetrakis-triphenylphosphine (0.289 g, 0.25 mmol), and Na_2CO_3(aq) (2.0 N, 10 mL, 20 mmol) in DME (20 mL). The mixture was heated at 80 °C for 14 h. Purification by flash chromatography (ethyl acetate/hexanes 1:19, 1:9) gave the desired compound as yellow oil (0.966 g, 2.55 mmol).

Hydrolysis of the ester using General Procedure C (LiOH (1.87 g, 25 mmol), THF (8 mL) and H_2O (2 mL). heated to 50 °C for 12 h furnished the acid as yellow solid which was used in the next step without purification.

The 3-(4-Bromo-phenyl)-2-(S)-[(4-Butoxy-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester was prepared following General Procedure A using 4-butoxy-3'-chloro-4'-fluoro-biphenyl-3-carboxylic acid from previous step, 2-(S)-amino-3-(4-bromo-phenyl)-propionic acid methyl ester hydrochloride salt (0.811 g, 2.75 mmol), HBTU (1.39 g,3.6 mmol) and DIEA (1.32 mL,7.5 mmol) in DMF (15 mL). Purification by flash chromatography (ethyl acetate/hexanes 1:7, 1:4) gave the title compound as colorless solid (0.677 g, 1.19 mmol).

2-(S)-[(4-Butoxy-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester was prepared following General Procedure D using 3-(4-bromo-phenyl)-2-(S)-[(4-Butoxy-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester ((0.677 g, 1.19 mmol), 3-trifluoromethyl-benzene boronic acid (0.349 g,1.8 mmol), palladium tetrakis-triphenylphosphine (69 mg, 0.06 mmol), and Na_2CO_3(aq) (2.0 N, 5 mL, 10 mmol) in DME (10 mL). The mixture was heated at 76 °C for 19 h. Purification by flash chromatography (ethyl acetate/hexanes 1:5, 1:4) gave the methyl ester of the title compound (177 mg, 0.28 mmol).

The title compound was obtained as a white solid (70 mg, 0.114 mmol).from -2-(S)-[(4-butoxy-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester (92 mg, 0.146 mmol), $LiOH_{(aq)}$ (2.0 N, 0.25 mL, 0.50 mmol), THF (1 mL) and MeOH (0.25 mL) following the general Procedure C.
^{1}H-NMR (400 MHz, DMSO-d_6): 13.15(b, 1H), 8.59(d, 1H), 8.12(d, 1H), 7.81-7.97(m, 4H), 7.63-7.73(m, 5H), 7.49(t, 1H), 7.24-7.31(m, 3H), 4.89(m, 1H), 4.09(m, 2H), 3.30(dd, 1H), 3.18(dd, 1H), 1.53(quin, 2H), 1.19(m, 2H), 0.71(t, 3H); LC-MS *m/z*: 614 $(M+1)^+$.

Example 123

2-(S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

5-Chloro-2-hydroxy-benzoic acid (2.5g, 28.97mmol) was coupled with 2-Amino-3-(4-bromo-phenyl)-propionic acid methyl ester hydrochloride (4.26g, 28.96mmol) with HBTU (6.59gms, 34.76mmol) and diisopropylethylamine (8ml, 86.91mmol) as per general procedure A to yield the 3-(4-Bromo-phenyl)-(2S)-(5-chloro-2-hydroxy-benzoylamino)-

propionic acid methyl ester. The above hydroxy compound (0.500g, 1.21g) was then alkylated with heptyliodide (0.410g, 1.815mmol) and potassium carbonate (0.050g, 3.025mmol) as per general procedure G to yield the 3-(4-Bromo-phenyl)-(2S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid methyl ester (0.500g).

The title compound was then prepared from 3-(4-Bromo-phenyl)-(2S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid methyl ester (0.090g, 0.176mmol) and 4-trifluoromethoxy boronic acid (0.067g, 0.352mmol) with Pd (PPh_3) (0.020g, 0.0176mmol) and 2N Na_2CO_3 (0.528ml, 0.528mmol) as per general procedure D to yield the (2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester which was further hydrolyzed as per general procedure C to give the title compound (0.050g). ^{1}H-NMR(400 MHz, $CDCl_3$): 1.11(t, 3H), 1.44(m, 8H), 1.87(m, 2H), 3.65(dddd, 2H), 4.27(m, 2H), 5.50(m, 1H), 7.18(m, 2H), 7.4(d, 1H), 7.57(m, 4H), 7.68-7.85(m, 4H), 8.52 (S, 1H), 8.98 (bs, 1H). LC/MS (m/z): 578.2(M+2).

Example 124

2-(S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid

5-Bromo-2-heptyloxy-benzoic acid was prepared by reacting 5-Bromo-2-hydroxy-benzoic acid methyl ester (1.0g, 4.32mmol) with Iodoheptane (1.46g, 6.49mmol) as per general procedure G with potassium carbonate (1.5 g, 10.8mmol) added to it. The ester thus obtained was subjected to hydrolysis as per general procedure C to yield the 5-Bromo-2-heptyloxy-benzoic acid (0.950g).

Also the (*2S*)-Amino-3- (2'-hydroxy-biphenyl-4-yl)-propionic acid was prepared from (S)- 4-bromophenylalanine (5.0g, 20.48 mmol), 2-hydroxyphenylboronic acid (4.23g, 30.72mmol) and Pd (PPh_3)$_4$ (2.36g, 2.038mmol) as per procedure D to yield the corresponding amino acid which was further esterified with methanolic solution containing 2-3 ml of HCl to yield the corresponding HCl salt of the (2S)-Amino-3- (2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (5.0 g).

5-Bromo-2-heptyloxy-benzoic acid (0.231g, 0.738mmol) and the (2S)-Amino-3- (2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (0.200g, 0.738mmol) were then combined as per general procedure A with HBTU (0.335g, 0.885mmol) and diisopropylethylamine (0.285g, 2.21mmol) to yield the (2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-(2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (0.200g).

The methyl ester of the title compound was the prepared from (2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-(2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (0.080g, 0.140mmol) and the trifluoromethylboronic acid (0.050g, 0.281mmol) as per general procedure F, which was further hydrolyzed as per general procedure C to give the title compound (0.020g). ^{1}H-NMR(400 MHz, $CDCl_3$): 1.14(t, 3H), 1.53 (m, 8H), 1.92(m, 2H), 3.6(m, 2H), 4.21(m, 2H), 5.21(m, 1H), 7.12(d, 1H), 7.22(m, 2H), 7.36(d, 1H), 7.5(d, 2H), 7.58(m, 2H), 7.66(m, 1H), 7.78 (m, 6H), 8.62 (S, 1H), 8.9 (bs, 1H). LC/MS (m/z): 700.2(M+2).

By analogous methods to those described above, the following compounds were synthesized

EX.	NAME	LC/MS (m/z)
125	2-(S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid	537
126	2-S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(3',4'-dichloro-biphenyl-4-yl)-propionic acid	562
127	2-(S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl]-propionic acid	687
128	3-(3'-Chloro-4'-fluoro-biphenyl-4-y l)-2-(S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid	546
129	2-(S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	562

Example 130

2-(S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

5-Bromo-salicylic acid (2.16 g, 10 mmol) was first transformed into 2-acetyl-5-bromo-salicylic acid (252 g) with acetyl chloride (2.34 g, 30 mmol) and pyridine (3.95 g, 50 mmol) in DCM, following the general procedure K. The above acid (1.29 g, 5.0 mmol) was converted into acid chloride by using oxalyl chloride (1.97 g, 15 mmol) and catalytic amount of DMF in DCM following the general procedure L, then 2-(S)-phenoxy-biphenyl alanine

(1.45 g, 5.0 mmol) and DIEA (0.77 g, 6.0 mmol) were added to the acid chloride to form the coupled product (using the general procedure M), which upon hydrolysis with aq. $NaHCO_3$ gave (*2S*)-[5-Bromo-2-hydroxybenzoylamine]-3-(2'-phenoxybiphenyl-4-yl)-propionic acid methyl ester (1.92 g). The methyl ester (25 mg, 0.046 mmol) was then reacted with iodocyclohexane (19 mg, 0.092 mmol) as described in general procedure G to provide (2S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (26 mg).

^{1}H NMR (400 MHz, $CDCl_3$): 1.15-1.45 (m, 7H), 1.75 (m, 1H), 1.95 (m, 1H), 3.24 (d, 2H), 3.75 (s, 3H), 4.30 (m, 1H), 5.05 (m, 2H), 6.90 (m, 2H), 7.01 (m, 2H), 7.10 (dd ,2H), 7.26 (m, 4H), 7.45 (m, 6H); LC/MS (*m/z*): 629 $(M+1)^+$.

Example 131

2-S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

(*2S*)-[5-Bromo-2-(4-trifluoromethylbenzyloxy)-benzoylamine]-3-(2'-phenoxybiphenyl-4-yl)-propionic acid methyl ester in Example 130 was hydrolyzed following general procedure C to give the title compound (22 mg).

^{1}H NMR (400 MHz, $CDCl_3$): 1.11-1.25 (m, 7H), 1.70 (m, 1H), 1.90(m, 1H), .328 (m, 2H), 4.28 (m, 1H), 5.06 (m, 2H), 6.89 (m, 2H), 6.99 (m, 2H), 7.17-7.51 (m, 12H); LC/MS (*m/z*): 615 $(M+1)^+$.

By analogous methods to those described above the following compounds were synthesized.

EX.	NAME	LC/MS (m/z)
132	3-Biphenyl-4-yl-2-(5-bromo-2-heptyloxy-benzoylamino)-propionic acid	539
133	3-Biphenyl-4-yl-2-(S)-[2-(4-tert-butyl-benzyloxy)-5-chlorobenzoyl amino] -propionic acid	542
134	2-(S)-[5-Bromo-2-(4-[1,2,4]triazol-1-yl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	690
135	2-(S)-[5-Bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	679

Example 136

2-S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-biphenyl-4-yl-propionic acid

3-Biphenyl-4-yl-2-(S)-(5-bromo-2-hydroxy-benzoylamino)-propionic acid methyl ester (425 mg) was prepared from 2-(S)-amino-3-biphenyl-4-yl-propionic acid methyl ester-hydrochloride (1.0 g, 3.4 mmol), and 5-bromo-2-hydroxy-benzoic acid (744 mg, 3.4 mmol) as described in general procedure A except for an adapted work-up. After reaction completion, the reaction mixture was poured onto 150 mL of 1N HCl and 150 mL of EtOAc. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, dried over sodium sulfate and evaporated. The crude material was purified over silica gel (8:2, DCM-hexanes).

2-(S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester (82 mg) was prepared from 3-biphenyl-4-yl-2-(S)-(5-bromo-2-hydroxy-benzoylamino)-propionic acid methyl ester (150 mg, 0.33 mmol) and benzyl bromide (0.047 mL, 0.40 mmol) as described in general procedure G and purified over silica gel (7:3, DCM-hexanes).

2-(S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester (50 mg, 0.092 mmol) was dissolved in 5 mL of THF-MeOH (4-1), cooled to 0 °C and 1.1 equiv of 2 N LiOH added. After 30 minutes, 3.3 additional equiv of 2N LiOH was added and the reaction stirred for 60 minutes. The reaction was worked up according to general procedure C to give 2-(S)-(2-benzyloxy-5-bromo-benzoylamino)-3-biphenyl-4-yl-propionic acid (34 mg)

^{1}H-NMR(400 MHz, DMSO-d_6): 2.92 (m, 1H), 3.17 (m, 1H), 4.71 (m, 1H), 5.25 (m, 2H), 7.18 (m, 3H), 7.28-7.42 (m, 8H), 7.52-7.64 (m, 5H), 7.81 (m, 1H), 7.52 (d, 1H); LC/MS (*m/z*): 532.0 $(M+1)^+$.

Example 137

3-Biphenyl-4-yl-2-(S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]-propionic acid

3-Biphenyl-4-yl-2-S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]-propionic acid methyl ester (340 mg) was prepared from 3-biphenyl-4-yl-2-(S)-(5-bromo-2-hydroxy-benzoylamino)-propionic acid methyl ester (400 mg, 0.92 mmol) (See example 136) and 1,2-bis-benzyloxy-4-chloromethyl-benzene (374 mg, 1.1 mmol) as described in general procedure G and purified over silica gel (8:2, DCM-hexanes).

3-Biphenyl-4-yl-2-(S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]-propionic acid methyl ester (60 mg, 0.079 mmol) was dissolved in 5 mL of THF-MeOH (4-

1), cooled to 0 °C and 1.1 equiv of 2 N LiOH added. After 30 minutes, 2.2 additional equiv of 2N LiOH was added and the reaction stirred for 30 minutes. The reaction was worked up according to general procedure C to give 3-biphenyl-4-yl-2-(S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]-propionic acid (47 mg).^{1}H-NMR(400 MHz, DMSO-d_6): 2.83 (m, 1H), 3.13 (m, 1H), 4.67 (m, 1H), 5.02 (s, 2H), 5.06 (s, 2H), 5.17, (m, 2H), 6.92 (m, 1H), 6.96 (m, 1H), 7.13 (d, 2H), 7.18-7.22 (m, 2H), 7.27-7.41 (m, 13H), 7.44 (d, 2H), 7.56 (m, 2H), 7.61 (m, 1H), 7.83 (m, 1H), 8.50 (d, 1H); LC/MS (*m/z*): 742 $(M+1)^+$.

Example 138

3-Biphenyl-4-yl-2-(S)-{[4-(4-tert-butyl-benzyloxy)-4'-trifluoromethyl-biphenyl-3-carbonyl]-amino}-propionic acid

The chloro compound (Example 133, 100 mg, 0.15 mmol) was reacted with 4-trifluoromethyl –phenyboronic acid (87.5 mg, 4.5 mmol) as described in general procedure D yielding the title compound (85 mg) as white solid. LC/MS (*m/z*): 651 $(M+1)^+$.

Example 139

3-Biphenyl-4-yl-2-(S)-{[4-(4-tert-butyl-benzoylamino)-3'-trifluoromethyl biphenyl-3-carbonyl]-amino}-propionic acid

(2S)-(2-Amino-5-iodo-benzoyl-amino)-3-biphenyl-4-yl-propionic acid methyl ester (1.53g) was prepared from (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 4.1 mmol), 5-iodo-2-amino-benzoic acid (1.23g, 4.9 mmol) as described in general procedure A .

To a stirring solution of (2S)-(2-amino-5-iodo-benzoyl-amino)-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 2 mmol) prepared above dissolved in DCM containing pyridine (1.58 g, 4 mmol), was added t-*butyl*-benzoyl chloride (1.20 g, 2.5 mmol) at 0 ^{0}C. The reaction mixture was stirred at rt for 3 h, extracted with DCM, washed with 1M HCl and brine evaporation followed by column chromatography purification (silica, CH_2Cl_2) giving 3-biphenyl-4-yl-(2S)-[2-(4-*tert*-butyl-benzoylamino)-5-iodo-benzoyl-amino]-propionic acid methyl ester (1.25 g) as a white solid which was hydrolyzed according to general procedure C yielding the title compound (1.23 g, 100%) as a white solid.^{1}H-NMR(400 MHz, DMSO-d_6): 1.26 (s, 9H), 3.09-3.19 (m, 1H), 3.21-3.29 (m, 1H), 4.74-4.76 (m, 1H), 7.27-7.29 (m, 1H), 7.42-7.39 (m, 4H), 7.44-7.57 (m, 7H), 7.67-7.77 (m, 3H), 7.99 (s, 1H), 8.54 (d, 1H, J = 8.0 Hz), 9.32 (d, 1H, J = 8.0 Hz), 11.98 (s, 1H); LC/MS (*m/z*): 647 $(M+1)^+$.

The iodo derivative (100 mg, 0.15 mmol) was reacted with 3-trifluoromethyl phenyl boronic acid (87.5 mg, 4.5 mmol) as described in general procedure D yielding the title compound (92 mg) as white solid. LC/MS (*m/z*): 665 $(M+1)^+$.

Example 140

3-Biphenyl-4-yl-2-(S)-[(5-chloro-2,4-dimethoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid

2-(S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (128 mg, 0.5 mmol) was reacted with 3-bromo-5-chloro-2,6-dimethoxybenzoic acid (148 mg, 0.5 mmol) as described in general procedure A. The resulting crude compound was reacted with 195 mg (1.0 mmol) of 4-(trifluoromethyl)phenylboronic acid as described in general procedure D. The product thus obtained was hydrolyzed according to general procedure C to afford the title product (180mg) as a pure white solid.

LC/MS (*m/z*): 584 $(M+1)^+$.

Example 141

3-Biphenyl-4-yl-2-(S)-(3-bromo-5-chloro-2,6-dimethoxy-benzoylamino)-propionic acid

2-(S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (128 mg, 0.5 mmol) was reacted with 3-bromo-5-chloro-2,6-dimethoxybenzoic acid (148 mg, 0.5 mmol) as described in general procedure A. The resulting compound was hydrolyzed according to general procedure C to afford the title product (209 mg) as a pure white solid.

LC/MS (*m/z*): 519 $(M+1)^+$.

Example 142

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (223 mg,) was prepared from 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (141 mg, 0.5 mmol) and *S*-2-amino-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester (155 mg, 0.5 mmol) following the general procedure A.

LC-MS (*m/z*): 586 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 3.24-3.38 (m, 2H), 3.76 (m, 1H), 3.80 (s, 3H), 3.90 (s, 3H), 5.14 (q, 1H), 6.68 (d, 1H), 7.06 (q, 1H), 7.18 (q, 1H), 7.24 (m, 3H), 7.44 (m, 2H), 7.52-7.60 (m, 2H), 7.68-7.72 (m, 3H) and 8.16 (dd, 1H).

Example 143

2-(S)-[(4-Acetoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester

Acetic acid 3-chlorocarbonyl-4'-trifluoromethyl-biphenyl-4-yl ester (334 mg) was prepared from 4-acetoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid (324 mg, 1.0 mmol) following the general procedure L.

2-(S)-[(4-Acetoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester (278 mg) was prepared from acetic acid 3-chlorocarbonyl-4'-trifluoromethyl-biphenyl-4-yl ester (171 mg, 0.5 mmol) and 2-(S)-amino-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester (155 mg, 0.5 mmol) following the general procedure M.

LC-MS (*m/z*): 614 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.24 (dd, 1H), 3.46 (dd, 1H), 3.70 (m, 1H), 3.84 (s, 3H), 5.13 (q, 1H), 7.16 (d, 2H), 7.18 (d, 1H), 7.22 (d, 1H), 7.38 (m, 1H), 7.43 (d, 2H), 7.49 (d, 1H), 7.60 (dd, 1H), 7.70 (s, 2H), 7.72 (d, 1H), 7.74 (d, 1H), and 8.26 (d, 1H).

Example 144

N-[4-(2,4-Dichloro-6-methyl-phenoxy)-2-hydroxy-phenyl]-2-(3'-trifluoromethyl-biphenyl-4-yl)-acetamide

The resin-bound 2-(4-bromo-phenyl)-*N*-[2-Hydroxy-4-(3,4-dichloro-6-methyl-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol, obtained from coupling reaction between the resin bound 2-Amino-5-(2,4-dichloro-6-methyl-phenoxy)-phenol and 4-bromophenyl acetic acid following the general procedure A) was reacted with 3-trifluormethyl-phenyl boronic acid (56.7mg, 0.3 mmol) as described in the general procedure D followed by cleavage as described in example 1, to afford (27.5 mg) of title compound.

^1H NMR (400 MHz, $CDCl_3$): 2.13 (s, 1H), 3.86 (s, 2H), 6.33 (dd, 1H, J = 8.8, 2.4 Hz), 6.37 (d, 1H, J = 2.4 Hz), 6.69 (d, 1H, J = 8.8 Hz), 7.15 (m, 1H), 7.30 (d, 1H, J = 0.8 Hz), 7.45 (dd, 2H, J = 6.4, 2.0 Hz), 7.59 –7.65 (m, 4H), 7.78 (m, 1H), 7.84 (s, 1H), 8.84 (s, 1H); LC/MS (*m/z*): 546 $(M+1)^+$.

Example 145

2-(4-tert-Butyl-benzoylamino)-benzoic acid methyl-amide

The 2-aminobenzoic acid (137 mg, 1.0 mmol) was reacted with 4-tert-butyl benzoyl chloride (196 mg, 1.0 mmol) as described in general procedure M. The resulting compound was coupled with methylamine (62 mg, 2.0 mmol) as described in general procedure A to afford the title product (186mg) as a pure white solid.

LC/MS (*m/z*): 311 $(M+1)^+$.

Example 146

2-(S)-[(3-Hydroxy-naphthalene-2-carbonyl)-(4-pyridin-3-yl-benzyl)-amino]-3-(4-pyridin-3-yl-phenyl)-propionic acid

1.0 g (2.5 mmol) of resin-bound naphthoic acid obtained in Example 1 was reacted with1.95 g (7.5 mmol) of (2S)-Amino-3-(4-bromophenyl)-propionic acid methyl ester as described in the general procedure A to give resin-bound 2-(S)-(3-Hydroxy-naphthalene-2-carbonyl)-amino-3-(4-bromophenyl)-propionic acid methyl ester.

0.05 g (0.1 mmol) of the above resin was treated with 4-bromobenzyl bromide (75 mg, 0.30 mmol), and Lithium tert-butoxide (0.6 mmol) in THF at RT for 6h, followed by 3-pyridyl boronic acid (123 mg, 1.0 mmol) as demonstrated in the general procedure D followed by the cleavage of the resin to afford 18 mg of the title compound. LC/MS (*m/z*) 594 $(M+1)^+$.

Example 147

3-Biphenyl-4-yl-2-(S)-{[5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carbonyl]-amino}-propionic acid

To a solution of 5-methyl-pyrazine-2-carboxylic acid methyl ester (2.0 g, 13.146 mmol) in CCl4 (25 mL0 was added NBS (2.57 g, 14.461 mmol) and benzoyl peroxide (0.318 g, 1.314 mmol) and the solution was heated at 70 C for 1 h. Upon cooling to RT, the organic layer was washed with $NaHCO_3$, water, dried (Na_2SO_4), and concentrated under reduced pressure to give 0.900 g 5-Bromomethyl-pyrazine-2-carboxylic acid methyl ester.

A solution of 5-bromomethyl-pyrazine-2-carboxylic acid methyl ester (0.305 g, 1.314 mmol) in DMF (6 mL) was treated with 3-trifluoromethoxyphenol (0.280 g, 1.577 mmol) and potassium carbonate (0.400 g, 2.89 mmol) by the general procedure G. The crude product was purified by flash column chromatography on silica gel to give 0.380 g of pure 5-(3-

Trifluoromethoxy-phenoxymethyl)-pyrazine-2-carboxylic acid methyl ester. LCMS: 330 $(M+2)^+$

A solution of 5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carboxylic acid methyl ester (0.234 g, 0.712 mmol) in THF:MeOH (4:1, 5 mL) was treated with LiOH (0.150 g, 3.564 mmol) in 1.5 mL of water by the general procedure C to give 0.182 g of 5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carboxylic acid. LCMS: 316 $(M+2)^+$

A solution of 5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carboxylic acid (0.182 g, 0.579 mmol) was treated with 2(S)-amino-3-biphenyl-4-yl-propionic acid methyl ester hydrochloride (0.162 g, 0.637 mmol), HBTU (0.440 g, 1.158 mmol), and DIEA (0.310 g, 1.737 mmol) by the general procedure A. The crude crude product was purified by flash column chromatography on silica gel to give 0.170 g of 3-biphenyl-4-yl-2(S)-{[5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carbonyl]-amino}-propionic acid methyl ester. LCMS: 553 $(M+2)^+$

A solution of biphenyl-4-yl-2(S)-{[5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carbonyl]-amino}-propionic acid methyl ester (0.170 g, 0.308 mmol) in THF:MeOH (4:1, 5 mL) was treated with LiOH (0.064 g, 1.54 mmol) in 1.5 mL of water by the general procedure C to give 0.140 g of pure 3-biphenyl-4-yl-2(S)-{[5-(3-trifluoromethoxy-phenoxymethyl)-pyrazine-2-carbonyl]-amino}-propionic acid as a white solid. LCMS: 539 $(M+2)^+$

Example 148

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-methoxymethyl-ethyl]-amide

2-(R)-*tert*-Butoxycarbonylamino-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid (2.0g, 5.07mmol) was dissolved in 15mL anhydrous THF and BH_3:THF (11mL, 11.0mmol, 1M solution in THF) was added drop wise at 0°C and stirred for 10h at room temperature. Excess BH_3:THF was quenched by adding methanol (~1mL) at 0°C. Solvent was removed under vacuum and residue was dissolved in EtOAc (20mL) and washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and silica gel column chromatography (CH_2Cl_2:MeOH) gave pure [1-(3'-Chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(R)-hydroxy-ethyl]-carbamic acid *tert*-butyl ester as white solid (1.6g)

NaH (55mg, 1.31 mmol, 60% by wt suspension in mineral oil) was added at 0°C to a solution of [1-(3'-Chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(R)-hydroxy-ethyl]-carbamic acid *tert*-butyl ester (0.5g, 1.31mmol) in 5mL anhydrous THF and stirred for 20min at 0°C. MeI

(0.37g, 2.63mmol) was added to the reaction mixture and stirred for 6h at room temperature. Reaction mixture was diluted with 5mL EtOAc, and washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and silica gel chromatography (EtOAc: Hexanes) gave pure [1-(3'-Chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(R)-methoxy-ethyl]-carbamic acid *tert*-butyl ester (0.38g).

[1-(3'-Chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(R)-methoxy-ethyl]-carbamic acid *tert*-butyl ester was converted to corresponding 1-(3'-Chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-methoxy-ethylamine hydrochloride salt according to the general procedure N.

4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-methoxymethyl-ethyl]-amide (45mg) was prepared from 1-(3'-Chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-methoxy-ethylamine hydrochloride salt (35mg, 0.1 mmol) and 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carbonyl chloride (32mg, 0.1mmol) in presence of triethyl amine (41mg, 0.41mmol) according to the general procedure M.
^{1}HNMR (400MHz, $CDCl_3$): 3.00 (dd, 1H), 3.10 (dd, 1H), 3.37-3.50 (m, 5H), 3.99 (s, 3H), 4.50-4.61 (m, 1H), 7.07(d, 1H), 7.19 (t, 1H), 7.34-7.51 (m, 5H), 7.60 (dd, 1H), 7.64-7.76 (m, 5H), 8.25 (d, 1H), 8.50 (d, 1H),
LC/MS (*m/z*): 572.2 $(M+1)^+$.

BBr_3:DMS (13mg, 0.04 mmol) was added to a solution of 4-Methoxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-methoxymethyl-ethyl]-amide (24mg, 0.04mmol) in 3mL of anhydrous CH_2Cl_2, at –78°C and slowly allowed to come to room temperature and stirred for 2h. After completion of the reaction, reaction was cooled to –78°C and 0.5 mL of MeOH was added, solvent was removed under vacuum and the residue was taken in ethyl acetate (4mL) and washed with aq $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and silica gel column chromatography (Ethyl acetate: Hexanes) gave pure 4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-methoxymethyl-ethyl]-amide (14mg).
^{1}HNMR (400MHz, $CDCl_3$): 3.00 (dd,1H), 3.10 (dd, 1H), 3.38-3.60 (m, 5H), 4.44-4.60 (m, 1H), 6.75 (d, 1H), 7.09 (d, 1H), 7.16-7.23 (m, 1H), 7.30-7.75 (m, 12H), 12.4 (s, 1H). LC/MS (*m/z*): 558.1 $(M+1)^+$.

Example 149

3-[4-(4-Cyano-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester

3-(4-Hydroxy-phenyl)-(2S)-[4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (664 mg) was prepared starting from 4'-trifluoromethyl-biphenyl-4-carboxylic acid (532 mg, 2.0 mmol) and tyrosine methyl ester (462 mg, 2.0 mmol) according to general procedure A. The above compound (443 mg, 1.0 mmol) was treated with 1-fluoro-4-cyanobenzene (181 mg, 1.5 mmol) following general procedure B to give 3-[4-(4-cyano-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (360 mg). The ester was hydrolyzed following general procedure C to give the title compound (345 mg)

^{1}H NMR (400MHz, $CDCl_3$): 3.28, 3.44 (ABX, 2H), 5.12 (dd, 1H), 6.65 (d, 1H), 6.99 (m, 4H), 7.28 (m, 2H), 7.58 (d, 2H), 7.69 (m, 6H), 7.84 (d, 2H); LC/MS (m/z): 530 $(M+1)^+$; LC/MS:545.

Example 150

3-(4'-Trifluoromethyl-biphenyl-4-yl)-2-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid methyl ester

4-(5-Trifluoromethyl-pyridin-2-yloxy)-benzaldehyde was prepared from 4-fluorobenzaldehyde (2.48 g, 20 mmol) and 2-hydroxy-5-trifluoromethylpyridine (3.29 g, 20 mmol) following general procedure B. (4.62 g)

To aq. NaOH (3.2 g, 80 mmol) was added silver nitrate (3.4 g, 40 mmol) and stirred for 10 min., then the mixture was cooled to 0 °C and the above aldehyde (4.62 g, 17 mmol) was added. The mixture was stirred overnight, then filtrate through celite. The filtrate was collected and acidified with conc. HCl. The solid was collected by filtration and dried under vacuum to give 4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoic acid. (3.5 g)

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoic acid (283 mg, 1.0 mmol) and 2-amino-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester (360 mg, 1.0 mmol) following general procedure A. (580 mg)

^{1}H-NMR(400 MHz, CD_3COCD_3): 3.24 (dd, 1H), 3.39 (dd, 1H), 3.74 (s, 3H), 4.98 (m, 1H), 6.64 (d, 1H), 7.50 (m, 2H), 7.60 (m, 2H), 7.69 (m, 3H), 7.78 (d, 2H), 7.88 (d, 2H), 7.98(m, 2H), 8.15 (m, 2H); LC/MS (*m/z*): 589 $(M+1)^+$.

By analogous methods to those described above, the following compound was synthesized

EX.	NAME	LC/MS (m/z)

151	3-(4'-Trifluoromethoxy-biphenyl-4-yl)-2-(S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid methyl ester	604.5

Biological Assay

The following assay methods may be used to identify compounds of Formula (I) that are effective in showing antiviral activity against vaccinia virus.

General Assay Procedures

Cytopathic effect was measured on the BSC40 african green monkey kidney cells using 100 μM concentrations of the compounds of Formula (I). In this assay, 96-well black Packard viewplates were seeded with BSC40 cells ($2.25x10^4$ cells/well) in Minimum Essential Media supplemented with 5% FCS, 2mM L-glutamine and 10 μg/mL gentamycin sulfate. When the cells became confluent (24 hrs) they were treated with 100 μM compound diluted in media. The cells were place in an incubator at 37°C (5% CO_2) for 24 hours, and checked for toxicity via direct observation under the microscope and also with alamar blue which assesses cell viability and proliferation (healthy cells produce a visible color change from blue to red). The cells were scored on a scale of 0-3 where 0 corresponds to normal healthy cells, 1 corresponds to sick cells but not rounding up, 2 corresponds to cells that are rounding up, and 3 corresponds to cells that have rounded up and pulled off the plate. Compounds at concentrations that scored 1 or greater were diluted and the above assay was repeated to find the concentration at which the compound scored 0.

A vaccinia virus green fluorescent protein (vvGFP) assay was performed to test the ability of compounds of Formula (I) to inhibit viral growth as measured by a reduction in fluorescence from vaccinia virus expressing the green fluorescent protein. In this assay, 96-well black Packard viewplates were seeded with BSC40 cells in Minimum Essential Media supplemented with 5% FCS, 2mM L-glutamine and 10 μg/mL gentamycin sulfate. When the cells became confluent, they were washed with PBS and then infected with vaccinia virus at a multiplicity of infection (moi) of 0.1 for 30 min in PBS. At 30 minutes, the cells were overlaid with 100 μl of infection media supplemented with 100 μM test compound. As controls infected cells are treated with rifampicin (blocks assembly of DNA and protein into mature virus particles), with no compound, or mock infected. Cells were placed in an incubator at 37° C (5% CO_2) for 24 hrs. At 24 hours post infection (hpi), the plates were

removed from the incubator, washed with PBS and fluorescence measure on a Wallac plate reader (excite at 485 nm and read at 535 nm). Wells that showed reduced fluorescence were checked visually under the microscope to verify a reduction in viral infection versus a loss of cells due to cytopathic effect from virus infection. Compounds that are found to inhibit viral replication were then checked for inhibitory effect at various concentrations to determine the IC_{50} and the therapeutic index.

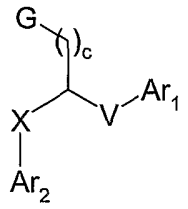
The compounds of Formula (I) listed in Table 1 have an IC_{50} of less than or equal to about 100 μM.

While the invention has been described and illustrated with reference to certain embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the dosages as set forth herein may be applicable as a consequence of variations in the responsiveness of the mammal being treated for orthopox -mediated disease(s). Likewise, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

CLAIMS

We Claim:

1. The compound of Formula (I):



(I)

wherein

c is equal to 0, 1, or 2; wherein the values of 0, 1, and 2 comprise a direct bond, -CH_2-, and -CH_2-CH_2-, optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl;

G comprises: -hydrogen, -alkyl, -heteroaryl, -aryl, -heterocyclycl, -CH=CH-CO_2R_1, -CO_2R_1, –CH_2OR_1, –CH_2SR_1 –C(O)-R_1, -C(O)NR_1R_2, -C(R_1)=N-O-R_2, -C(O)C(O)R_1, -C(O)C(O)NR_1R_2, -CH=CH-NO_2, -CH=CH-CN, -C(O)-C(O)-OR_1, an acid isostere, or an ester isostere;

wherein

R_1 and R_2 independently comprise: -hydrogen, -alkyl, -aryl, -alkenyl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -heterocyclyl, or -heteroaryl; or when R_1 and R_2 are bonded to a nitrogen group in G,

R_1 and R_2 may be taken together to form a ring having the formula -$(CH_2)_m$-Z_2-$(CH_2)_n$-,

wherein

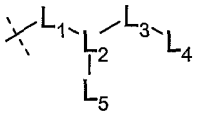
m and n are, independently, 1, 2, 3, or 4 and

Z_2 comprises -CH_2-, -C(O)-, -O-, -N(H)-, -S-, -S(O)-, -$S(O_2)$-, -CON(H)-, -NHC(O)-, -NHC(O)N(H)-, -$NH(SO_2)$-, -$S(O_2)$N(H)-, -(O)CO-, -$NHS(O_2)NH$-, -OC(O)-, -$N(R_{21})$-, -$N(C(O)R_{21})$-, -$N(C(O)NHR_{21})$-, -$N(S(O_2)NHR_{21})$-, -$N(SO_2R_{21})$-, or -$N(C(O)OR_{21})$-;

wherein

R_{21} comprises hydrogen, aryl, alkyl, or alkylene-aryl; or

R_2 comprises a substituent of the formula



;

wherein

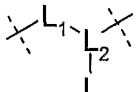
L_1 comprises a direct bond, alkylene, -O-alkylene-, alkylene-O-, -NH-C(O)-, -C(O)-NH- or –NH-C(O)-NH-;

L_2 comprises alkyline, alkenyline, heteroaryline, aryline, or heterocyclyline;

L_3 comprises –O-, -N(R_3)-, -C(O)-N(R_3)-, -C(O)-O-, -C(O)-, –N(R_3)-C(O)-N(R_4)-, -CH=CH-CO_2R_1, -C(O)R_1, -C(O)C(O)R_1, or -C(O)C(O)NR_1R_2;

L_4 comprises hydrogen, alkyl, alkenyl, alkynyl, heterocyclyl, heteroaryl, or –alkylene-aryl; and

L_5 comprises hydrogen, alkyl, alkenyl, alkynyl, -akylene-aryl, -alkylene-heteroaryl, alkylene-O-alkylene-aryl, -alkylene-S-alkylene-aryl, -alkylene-O-alkyl, -alkylene-S-alkyl, -alkylene-NH_2, -alkylene-OH, -alkylene-SH, -alkylene-C(O)-OR_5, -alkylene-C(O)-NR_5R_6, -alkylene-NR_5R_6, -alkylene-N(R_5)-C(O)-R_6, or –alkylene-N(R_5)-S(O_2)-R_6; or



; may be taken together to constitute a direct bond;

wherein

R_3, R_4, R_5, and R_6 independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or, -alkylene-heteroaryl;

V comprises: -$(CH_2)_b$-O-$(CH_2)_a$-, -$(CH_2)_b$-N(R_8)-$(CH_2)_a$-, -$(CH_2)_b$-O-, -$(CH_2)_b$-N(R_8), -$(CH_2)_a$-, -CH=CH-(R_8)- or a direct bond; in which a is equal to 0, 1, or 2, b is equal to 1 or 2, and R_8 comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; wherein the -CH_2- groups may be optionally substituted 1 to 4

times with a substituent group comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, –hydroxyl, -S-alkyl, or -S-aryl;

X comprises: -$N(R_9)$-, -$CON(R_9)$-, -$N(R_9)CO$-, -$N(R_9)CON(R_{10})$-, -$OC(O)N(R_8)$-, -$SO_2N(R_9)$-, -$N(R_9)$ SO_2-, or -$N(R_9)SO_2N(R_{10})$-; wherein R_9 and R_{10} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, or –$(CH_2)_dY$-, wherein d is equal to 0, 1, or 2,

wherein

Y comprises: -hydrogen, –CO_2R_{11}, –CH_2OR_{11}, –$C(O)$-R_{11}, -$C(O)NR_{11}R_{12}$, -$C(R_{11})$=N-O-R_{12}, -$NR_{11}R_{12}$, or an acid isostere;

wherein R_{11} and R_{12} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -heterocyclyl, or -heteroaryl;

Ar_1 comprises an aryl, heteroaryl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, or fused heterocyclylheteroaryl group optionally substituted 1 to 7 times, wherein the substitutents independently comprise:

a) -fluoro;
b) -chloro;
c) -bromo;
d) -iodo;
e) -cyano;
f) -nitro;
g) -perfluoroalkyl;
h) -D-R_{12};
i) -alkyl;
j) -aryl;
k) -heteroaryl;
l) -heterocyclyl;
m) -cycloalkyl;
n) -alkylene-aryl;
o) -alkylene-arylene-aryl;
p) -alkylene-arylene-alkyl;
q) -arylene-alkyl;

r) -arylene-arylene-alkyl;

s) -D-alkyl;

t) -D-aryl;

u) -D-alkylene-aryl;

v) -D-arylene-alkyl;

w) -D-alkylene-arylene-aryl;

x) -D-arylene-arylene-aryl;

y) -D-alkylene-arylene-alkyl;

z) -alkylene-D-alkylene-aryl;

aa) -arylene-D-alkyl;

bb) -alkylene-D-aryl;

cc) -alkylene-D-heteroaryl;

dd) -alkylene-D-cycloalkyl;

ee) -alkylene-D-heterocyclyl;

ff) -alkylene-D-arylene-alkyl;

gg) -alkylene-D-alkylene-arylene-alkyl;

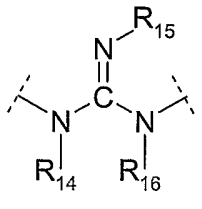
hh) -alkylene-D-alkyl;

ii) -alkylene-D-R_{13};

jj) -arylene-D-R_{13}; or

kk) -hydrogen;

wherein D comprises $-CH_2-$, -O-, $-N(R_{14})-$, -C(O)-, $-CON(R_{14})-$, $-N(R_{14})C(O)-$, $-N(R_{14})CON(R_{15})-$, $-N(R_{14})C(O)O-$, $-OC(O)N(R_{14})-$, $-N(R_{14})SO_2-$, $-SO_2N(R_{14})-$, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, $-S(O_2)-$, $-N(R_{14})SO_2N(R_{15})-$,



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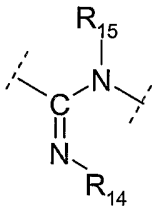


, and

wherein

R_{13}, R_{14}, R_{15}, and R_{16} independently comprise: -hydrogen, hydroxyl, -cyano, nitro, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; and

Ar_2 comprises an aryl or heteroaryl group optionally substituted 1 to 7 times, wherein the substitutents independently comprise:

a) -fluoro;
b) -chloro;
c) -bromo;
d) -iodo;
e) -cyano;
f) -nitro;
g) -perfluoroalkyl;
h) -T-R_{17};
i) -alkyl;
j) -aryl;
k) -heteroaryl;
l) -heterocyclyl;
m) -cycloalkyl;
n) -alkylene-aryl;
o) -alkylene-arylene-aryl;
p) -alkylene-arylene-alkyl;
q) -arylene-alkyl;
r) -arylene-arylene-alkyl;
s) -T-alkyl;
t) -T-aryl;
u) -T-alkylene-aryl;
v) -T-arylene-alkyl;
w) -T-alkylene-arylene-aryl;
x) -T-arylene-arylene-aryl;
y) -T-alkylene-arylene-alkyl;
z) -alkylene-T-alkylene-aryl;
aa) -arylene-T-alkyl;
bb) -alkylene-T-aryl;
cc) -alkylene-T-heteroaryl;
dd) -alkylene-T-cycloalkyl;
ee) -alkylene-T-heterocyclyl;
ff) -alkylene-T-arylene-alkyl;
gg) -alkylene-T-alkylene-arylene-alkyl;
hh) -alkylene-T-alkyl;

ii) -alkylene-T-R_{17};

jj) -arylene-T-R_{17}; or

kk) -T-alkylene-arylene-heteroaryl;

ll) -T-alkylene-heterocyclyl;

mm)-T-alkylene-heteroaryl;

nn) -T-heteroaryl;

oo) -T-fused heterocyclylaryl;

pp) -T-fused cycloalkylaryl;

qq) -T-fused arylcycloalkyl;

rr) -T-fused fused heterocyclylaryl;

ss) -T-fused fused arylheterocyclyl;

tt) -T-fused fused cycloalkylheteroaryl;

uu) -T-fused fused heteroarylcycloalkyl;

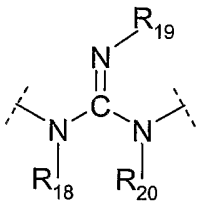
vv) -T-fused heterocyclylheteroaryl;

ww)-T-fused heteroarylheterocyclyl; or

xx) -hydrogen;

wherein

T comprises a direct bond, $-CH_2-$, -O-, $-N(R_{18})-$, -C(O)-, $-CON(R_{18})-$, $-N(R_{18})C(O)-$, $-N(R_{18})CON(R_{19})-$, $-N(R_{18})C(O)O-$, $-OC(O)N(R_{18})-$, $-N(R_{18})SO_2-$, $-SO_2N(R_{18})-$, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, $-S(O_2)-$, $-N(R_{18})SO_2N(R_{19})-$,



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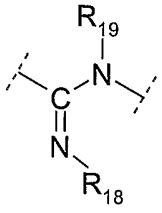


and

wherein R_{17}, R_{18}, R_{19} and R_{20}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl;

and wherein

the alkyl, aryl, heteroaryl, alkylene, and arylene groups in Ar_1, Ar_2, G, R_1-R_{21}, may be optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising:

a) -hydrogen;

b) -fluoro;

c) -chloro;

d) -bromo;

e) -iodo;

f) -cyano;

g) -nitro;

h) -perfluoroalkyl;

i) -Q-R_{22};

j) -Q-alkyl;

k) -Q-aryl;

l) -Q-alkylene-aryl;

m) -Q-alkylene-$NR_{23}R_{24}$; or

n) -Q-alkyl-W-R_{25};

wherein

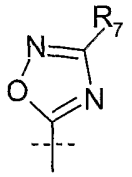
Q and W independently comprise: $-CH_2-$, -O-, -$N(R_{26})$-, -C(O)-, -$CON(R_{26})$-, -$N(R_{26})C(O)$-, -$N(R_{26})CON(R_{27})$-, -$N(R_{26})C(O)O$-, -$OC(O)N(R_{26})$-, -$N(R_{26})SO_2$-, -$SO_2N(R_{26})$-, -C(O)-O-, -O-C(O)-, or -$N(R_{26})SO_2N(R_{27})$-, wherein

R_{22}, R_{23}, R_{24}, R_{25}, R_{26} and R_{27}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

2. The compound of Formula (I) in claim 1, wherein c is equal to 0 or 1.

3. The compound of Formula (I) in claim 1, wherein c is equal to 0.

4. The compound of Formula (I) in claim 1, wherein G comprises: -hydrogen, -CO_2R_1, -$C(O)NR_1R_2$, or -$C(O)R_1$, wherein R_1 and R_2 independently comprise : -hydrogen, -alkyl, -alkenyl, -aryl.

5. The compound of Formula (I) in claim 1, wherein G comprises an ester isostere comprising the substituted oxadiazole:  , wherein R_7 comprises alkyl, aryl, alkylene-sulfonyl-alkyl or alkylene-sulfonyl-aryl.

6. The compound of Formula (I) in claim 5, wherein R_7 comprises an alkyl group.

7. The compound of Formula (I) in claim 1, wherein G comprises: - hydrogen.

8. The compound of Formula (I) in claim 1, wherein G comprises: $-CO_2R_1$ wherein R_1 comprises alkyl.

9. The compound of Formula (I) in claim 1, wherein V comprises: $-(CH_2)_a-$, $-(CH_2)_b-O-(CH_2)_a-$, or a direct bond, wherein a is equal to 1 or 2, and b is equal to 1.

10. The compound of Formula (I) in claim 1, wherein V comprises: $-(CH_2)_a-$ or a direct bond, wherein a is equal to 1.

11. The compound of Formula (I) in claim 1, wherein X comprises: $-N(R_9)-$, $-CON(R_9)-$, $-N(R_9)CO-$, or $-N(R_9)CON(R_{10})-$, wherein R_9 and R_{10} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

12. The compound of Formula (I) in claim 1, wherein X comprises: $-N(R_9)-$, $-CON(R_9)-$, or $-N(R_9)CO-$, wherein R_9 comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

13. The compound of Formula (I) in claim 1, wherein X comprises $-CON(R_9)-$, wherein R_9 comprises: -hydrogen.

14. The compound of Formula (I) in claim 1, wherein Ar_1 comprises a mono- or bicyclic aryl or heteroaryl group optionally substituted 1 to 7 times.

15. The compound of Formula (I) in claim 1, wherein Ar_1 comprises a phenyl group having 1 to 5 substituents, wherein the substituents independently comprise:

a) -fluoro;

b) -chloro;

c) -bromo;

d) -iodo;

e) -cyano;

f) -nitro;

g) -perfluoroalkyl;

h) $-D-R_{12}$;

i) -alkyl;

j) -aryl;

k) -heteroaryl;

l) -heterocyclyl;

m) -cycloalkyl;

n) -alkylene-aryl;

o) -alkylene-arylene-aryl;

p) -alkylene-arylene-alkyl;

q) -arylene-alkyl;

r) -arylene-arylene-alkyl;

s) -D-alkyl;

t) -D-aryl;

u) -D-alkylene-aryl;

v) -D-arylene-alkyl;

w) -D-alkylene-arylene-aryl;

x) -D-arylene-arylene-aryl;

y) -D-alkylene-arylene-alkyl;

z) -alkylene-D-alkylene-aryl;

aa) -arylene-D-alkyl;

bb) -alkylene-D-aryl;

cc) -alkylene-D-heteroaryl;

dd) -alkylene-D-cycloalkyl;

ee) -alkylene-D-heterocyclyl;

ff) -alkylene-D-arylene-alkyl;

gg) -alkylene-D-alkylene-arylene-alkyl;

hh) -alkylene-D-alkyl;

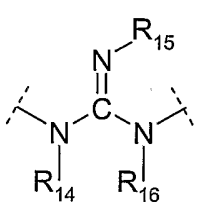
ii) -alkylene-D-R_{13};

jj) -arylene-D-R_{13}; or

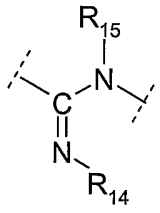
kk) -hydrogen;

wherein

D comprises $-CH_2-$, -O-, $-N(R_{14})-$, -C(O)-, $-CON(R_{14})-$, $-N(R_{14})C(O)-$, $-N(R_{14})CON(R_{15})-$, $-N(R_{14})C(O)O-$, $-OC(O)N(R_{14})-$, $-N(R_{14})SO_2-$, $-SO_2N(R_{14})-$, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, $-S(O_2)-$, $-N(R_{14})SO_2N(R_{15})-$,



, or



,

wherein

R_{13}, R_{14}, R_{15}, and R_{16} independently comprise: -hydrogen, hydroxyl, -cyano, nitro, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

16. The compound of Formula (I) in claim 1, wherein Ar_1 comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl, -arylene-alkyl, -D-aryl, -D-alkylene-arylene-alkyl, or -arylene-D-alkyl; wherein D comprises -O-, -N(R_{14})-, -CON(R_{14})-, or -N(R_{14})C(O)-, wherein R_{14} comprises: -hydrogen; -alkyl; or -aryl.

17. The compound of Formula (I) in claim 1, wherein Ar_1 comprises: 2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl, 2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl, 2'-phenoxy-biphenyl-4-yl, 2'-trifluoromethyl-biphenyl-4-yl, 3',4'-dichloro-biphenyl-4-yl, 3',4'-difluoro-biphenyl-4-yl, 3',5'-bis-trifluoromethyl-biphenyl-4-yl, 3',5'-difluoro-biphenyl-4-yl, 3'-chloro-4'-fluoro-6-methoxy-biphenyl-3-yl, 3'-chloro-4'-fluoro-biphenyl-2-yl, 3'-chloro-4'-fluoro-biphenyl-3-yl, 3'-chloro-4'-fluoro-biphenyl-4-yl, 3'-chloro-biphenyl-4-yl, 3'-nitro-biphenyl-4-yl, 3'-trifluoromethoxy-biphenyl-4-yl, 3'-trifluoromethyl-biphenyl-4-yl, 4'-benzyloxy-3'-fluoro-biphenyl-4-yl, 4-benzyloxy-phenyl, 4'-chloro-biphenyl-4-yl, 4'-fluoro-biphenyl-4-yl, 4'-methanesulfonyl-biphenyl-4-yl, 4-naphthalen-2-yl-phenyl, 4'-nitro-biphenyl-4-yl, 4'-phenoxy-biphenyl-4-yl, 4-pyridin-3-yl-phenyl4'-tert-butyl-biphenyl-4-yl, 4'-trifluoromethyl-biphenyl-4-yl, 6-methoxy-4'-nitro-biphenyl-3-yl, biphenyl, biphenyl-4-yl, chlorofluorophenoxy-phenyl, or (cyano-phenoxy)-phenyl.

18. The compound of Formula (I) in claim 1, wherein Ar_1 comprises: [2-(4-Chloro-phenyl)-ethoxy]-phenyl, (4-nitro-phenoxy)-phenyl, (3-phenyl-propylamino)-phenyl, 4-methoxy-4'-nitro-biphenyl-3-yl, (4'-methanesulfonyl-4-methoxy-biphenyl-3-yl), or (4'-methanesulfonyl-4-hydroxy-biphenyl-3-yl).

19. The compound of Formula (I) in claim 1, wherein Ar_1 comprises an unsubstituted biphenyl group.

20. The compound of Formula (I) in claim 1, wherein Ar_1 comprises a biphenyl group substituted with at least one of the following groups fluoro, chloro, trifluoroalkyl, trifluoroalkoxy, nitro, benzyloxy, phenoxy, and alkylsulfonyl.

21. The compound of Formula (I) in claim 1, wherein Ar_2 comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents independently comprising:

a) -fluoro;

b) -chloro;

c) -bromo;

d) -iodo;

e) -cyano;

f) -nitro;

g) -perfluoroalkyl;

h) -T-R_{17};

i) -alkyl;

j) -aryl;

k) -arylene-alkyl;

l) -T-alkyl;

m) -T-alkylene-aryl;

n) -T-alkylene-arylene-aryl;

o) -T-alkylene-arylene-alkyl; or

p) -arylene-T-alkyl;

wherein

T comprises $-CH_2-$, -O-, $-N(R_{18})-$, $-CON(R_{18})-$, or $-N(R_{18})C(O)-$; wherein R_{17}, and R_{18}, independently comprise: -hydrogen, -alkyl, or -aryl.

22. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: 3'-chloro-4'-fluoro-4-hydroxy-biphenyl, 2-hydroxy-5-[2-(4'-trifluoromethyl-biphenyl-3-yl)-acetylamino]-phenyl, 2-hydroxy-5-pyridin-3-yl-phenyl, 3',5'-difluoro-4-hydroxy-biphenyl, 3'-chloro-4'-fluoro-4-hydroxy-biphenyl, 3'-fluoro-4-hydroxy-biphenyl, 3'-trifluoromethyl-biphenyl-4-yl, 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl, 4'-amino-4-hydroxy-biphenyl, 4'-fluoro-4-hydroxy-biphenyl, 4-Hydroxy-2'-trifluoromethyl-biphenyl, 4-hydroxy-3',5'-bis-trifluoromethyl-biphenyl, 4-hydroxy-3'-nitro-biphenyl, 4-hydroxy-4'-trifluoromethoxy-biphenyl, 4-hydroxy-4'-trifluoromethyl-biphenyl, 4-hydroxy-biphenyl, 5-benzo[1,3]dioxol-5-yl-2-hydroxy-phenyl, 5-bromo-2-hydroxy-phenyl, 5-chloro-4-hydroxy-4'-trifluoromethyl-biphenyl, 5-fluoro-4-hydroxy-4'-trifluoromethyl-biphenyl, or 6-benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl.

23. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: 3'-chloro-4'-fluoro-4-hydroxy-biphenyl, or 4-hydroxy-4'-trifluoromethyl-biphenyl.

24. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: [2-(3,4-bis-benzyloxy-benzyloxy)-benzyloxy]-5-bromo-phenyl, 2-(4-tert-butyl-benzyloxy)-5-chlorophenyl, 3-bromo-5-chloro-2,6-dimethoxy-phenyl, 4-(4-tert-butyl-benzyloxy)-4'-trifluoromethyl-biphenyl, 4-acetoxy-2-phneyl-4'-trifluoromethyl-biphenyl, 4-acetoxy-4'-trifluoromethyl-biphenyl, 4-amino-4'-trifluoromethyl-biphenyl, 4-butoxy-3'-chloro-4'-fluoro-

biphenyl, 4-methanesulfonylamino-4'-trifluoromethyl-biphenyl, 4-methoxy-4'-trifluoromethyl-biphenyl, 5-bromo-2-(4-[1,2,4]triazol-1-yl-benzyloxy)-phenyl, 5-bromo-2-(4-tert-butyl-benzyloxy)-phenyl, 5-bromo-2-cyclohexyloxy-phenyl, 5-bromo-2-heptyloxy-phenyl, 5-chloro-2,4-dimethoxy-4'-trifluoromethyl-biphenyl, 5-chloro-2-heptyloxy-phenyl.

25. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: 5-bromo-2-(3-pyridin-4-yl-propoxy)-phenyl, 5-bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-ethoxy]-phenyl, 5-bromo-2-(2-morpholin-4-yl-ethoxy)-phenyl, 5-bromo-2-(4,4,4-trifluoro-butoxy)-phneyl, or 5-Bromo-2-(2-piperidin-1-yl-ethoxy)-phenyl.

26. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: 3-hydroxy-naphthalene.

27. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: a phenyl or biphenyl group containing a hydroxy, alkyloxy, or acetoxy group ortho to the Ar_2 group's point of attachment to X.

28. The compound of Formula (I) in claim 1, wherein Ar_2 comprises: a phenyl or biphenyl group containing a hydroxy, alkyloxy, or acetoxy group ortho to the Ar_2 group's point of attachment to X and further substituted with at least one of the following groups fluoro, chloro, trifluoroalkyl, trifluoroalkoxy, nitro, benzyloxy, phenoxy, phenyl, and alkylsulfonyl.

29. The compound of Formula (I) in claim 1 comprising:

3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-4 -hydroxy- biphenyl-3-carbonyl)-amino]-propionic acid methyl ester,

3-Biphenyl-4-yl-2-(S)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester,

2-(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-nitro-biphenyl-4-yl)-propionic acid methyl ester,

2-(2S)-(5-Benzo[1,3]dioxol-5-yl-2-hydroxy-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester,

2-(S)-[(4-Hydroxy-4'-fluoro -biphenyl-3-carbonyl)-amino]-3-biphenyl-4-yl)propionic acid methyl ester,

3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-2-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester,

2-(S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)propionic acid methyl ester,

2-(S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester,

3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-2-(S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester,

2-(S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester,

2-(S)-(5-Chloro-2-hydroxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester,

2-(S)-(5-Bromo-2-hydroxy-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-6-methoxy-biphenyl-3-yl)-ethyl]-amide,

2-(S)-[(4-Acetoxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid methyl ester,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-(S)-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1-(R)-(3'-chloro-4'-fluoro-biphenyl-4-ylmethyl)-2-oxo-propyl]-amide,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-benzyloxy-3'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

4-Hydroxy-4'-nitro-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

Acetic acid 3-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethylcarbamoyl]-4'-trifluoromethyl-biphenyl-4-yl ester,

6-Benzyloxy-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

5-Bromo-N-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-2-hydroxy-benzamide,

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-biphenyl-4-yl-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

4-Hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4'-methanesulfonyl-biphenyl-4-yl)-1-(R)-(-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

Acetic acid 5'-[2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl) ethylcarbamoyl]-4-trifluoromethyl[1,1';3',1"]terphenyl-4'-yl ester

5-Chloro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(4-benzyloxy-phenyl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

5-Fluoro-4-hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

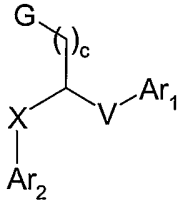
4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [2-[4-(3-chloro-4-fluoro-phenoxy)-phenyl]-1-(R)-(3-methyl 1,2,4]oxadiazol-5-yl)-ethyl]-amide,

3-Hydroxy-naphthalene-2-carboxylic acid [2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-1-(R)-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amide,

3-Hydroxy-naphthalene-2-carboxylic acid [2-(4'-methanesulfonyl-4-methoxy-biphenyl-3-yl)-ethyl]-amide, or

4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carboxylic acid [1(R)-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-2-(3'-chloro-4'-fluoro-biphenyl-4-yl)-ethyl]-amide.

30. A pharmaceutical composition comprising a compound of Formula (I)



(I)

wherein

c is equal to 0, 1, or 2; wherein the values of 0, 1, and 2 comprise a direct bond, -CH_2-, and -CH_2-CH_2-, optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl;

G comprises: -hydrogen, -alkyl, -heteroaryl, -aryl, -heterocyclycl, -CH=CH-CO_2R_1, -CO_2R_1, –CH_2OR_1, –CH_2SR_1 –C(O)-R_1, -C(O)NR_1R_2, -C(R_1)=N-O-R_2, -C(O)C(O)R_1, -C(O)C(O)NR_1R_2, an acid isostere, or an ester isostere;

wherein

R_1 and R_2 independently comprise: -hydrogen, -alkyl, -aryl, -alkenyl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -heterocyclyl, or -heteroaryl;

or when R_1 and R_2 are bonded to a nitrogen group in G,

R_1 and R_2 may be taken together to form a ring having the formula -$(CH_2)_m$-Z_2-$(CH_2)_n$-,

wherein

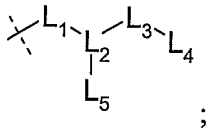
m and n are, independently, 1, 2, 3, or 4 and

Z_2 comprises -CH_2-, -C(O)-, -O-, -N(H)-, -S-, -S(O)-, -$S(O_2)$-, -CON(H)-, -NHC(O)-, -NHC(O)N(H)-, -$NH(SO_2)$-, -$S(O_2)$N(H)-, -(O)CO-, -$NHS(O_2)NH$-, -OC(O)-, -$N(R_{21})$-, -$N(C(O)R_{21})$-, -$N(C(O)NHR_{21})$-, -$N(S(O_2)NHR_{21})$-, -$N(SO_2R_{21})$-, or -$N(C(O)OR_{21})$-;

wherein

R_{21} comprises hydrogen, aryl, alkyl, or alkylene-aryl; or

R_2 comprises a substituent of the formula



;

wherein

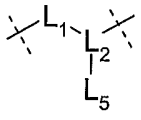
L_1 comprises a direct bond, alkylene, -O-alkylene-, alkylene-O-, -NH-C(O)-, -C(O)-NH- or –NH-C(O)-NH-;

L_2 comprises alkyline, alkenyline, heteroaryline, aryline, or heterocyclyline;

L_3 comprises –O-, -N(R_3)-, -C(O)-N(R_3)-, -C(O)-O-, -C(O)-, –N(R_3)-C(O)-N(R_4)-, -CH=CH-CO_2R_1, -C(O)R_1, -C(O)C(O)R_1, or -C(O)C(O)NR_1R_2;

L_4 comprises hydrogen, alkyl, alkenyl, alkynyl, heterocyclyl, heteroaryl, or –alkylene-aryl; and

L_5 comprises hydrogen, alkyl, alkenyl, alkynyl, -akylene-aryl, -alkylene-heteroaryl, alkylene-O-alkylene-aryl, -alkylene-S-alkylene-aryl, -alkylene-O-alkyl, -alkylene-S-alkyl, -alkylene-NH_2, -alkylene-OH, -alkylene-SH, -alkylene-C(O)-OR_5, -alkylene-C(O)-NR_5R_6, -alkylene-NR_5R_6, -alkylene-N(R_5)-C(O)-R_6, or –alkylene-N(R_5)-S(O_2)-R_6; or



; may be taken together to constitute a direct bond;

wherein

R_3, R_4, R_5, and R_6 independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or, -alkylene-heteroaryl;

V comprises: -$(CH_2)_b$-O-$(CH_2)_a$-, -$(CH_2)_b$-N(R_8)-$(CH_2)_a$-, -$(CH_2)_b$-O-, -$(CH_2)_b$-N(R_8), -$(CH_2)_a$-, -CH=CH-(CR_8)- or a direct bond; in which a is equal to 0, 1, or 2, b is equal to 1 or 2, and R_8 comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; wherein the -CH_2- groups may be optionally substituted 1 to 4 times with a substituent group comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or –hydroxyl;

X comprises: -N(R_9)-, -CON(R_9)-, -N(R_9)CO-, -N(R_9)CON(R_{10})-, -OC(O)N(R_8)-, -SO_2N(R_9)-, -N(R_9) SO_2-, or -N(R_9)SO_2N(R_{10})-; wherein R_9 and R_{10} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, or –$(CH_2)_d$Y-, wherein d is equal to 0, 1, or 2,

wherein

Y comprises: -hydrogen, –CO_2R_{11}, –CH_2OR_{11}, –C(O)-R_{11}, -C(O)$NR_{11}R_{12}$, -C(R_{11})=N-O-R_{12}, -$NR_{11}R_{12}$, or an acid isostere;

wherein R_{11} and R_{12} independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -heterocyclyl, or -heteroaryl;

Ar_1 comprises an aryl, heteroaryl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, or fused heterocyclylheteroaryl group optionally substituted 1 to 7 times, wherein the substitutents independently comprise:

a) -fluoro;
b) -chloro;
c) -bromo;
d) -iodo;
e) -cyano;
f) -nitro;
g) -perfluoroalkyl;
h) -D-R_{12};
i) -alkyl;
j) -aryl;
k) -heteroaryl;
l) -heterocyclyl;
m) -cycloalkyl;
n) -alkylene-aryl;
o) -alkylene-arylene-aryl;
p) -alkylene-arylene-alkyl;
q) -arylene-alkyl;
r) -arylene-arylene-alkyl;
s) -D-alkyl;
t) -D-aryl;

u) -D-alkylene-aryl;

v) -D-arylene-alkyl;

w) -D-alkylene-arylene-aryl;

x) -D-arylene-arylene-aryl;

y) -D-alkylene-arylene-alkyl;

z) -alkylene-D-alkylene-aryl;

aa) -arylene-D-alkyl;

bb) -alkylene-D-aryl;

cc) -alkylene-D-heteroaryl;

dd) -alkylene-D-cycloalkyl;

ee) -alkylene-D-heterocyclyl;

ff) -alkylene-D-arylene-alkyl;

gg) -alkylene-D-alkylene-arylene-alkyl;

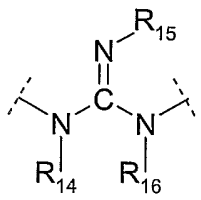
hh) -alkylene-D-alkyl;

ii) -alkylene-D-R_{13};

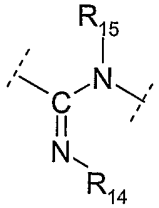
jj) -arylene-D-R_{13}; or

kk) -hydrogen;

wherein D comprises $-CH_2-$, -O-, $-N(R_{14})-$, -C(O)-, $-CON(R_{14})-$, $-N(R_{14})C(O)-$, $-N(R_{14})CON(R_{15})-$, $-N(R_{14})C(O)O-$, $-OC(O)N(R_{14})-$, $-N(R_{14})SO_2-$, $-SO_2N(R_{14})-$, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, $-S(O_2)-$, $-N(R_{14})SO_2N(R_{15})-$,



, or



, and

wherein

R_{13}, R_{14}, R_{15}, and R_{16} independently comprise: -hydrogen, hydroxyl, -cyano, nitro, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; and

Ar_2 comprises an aryl or heteroaryl group optionally substituted 1 to 7 times, wherein the substitutents independently comprise:

a) -fluoro;

b) -chloro;

c) -bromo;

d) -iodo;
e) -cyano;
f) -nitro;
g) -perfluoroalkyl;
h) -T-R_{17};
i) -alkyl;
j) -aryl;
k) -heteroaryl;
l) -heterocyclyl;
m) -cycloalkyl;
n) -alkylene-aryl;
o) -alkylene-arylene-aryl;
p) -alkylene-arylene-alkyl;
q) -arylene-alkyl;
r) -arylene-arylene-alkyl;
s) -T-alkyl;
t) -T-aryl;
u) -T-alkylene-aryl;
v) -T-arylene-alkyl;
w) -T-alkylene-arylene-aryl;
x) -T-arylene-arylene-aryl;
y) -T-alkylene-arylene-alkyl;
z) -alkylene-T-alkylene-aryl;
aa) -arylene-T-alkyl;
bb) -alkylene-T-aryl;
cc) -alkylene-T-heteroaryl;
dd) -alkylene-T-cycloalkyl;
ee) -alkylene-T-heterocyclyl;
ff) -alkylene-T-arylene-alkyl;
gg) -alkylene-T-alkylene-arylene-alkyl;
hh) -alkylene-T-alkyl;
ii) -alkylene-T-R_{17};
jj) -arylene-T-R_{17}; or
kk) -T-alkylene-arylene-heteroaryl;

ll) -T-alkylene-heterocyclyl;

mm)-T-alkylene-heteroaryl;

nn) -T-heteroaryl;

oo) -T-fused heterocyclylaryl;

pp) -T-fused cycloalkylaryl;

qq) -T-fused arylcycloalkyl;

rr) -T-fused fused heterocyclylaryl;

ss) -T-fused fused arylheterocyclyl;

tt) -T-fused fused cycloalkylheteroaryl;

uu) -T-fused fused heteroarylcycloalkyl;

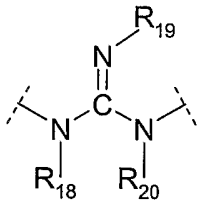
vv) -T-fused heterocyclylheteroaryl;

ww)-T-fused heteroarylheterocyclyl; or

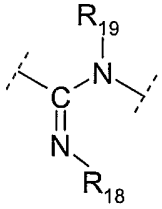
xx) -hydrogen;

wherein

T comprises a direct bond, $-CH_2-$, -O-, $-N(R_{18})-$, -C(O)-, $-CON(R_{18})-$, $-N(R_{18})C(O)-$, $-N(R_{18})CON(R_{19})-$, $-N(R_{18})C(O)O-$, $-OC(O)N(R_{18})-$, $-N(R_{18})SO_2-$, $-SO_2N(R_{18})-$, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, $-S(O_2)-$, $-N(R_{18})SO_2N(R_{19})-$,



, or



and

wherein R_{17}, R_{18}, R_{19} and R_{20}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl;

and wherein

the alkyl, aryl, heteroaryl, alkylene, and arylene groups in Ar_1, Ar_2, G, R_1-R_{21}, may be optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising:

a) -hydrogen;

b) -fluoro;

c) -chloro;

d) -bromo;

e) -iodo;

f) -cyano;

g) -nitro;

h) -perfluoroalkyl;

i) -Q-R_{22};

j) -Q-alkyl;

k) -Q-aryl;

l) -Q-alkylene-aryl;

m) -Q-alkylene-$NR_{23}R_{24}$; or

n) -Q-alkyl-W-R_{25};

wherein

Q and W independently comprise: $-CH_2-$, -O-, $-N(R_{26})-$, -C(O)-, $-CON(R_{26})-$, $-N(R_{26})C(O)-$, $-N(R_{26})CON(R_{27})-$, $-N(R_{26})C(O)O-$, $-OC(O)N(R_{26})-$, $-N(R_{26})SO_2-$, $-SO_2N(R_{26})-$, -C(O)-O-, -O-C(O)-, or $-N(R_{26})SO_2N(R_{27})-$, wherein

R_{22}, R_{23}, R_{24}, R_{25}, R_{26} and R_{27}, independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

31. The pharmaceutical compostion of claim 30, comprising a therapeutically effective amount of the compound of Formula (I).

32. The pharmaceutical composition of claim 30, further comprising one or more pharmaceutically acceptable carriers, excipients, or diluents.

33. The pharmaceutical composition of claim 30, wherein the compound of Formula (I) inhibits smallpox virus.

34. The pharmaceutical composition of claim 30, further comprising one or more additional therapeutic agents.

35. The pharmaceutical composition of claim 30 in the form of an oral dosage.

36. The pharmaceutical composition of claim 30 in the form of a parenteral dosage unit.

37. The pharmaceutical composition of claim 30, wherein said compound of Formula (I) comprises a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day.

38. The pharmaceutical composition of claim 30, wherein said compound of Formula (I) comprises a dose in a range from about 0.1 to 100 mg/kg of body weight per day.

39. The pharmaceutical composition of claim 30 wherein said compound of Formula (I) comprises a dose in a range from about 0.5 to 10 mg/kg of body weight per day.

40. A method comprising administering to a subject the compound of Formula (I) in claim 1.

41. The method of claim 40, wherein the compound of Formula (I) comprises an amount sufficient to reduce a viral load in a subject.

42. The method of claim 40, wherein said compound of Formula (I) is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day.

43. The method of claim 40, wherein said compound of Formula (I) is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day.

44. The method of claim 40, wherein said compound of Formula (I) is administered as a dose in a range from about 0.5 to 10 mg/kg of body weight per day.

45. A method for inhibiting propagation of a virus comprising the method of claim 40.

46. The method of claim 45, wherein the virus comprises an orthopox virus.

47. The method of claim 45, wherein the virus comprises smallpox, vaccinia virus, monkey pox, or cow pox.

48. The method of claim 40, wherein said compound of Formula (I) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents.

49. The method of claim 48, wherein the compound of Formula (I) is administered with another antiviral agent.

50. The method of claim 48, wherein the compound of Formula (I) is administered in an amount sufficient to reduce a viral load in a subject.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/025478

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C271/20 C07C233/29 C07C233/87 C07C235/42 C07C235/52
C07C235/60 C07C235/66 A61P31/12 A61K31/166

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	SIRCAR I ET AL: "Synthesis and SAR of N-benzoyl-L-Biphenylalanine derivatives: DISCOVERY OF TR-14035, A DUAL ALPHA4BETA7/ALPHA4BETA1 INTEGRIN ANTAGONIST" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 10, June 2002 (2002-06), pages 2051-2066, XP002250477 ISSN: 0968-0896 Tables 1-9 ----- -/--	1-40, 42-44,48

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

[X] Patent family members are listed in annex

° Special categories of cited documents

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2005	26/01/2005

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

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	CASTANEDO G M ET AL: "Solid-Phase synthesis of dual alpha4beta1/alpha4beta7 Integrin antagonists: TWO SCAFFOLDS WITH OVERLAPPING PHARMACOPHORES" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 12, October 2002 (2002-10), pages 2913-2917, XP002250476 ISSN: 0960-894X Scheme 1, Tables 1-2	1-40, 42-44,48
X	BURDICK D ET AL: "N-Benzoyl Amino Acids as LFA-1/ICAM Inhibitors 1: Amino Acid Structure-Activity Relationship" BIOORGANIC MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 6, 2003, pages 1015-118, XP002313197 Tables 1-3	1-40, 42-44,48
X	WO 00/76971 A (JONES STUART DONALD ; LYONS AMANDA JANE (GB); MORGAN PHILLIP JOHN (GB)) 21 December 2000 (2000-12-21) claims 5-6	1-40, 42-44,48
X	DE 199 28 424 A (AVENTIS PHARMA GMBH) 28 December 2000 (2000-12-28) the whole document	1-20, 30-40, 42-44,48
P,X	FR 2 847 251 A (GALDERMA RES & DEV) 21 May 2004 (2004-05-21) the whole document	1-40, 42-44,48
X	GB 2 354 440 A (MERCK & CO INC) 28 March 2001 (2001-03-28) the whole document	1-40, 42-44,48
X	US 2002/016461 A1 (STELTE-LUDWIG BEATRIX ET AL) 7 February 2002 (2002-02-07) the whole document	1-40, 42-44,48
X	WO 00/35864 A (STELTE LUDWIG BEATRIX ; ALBERS MARKUS (DE); URBAHNS KLAUS (DE); VAUPEL) 22 June 2000 (2000-06-22) eg. examples 1.1-1.24, 1.31-1.44, 1.46, 1.74, 2.1-2.3, 3.1 , 4.3-4.9, 5, 7.1, 8.1-8.7, 9, 10 etc	1-10, 14-28, 30-40, 42-44,48
X	WO 01/21584 A (GENENTECH INC ; JACKSON DAVID Y (US); SAILES FREDERICK C (US); SUTHERL) 29 March 2001 (2001-03-29) the whole document	1-40, 42-44,48

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/025478

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 02/18320 A (TANABE SEIYAKU CO ; KUME TOSHIYUKI (JP); NOMURA SUMIHIRO (JP); KAWAGUC) 7 March 2002 (2002-03-07) the whole document	1-40, 42-44,48
P,X	WO 2004/046091 A (RIVIER MICHEL ; CLARY LAURENCE (FR); COLLETTE PASCAL (FR); JOMARD ANDR) 3 June 2004 (2004-06-03) the whole document	1-40, 42-44,48
E	WO 2004/084842 A (WILLIAMS JENNIFER ; IRM LLC (US); TULLY DAVID (US); BURSULAYA BADRY (U) 7 October 2004 (2004-10-07) the whole document	1-40, 42-44,48
X	WO 99/26923 A (HAGMANN WILLIAM K ; MERCK & CO INC (US); DELASZLO STEPHEN E (US)) 3 June 1999 (1999-06-03) the whole document	1-40, 42-44,48
X	WO 99/36393 A (TANABE SEIYAKU CO ; MARTIN RICHARD (US); SIRCAR ILA (US); GUDMUNDSSON) 22 July 1999 (1999-07-22) the whole document	1-40, 42-44,48
X	WO 01/10823 A (BOEHRINGER INGELHEIM PHARMA ; NAR HERBERT (DE); HECKEL ARMIN (DE); PRI) 15 February 2001 (2001-02-15) the whole document	1-40, 42-44,48
X	WO 02/062748 A (BOEHRINGER INGELHEIM PHARMA ; NAR HERBERT (DE); PRIEPKE HENNING (DE);) 15 August 2002 (2002-08-15) the whole document	1-40, 42-44,48
X	US 5 750 520 A (DANILEWICZ JOHN CHRISTOPHER ET AL) 12 May 1998 (1998-05-12) the whole document	1-10, 14-28, 30-40, 42-44,48
X	WO 03/033496 A (YARRAGUNTA RAVINDRA R ; REN TAN (US); XIE RONGYUAN (US); ANDREWS ROBER) 24 April 2003 (2003-04-24) the whole document	1-40, 42-44,48
P,X	WO 2004/014844 A (BEHME CHRISTOPHER ; CHRISTEN DANIEL PETER (US); GOHIMMUKKULA DEVI REDD) 19 February 2004 (2004-02-19) the whole document	1-40, 42-44,48
X	WO 98/37075 A (BOEHRINGER INGELHEIM PHARMA) 27 August 1998 (1998-08-27) the whole document	1-40, 42-44,48

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/025478

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 5 518 735 A (WIKSTROEM PETER ET AL) 21 May 1996 (1996-05-21) claim 2	1-10, 14-28, 30-40, 42-44,48
X	WO 03/007945 A (BEAULIEU PIERRE LOUIS ; BOEHRINGER INGELHEIM CA LTD (CA); GOULET SYLVI) 30 January 2003 (2003-01-30) the whole document	1-50
E	WO 2004/080970 A (BOEHRINGER INGELHEIM PHARMA ; DAHMANN GEORG (DE); GERLACH KAI (DE); NA) 23 September 2004 (2004-09-23) the whole document	1-40, 42-44,48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/025478

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.: 1-50 (part.)
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 40-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-50(part.)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 40-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 1-50(part.)

Present claims 1-50 relate to an extremely large number of possible compounds, pharmaceutical compositions thereof and methods of treatment using said compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to those compounds prepared in the examples and closely related homologous compounds, namely the compounds of claim 1 wherein:

Ar2 represents an optionally substituted phenyl or naphthyl group.
X represents a CONH
c = 0
G represents a CO2R1, CONR1R2 and CONHNH2
V represents a CH2
Ar1 represents a biphenyl-4-yl

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds mentioned above. However, a representative number of documents which are also novelty destroying for compounds of present claim 1 not falling within the mentioned definition are also cited.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/025478

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/025478

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