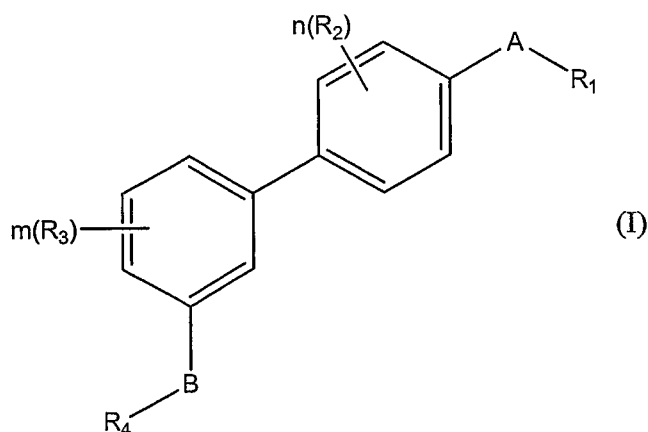


BIPHENYL DERIVATIVES AND THEIR USE IN TREATING HEPATITIS C

The present invention relates to a series of biphenyl derivatives which are useful in treating or preventing a hepatitis C viral (HCV) infection. Similar compounds are disclosed in copending application no. PCT/GB06/003469, from which the present application claims priority.

The present invention provides, in a first embodiment, the use of a compound which is a biphenyl derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or alleviating HCV



wherein:

- R_1 is a moiety $-A_1-L_1-A_1'$, $-A_1-L_1-A_1'-A_1''$ or $-A_1-L_1-A_1'-Y_1-A_1''$;
- 15 - A and B are the same or different and each represent a direct bond or a $-CO-NR'$, $-NR'-CO-$, $-NR'-CO-NR''$, $-NR'-S(O)_2-$, $-S(O)_2-NR'-$ or $-NR'-$ moiety, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl;
- R_2 and R_3 are the same or different and each represent C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, halogen, hydroxy, thio,
- 20 - $-NR'R''$, $-SO_2-R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1-C_4 alkyl and R''' represents C_1-C_4 alkyl;
- n and m are the same or different and each represent 0, 1 or 2;
- R_4 is a C_1-C_6 alkyl or C_1-C_6 haloalkyl group or a moiety $-A_4$, $-A_4-A_4'$, $-L_4-A_4$, $-A_4-L_4-A_4'$, $-A_4-Het_4-L_4-Het_4'-L_4'$ or $-L_4-Het_4-L_4'$,

- each A_1 , A_4 , A_1' , A_1'' and A_4' are the same or different and represent a phenyl, 5- to 10- membered heteroaryl, 5- to 10- membered heterocyclyl or C_3 - C_6 carbocyclyl moiety;
- each L_1 and L_4 is the same or different and represents a C_1 - C_4 alkylene or a C_1 -
5 C_4 hydroxyalkylene group;
- Y_1 represents $-\text{CO}-\text{NR}'$ -, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})$ -, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}'$ -, $-\text{NR}'-\text{CO}-$, $-\text{CO}-$, $-\text{O}-\text{CO}-$ or $-\text{CO}-\text{O}-$, wherein R' is hydrogen or C_1 - C_4 alkyl;
- L_4' represents hydrogen or a C_1 - C_4 alkyl group;
- Het_4 and Het_4' are the same or different and represent $-\text{O}-$, $-\text{S}-$ or $-\text{NR}'$ -, wherein
10 R' is hydrogen or a C_1 - C_4 alkyl group;

the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4 being unsubstituted or substituted by (a) a single unsubstituted substituent selected from $-\text{CO}_2R'$, $-\text{SO}_2\text{NR}''R''$, $-\text{S}(\text{O})_2-R'$, $-\text{CONR}''R''$, $-\text{COR}'''$, $-\text{CO}-\text{CO}-\text{OR}'''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''R''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''-\text{CO}-R'''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{CO}-\text{NR}''R''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{SO}_2-R'''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{O}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{O}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''R''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''R''$, $-\text{SO}_2-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$, $-\text{NR}''-\text{SO}_2-R'''$, $-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{CO}_2-R'''$, $-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{CO}-\text{NR}''R''$ and $-\text{SO}_2-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{SO}_2-R'$ and/or (b) 1, 2 or 3 unsubstituted substituents selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, C_1 - C_4 hydroxyalkyl, hydroxy, cyano, nitro and $-\text{NR}''R''$, wherein each R' is the same or different and represents hydrogen, C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and
25 represents C_1 - C_4 alkyl,

provided that either:

- (a) R_1 is $-\text{A}_1-\text{L}_1-\text{A}_1'-\text{A}_1''$ or $-\text{A}_1-\text{L}_1-\text{A}_1'-\text{Y}_1-\text{A}_1''$; or
- (b) R_1 is $-\text{A}_1-\text{L}_1-\text{A}_1'$ and A_1' is substituted by a $-\text{CO}_2R'$, $-\text{SO}_2\text{NR}''R''$, $-\text{SO}_2-R'$, $-\text{CONR}''R''$, $-\text{COR}'''$, $-\text{CO}-\text{CO}-\text{OR}'''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''R''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''-\text{CO}-R'''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{CO}-\text{NR}''R''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{SO}_2-R'''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{O}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{O}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''R''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{NR}''R''$, $-\text{SO}_2-(\text{C}_1\text{-C}_4 \text{ alkylene})-\text{OR}''$,

-NR^{''}-SO₂-R^{'''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R^{'''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO-NR^{''}R^{''} or -SO₂-(C₁-C₄ alkylene)-SO₂-R['] substituent, wherein each R['] is the same or different and represents hydrogen, C₁-C₄ alkyl or C₁-C₄ haloalkyl, each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and each R^{'''} is the

5 same or different and represents C₁-C₄ alkyl; or

(c) n is 1 and R₂ is C₁-C₄ alkylthio, hydroxy, thio, -NR[']R^{''}, -SO₂-R^{'''}, -NR[']-COR^{'''} or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl; or

(d) m is 1 and R₃ is C₁-C₄ alkylthio, hydroxy, thio, -NR[']R^{''}, -SO₂-R^{'''}, -NR[']-COR^{'''} or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl; or

(e) R₄ is -A₄-Het₄-L₄-Het₄[']-L₄['].

In a further embodiment, the present invention provides the use of a compound which is a biphenyl derivative of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or

15 alleviating HCV, wherein:

- R₁ is a moiety -A₁-L₁-A₁['], -A₁-L₁-A₁[']-A₁^{''} or -A₁-L₁-A₁[']-Y₁-A₁^{''};

- A and B are the same or different and each represent a direct bond or a -CO-NR[']-, -NR[']-CO-, -NR[']-CO-NR^{''}-, -NR[']-S(O)₂-, -S(O)₂-NR[']- or -NR[']- moiety, wherein R['] and R^{''} are the same or different and each represent hydrogen or C₁-C₄ alkyl;

- R₂ and R₃ are the same or different and each represent C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, halogen, hydroxy, thio, -NR[']R^{''}, -SO₂-R^{'''}, or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl;

25 - n and m are the same or different and each represent 0, 1 or 2;

- R₄ is a C₁-C₆ alkyl or C₁-C₆ haloalkyl group or a moiety -A₄, -A₄-A₄['], -A₄-L₄-A₄['], -A₄-Het₄-L₄-Het₄[']-L₄['] or -L₄-Het₄-L₄['],

- each A₁, A₄, A₁['], A₁^{''} and A₄['] are the same or different and represent a phenyl, 5- to 10- membered heteroaryl, 5- to 10- membered heterocyclyl or C₃-C₆ carbocyclyl

30 moiety;

- each L₁ and L₄ is the same or different and represents a C₁-C₄ alkylene or a C₁-C₄ hydroxyalkylene group;

- Y_1 represents $-\text{CO}-\text{NR}'-$, $-\text{NR}'-\text{CO}-$, $-\text{O}-\text{CO}-$ or $-\text{CO}-\text{O}-$, wherein R' is hydrogen or C_1 - C_4 alkyl;
 - L_4' represents hydrogen or a C_1 - C_4 alkyl group;
 - Het_4 and Het_4' are the same or different and represent $-\text{O}-$, $-\text{S}-$ or $-\text{NR}'-$, wherein
- 5 R' is hydrogen or a C_1 - C_4 alkyl group;
- the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4 being unsubstituted or substituted by (a) a single unsubstituted substituent selected from $-\text{CO}_2\text{R}'$, $-\text{SO}_2\text{NR}''\text{R}''$, $-\text{S}(\text{O})_2-\text{R}'$, $-\text{CONR}''\text{R}''$, $-\text{COR}'''$ and $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{SO}_2-\text{R}'$ and/or (b) 1, 2 or 3 unsubstituted substituents selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, C_1 - C_4 hydroxyalkyl, hydroxy, cyano, nitro
- 10 and $-\text{NR}''\text{R}''$, wherein each R' is the same or different and represents hydrogen, C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl,
- provided that either:
- 15 (a) R_1 is $-\text{A}_1-\text{L}_1-\text{A}_1'-\text{A}_1''$ or $-\text{A}_1-\text{L}_1-\text{A}_1'-\text{Y}_1-\text{A}_1''$; or
- (b) R_1 is $-\text{A}_1-\text{L}_1-\text{A}_1'$ and A_1' is substituted by a $-\text{CO}_2\text{R}'$, $-\text{SO}_2\text{NR}''\text{R}''$, $-\text{SO}_2-\text{R}'$, $-\text{CONR}''\text{R}''$, $-\text{COR}'''$ or $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{SO}_2-\text{R}'$ substituent, wherein each R' is the same or different and represents hydrogen, C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or
- 20 different and represents C_1 - C_4 alkyl; or
- (c) n is 1 and R_2 is C_1 - C_4 alkylthio, hydroxy, thio, $-\text{NR}'\text{R}''$, $-\text{SO}_2-\text{R}'''$, or $-\text{CO}_2\text{R}'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl; or
- (d) m is 1 and R_3 is C_1 - C_4 alkylthio, hydroxy, thio, $-\text{NR}'\text{R}''$, $-\text{SO}_2-\text{R}'''$ or
- 25 $-\text{CO}_2\text{R}'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl; or
- (e) R_4 is $-\text{A}_4-\text{Het}_4-\text{L}_4-\text{Het}_4'-\text{L}_4'$.

As used herein, a C_1 - C_6 alkyl moiety is a linear or branched alkyl moiety containing from 1 to 6 carbon atoms, such as C_1 - C_4 alkyl moiety. Examples of C_1 - C_6

30 alkyl moieties include methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl moieties. For the avoidance of doubt, where two alkyl moieties are present in a substituent, the alkyl moieties may be the same or different.

As used herein, a C₁-C₄ alkylene group is any divalent linear or branched C₁-C₄ or C₁-C₂ alkyl moiety. Linear C₁-C₄ alkylene groups are methylene, ethylene, n-propylene and n-butylene groups. Methylene and ethylene groups are preferred. Branched C₁-C₄ alkylene groups include -CH(CH₃)-, -CH(CH₃)-CH₂- and -CH₂-CH(CH₃)-.

As used herein, a C₁-C₄ hydroxyalkylene group is a said C₁-C₄ alkylene group which is substituted by a single hydroxy group.

As used herein, a halogen is chlorine, fluorine, bromine or iodine. A halogen is typically fluorine, chlorine or bromine.

As used herein, a C₁-C₄ alkoxy moiety is a said C₁-C₄ alkyl moiety attached to an oxygen atom. A preferred C₁-C₄ alkoxy moiety is methoxy. A C₁-C₄ hydroxyalkyl moiety is a said C₁-C₄ alkyl moiety substituted by a single hydroxyl moiety. Preferred hydroxyalkyl moieties are C₁-C₂ hydroxyalkyl moieties, for example -C(OH)-CH₃ and -CH₂OH.

A C₁-C₄ haloalkyl or C₁-C₄ haloalkoxy moiety is typically a said C₁-C₄ alkyl or C₁-C₄ alkoxy moiety substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl and haloalkoxy moieties are perhaloalkyl and perhaloalkoxy moieties such as -CX₃ and -OCX₃ wherein X is a said halogen atom, for example chlorine and fluorine. A particularly preferred haloalkyl moiety is -CF₃. A particularly preferred haloalkoxy moiety is -OCF₃.

Preferably, the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R₁ and R₄ are unsubstituted or substituted by (a) a single unsubstituted substituent selected from -CO₂R', -S(O)₂-R', -CONR''R'', -COR''', -CO-CO-OR''', -CO-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-CO-R''', -CO-(C₁-C₄ alkylene)-SO₂-R''', -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR'', -SO₂-(C₁-C₄ alkylene)-OR'', -NR''-SO₂-R''', -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R''', and -SO₂-(C₁-C₄ alkylene)-SO₂-R' and/or (b) 1, 2 or 3 unsubstituted substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl and C₁-C₄ haloalkoxy substituents, wherein each R' is the same or different and represents hydrogen, C₁-C₄ alkyl or C₁-C₄ haloalkyl, each R'' is the same or different and represents hydrogen or C₁-C₄ alkyl and each R''' is the same or different and represents C₁-C₄ alkyl. More typically, in this embodiment, the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R₁ and R₄ are unsubstituted or substituted by (a) a single unsubstituted

substituent selected from $-\text{CO}_2\text{R}'$, $-\text{S}(\text{O})_2\text{R}'$, $-\text{CONR}''\text{R}''$, $-\text{COR}'''$ and $-\text{SO}_2-(\text{C}_1-\text{C}_4$
alkylene)- $\text{SO}_2\text{R}'$ and/or (b) 1, 2 or 3 unsubstituted substituents selected from halogen,
 C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 haloalkoxy substituents, wherein
each R' is the same or different and represents hydrogen, C_1-C_4 alkyl or C_1-C_4 haloalkyl,
5 each R'' is the same or different and represents hydrogen or C_1-C_4 alkyl and each R''' is
the same or different and represents C_1-C_4 alkyl.

More preferably, the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties
in R_1 and R_4 are unsubstituted or substituted by (a) a single unsubstituted substituent
selected from $-\text{S}(\text{O})_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{S}(\text{O})_2-(\text{C}_1-\text{C}_4 \text{ haloalkyl})$, $-\text{CO}-\text{NHR}'''$, $-\text{COR}'''$, $-\text{CO}-$
10 $\text{CO}-\text{OR}'''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{NR}''\text{R}''$, $-\text{CO}-(\text{C}_1-\text{C}_2$
alkylene)- $\text{NH}-\text{CO}-\text{R}'''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-\text{R}'''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{O}-(\text{C}_1-\text{C}_2$
alkylene)- OR'' , $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{OH}$, $-\text{NH}-\text{SO}_2-\text{R}'''$, $-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{CO}-(\text{C}_1-\text{C}_2$
alkylene)- $\text{CO}_2-\text{R}'''$, and $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-\text{R}'''$ and/or (b) 1 or 2 unsubstituted
substituents selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl substituents,
15 wherein, each R'' is the same or different and represents hydrogen or C_1-C_4 alkyl and
each R''' is the same or different and represents C_1-C_4 alkyl. More typically, in this
embodiment, the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4
are unsubstituted or substituted by (a) a single unsubstituted substituent selected from
 $-\text{S}(\text{O})_2\text{R}'$, $-\text{CO}-\text{NHR}'''$, $-\text{COR}'''$ and $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-\text{R}'''$ and/or (b) 1 or 2
20 unsubstituted substituents selected from halogen, C_1-C_4 alkyl and C_1-C_4 haloalkyl
substituents, wherein each R' is the same or different and represents C_1-C_4 alkyl or C_1-
 C_4 haloalkyl and each R''' is the same or different and represents C_1-C_4 alkyl.

As used herein, a 5- to 10-membered heteroaryl moiety is a 5- to 10-membered
aromatic ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms,
25 selected from O, S and N. Typically, a heteroaryl moiety is monocyclic. Typically a 5-
to 10-membered heteroaryl moiety is a 5- to 6-membered heteroaryl moiety. Examples
include imidazolyl, isoxazolyl, pyrrolyl, thienyl, thiazolyl, furanyl, pyridyl, pyrazinyl,
pyrimidinyl, pyridazinyl, oxadiazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,
thiadiazolyl, pyrazolyl and triazolyl moieties. Pyridyl and triazolyl moieties are
30 preferred.

A said heteroaryl moiety is unsubstituted or substituted as set out above.
Preferably, it is unsubstituted or substituted by 1 or 2 unsubstituted substituents selected

from halogen, C₁-C₄ alkyl and C₁-C₂ haloalkyl substituents. More preferably, it is unsubstituted.

As used herein, a 5- to 10-membered heterocyclyl moiety is a non-aromatic, saturated or unsaturated C₅-C₁₀ carbocyclic ring, in which at least one, for example 1, 2
5 3 or 4, carbon atoms in the ring are replaced with a moiety selected from O, S, SO, SO₂, CO and N. Typically, it is saturated or contains a single double bond within the ring structure. More typically, it is a saturated C₅-C₁₀ ring (preferably a C₅-C₆ ring) in which 1, 2 or 3 of the carbon atoms in the ring are replaced with a moiety selected from O, S, SO₂, CO and NH. Typically, a heterocyclyl moiety is monocyclic. Preferably, a
10 heterocyclyl moiety contains up to two CO moieties.

Preferably, a heterocyclyl moiety is a 5- to 6- membered ring. Examples include pyrazolidinyl, piperidyl, piperidin-2,6-dionyl, piperidin-2-onyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl, S,S-dioxothiomorpholinyl, 1,3-dioxolanyl, 1,4-dioxanyl, pyrrolidinyl, imidazolidinyl, imidazol-2-onyl, pyrrolidin-2-
15 onyl, tetrahydrofuranyl, tetrahydrothienyl, dithiolanyl, thiazolidinyl, oxazolidinyl, tetrahydropyranyl, pyrimidin-2,4 (1H, 3H)-dionyl and pyrazolinyl moieties. Piperidyl, piperidin-2,6-dionyl, pyrrolidin-2-onyl, imidazolin-2-onyl, pyrimidine-2,4 (1H, 3H)-dionyl, piperazinyl, morpholinyl, thiomorpholinyl, S,S-dioxothiomorpholinyl and pyrrolidinyl moieties are preferred.

20 A said heterocyclyl moiety is unsubstituted or substituted as set out above.

For the avoidance of doubt, although the above definitions of heteroaryl and heterocyclyl groups refer to an "N" moiety which can be present in the ring, as will be evident to a skilled chemist the N atom will be protonated (or will carry a substituent as defined above) if it is attached to each of the adjacent ring atoms via a single bond.

25 A said phenyl group is unsubstituted or substituted as set out above. Preferably, it is unsubstituted or substituted by 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy and C₁-C₂ haloalkyl substituents. More preferably, it is unsubstituted.

As used herein, a C₃-C₆ carbocyclic moiety is a non-aromatic saturated or
30 unsaturated hydrocarbon ring having from 3 to 6 carbon atoms. Typically, it is monocyclic. Preferably it is a saturated hydrocarbon ring (i.e. a cycloalkyl moiety) having from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Cyclopropyl and cyclohexyl are preferred.

A said carbocyclyl moiety is unsubstituted or substituted as set out above. Preferably, it is unsubstituted or substituted by 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl and C₁-C₂ haloalkyl substituents. More preferably, it is unsubstituted.

5 Typically, A₁ represents a phenyl group or a 5- to 6- membered heteroaryl group. Preferably, A₁ is a phenyl group.

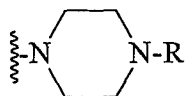
Typically, A₁ is unsubstituted or substituted by 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy and C₁-C₂ haloalkyl substituents. Typically, these substituents are selected from halogen, C₁-C₄ alkyl and C₁-C₂ haloalkyl
10 substituents. More preferably, A₁ is unsubstituted.

Preferably, A₁ is a phenyl group which is unsubstituted or substituted by one or two unsubstituted halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy and C₁-C₂ haloalkyl substituents.

In a preferred embodiment, A₁ is a phenyl group which is unsubstituted or substituted by a C₁-C₂ alkoxy, for example a methoxy, group. Most preferably, A₁ is an
15 unsubstituted phenyl group.

Typically, the A₁' moiety represents a 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl group. More preferably, A₁' is a 5- to 6- membered heterocyclyl moiety, such as a piperazinyl, pyrrolidinyl or S,S-dioxothiomorpholinyl group, in particular a piperazinyl or S,S-dioxothiomorpholinyl group. Most preferably,
20 A₁' is a piperazinyl group.

In a preferred embodiment of the invention, A₁' represents an unsubstituted S,S-dioxothiomorpholino group, a pyrrolidinyl group substituted with -NR''-SO₂-R''' or a moiety



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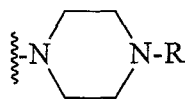
wherein R represents -CO₂R', -SO₂NR''R'', -S(O)₂-R', -CONR''R'', -COR''', -CO-CO-OR''', -CO-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-CO-R''', -CO-(C₁-C₄ alkylene)-CO-NR''R'', -CO-(C₁-C₄ alkylene)-SO₂-R''', -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''-(C₁-C₄ alkylene)-NR''R'', -SO₂-(C₁-C₄ alkylene)-OR'', -NR''-SO₂-R''',
30

5 -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R^{'''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO-NR^{''}R^{''} and -SO₂-(C₁-C₄ alkylene)-SO₂-R['], wherein each R['] is the same or different and represents hydrogen, C₁-C₄ alkyl or C₁-C₄ haloalkyl, each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and each R^{'''} is the same or different and represents C₁-C₄ alkyl.

10 Preferably, R represents -CO₂R['], -S(O)₂-R['], -CONR^{''}R^{''}, -COR^{'''}, -CO-CO-OR^{'''}, -CO-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-CO-R^{'''}, -CO-(C₁-C₄ alkylene)-SO₂-R^{'''}, -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR^{''}, -SO₂-(C₁-C₄ alkylene)-OR^{''}, -NR^{''}-SO₂-R^{'''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R^{'''} and -SO₂-(C₁-C₄ alkylene)-SO₂-R['], wherein wherein each R['] is the same or different and represents hydrogen, C₁-C₄ alkyl or C₁-C₄ haloalkyl, each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and each R^{'''} is the same or different and represents C₁-C₄ alkyl.

15 More preferably, R represents -S(O)₂-(C₁-C₄ alkyl), -S(O)₂-(C₁-C₄ haloalkyl), -CONHR^{'''}, -COR^{'''}, -CO-CO-OR^{'''}, -CO-(C₁-C₂ alkylene)-OR^{''}, -CO-(C₁-C₂ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₂ alkylene)-NH-CO-R^{'''}, -CO-(C₁-C₂ alkylene)-SO₂-R^{'''}, -CO-(C₁-C₂ alkylene)-O-(C₁-C₂ alkylene)-OR^{''}, -SO₂-(C₁-C₄ alkylene)-OH, -NH-SO₂-R^{'''}, -(C₁-C₂ alkylene)-CO-(C₁-C₂ alkylene)-CO₂-R^{'''} and -SO₂-(C₁-C₂ alkylene)-SO₂-R^{'''}, wherein each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and each R^{'''} is the same or different and represents C₁-C₄ alkyl.

20 Most preferably, A₁['] represents an unsubstituted S,S-dioxothiomorpholino group or a moiety



25 wherein R represents -CO-(C₁-C₄ alkyl), -SO₂-(C₁-C₄ alkyl), -SO₂-(C₁-C₂ haloalkyl) or -SO₂-(C₁-C₂ alkylene)-SO₂-(C₁-C₄ alkyl).

Typically, the A₁^{''} moiety is a phenyl, 5- to 6- membered heterocyclyl or C₃-C₆ carbocyclic group. Preferably, the A₁^{''} moiety is a phenyl, C₃-C₆ cycloalkyl, morpholino, S,S-dioxothiomorpholino, pyrrolidin-2-onyl, imidazolin-2-onyl or
30 pyrimidin-2,4 (1H, 3H)-dionyl group. In a further embodiment, the A₁^{''} moiety is a C₃-C₆ carbocyclyl group, preferably a C₃-C₆ cycloalkyl group. Typically, the A₁^{''} moiety is

unsubstituted or substituted by 1 or 2 substituents selected from C₁-C₄ alkyl, halogen and hydroxy substituents.

Typically, each A₄ moiety is the same or different and is phenyl, 5- to 6-membered heteroaryl, 5- to 6- membered heterocyclyl or C₃-C₆ cycloalkyl. Preferably, each A₄ moiety is the same or different and represents a phenyl, piperidiny, pyridyl, piperazinyl, pyrrolidiny, cyclopropyl or cyclohexyl moiety.

Preferably, each A₄ moiety is unsubstituted or substituted by 1, 2 or 3 unsubstituted substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl and C₁-C₄ haloalkoxy substituents. More preferably, each A₄ moiety is unsubstituted or substituted by 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl and C₁-C₂ haloalkyl substituents. Most preferably, each A₄ moiety is unsubstituted or substituted with a C₁-C₂ alkyl group.

Typically, each A₄' moiety is the same or different and represents a phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl group. Preferably, each A₄' moiety is the same or different and represents a morpholinyl, phenyl, 2,6-dioxo-piperidiny or triazolyl group.

Preferably, each A₄' moiety is unsubstituted or substituted by 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl and C₁-C₄ haloalkyl substituents. More preferably, each A₄' moiety is unsubstituted or substituted by a C₁-C₂ alkyl group.

Preferably, L₁ is a C₁-C₄ alkylene group. More preferably, L₁ is a C₁-C₂ alkylene group. Most preferably, L₁ is a methylene group (-CH₂-).

Preferably, L₄ is a C₁-C₄ alkylene group. More preferably, L₄ is a C₁-C₂ alkylene group.

Preferably, Y₁ represents -CO-(C₁-C₂ alkyl)-, -CO-(C₁-C₂ alkyl)-NR', -CO-, -CO-NR' or -NR'-CO-, wherein R' is hydrogen or C₁-C₄ alkyl. More preferably, Y₁ represents -CO-CH₂-, -CO-CH₂-NH-, -CO-, -CO-NH- or -NH-CO-. In one embodiment, Y₁ represents -CO-NR' or -NR'-CO-, wherein R' is hydrogen or C₁-C₄ alkyl. In a further embodiment, Y₁ represents -CO-NH- or -NH-CO-. Most preferably, Y₁ represents -CO-NH-. For the avoidance of doubt, the left hand side of the Y₁ moieties depicted above is attached to A₁', and the right hand side of the depicted moieties is attached to A₁'.

Preferably, L₄' is a C₁-C₂ alkyl group. More preferably, L₄' is a methyl group.

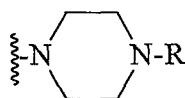
Preferably, each Het₄ and Het₄' are the same or different and represent -O- or -NR'- wherein R' is hydrogen or C₁-C₂ alkyl. Preferably, Het₄ represents -NR'-, more preferably -NH- or -N(CH₃)-. Preferably, Het₄' represents -O-.

When R₁ represents -A₁-L₁-A₁'-A'', it is typically a moiety -phenyl-CH₂-A₁'-(C₃-C₆ cycloalkyl), wherein A₁' is as defined above. Typically, A₁' is a piperazinyl group which is attached to the A'' moiety and to the -L₁-A₁ moiety via N atoms. More typically, A₁' is unsubstituted. More typically, A₁' is an unsubstituted piperazinyl group which is attached to the -A'' moiety and to the -L₁-A₁ moiety via N atoms. Preferably, in this embodiment, R₁ represents an unsubstituted -phenyl-CH₂-(1,4-piperazinyl)-(C₃-C₆ cycloalkyl) group.

When R₁ represents -A₁-L₁-A₁'-Y₁-A₁'', it is typically a moiety -phenyl-CH₂-A₁'-Y₁-A₁'', wherein A₁', Y₁ and A₁' are as defined above. Typically, A₁' is a piperazinyl group which is attached to the A'' moiety and to the -L₁-A₁ moiety via N atoms. More typically, A₁' is unsubstituted. More typically, A₁' is an unsubstituted piperazinyl group which is attached to the -A'' moiety and to the -L₁-A₁ moiety via N atoms. Typically, Y₁ is -CO-, -CO-CH₂-, -CO-CH₂-NH- or -CO-NH-. Preferably, in this embodiment, R₁ represents a -phenyl-CH₂-(1,4-piperazinyl)-Y₁-A₁' group, wherein Y and A₁' are as defined above. More preferably, R₁ represents an unsubstituted -phenyl-CH₂-(1,4-piperazinyl)-CO-NH-(C₃-C₆ cycloalkyl) group.

Preferably, R₁ represents a moiety -A₁-L₁-A₁' or -A₁-L₁-A₁'-Y₁-A₁' wherein A₁, L₁, A₁', Y₁ and A₁' are as defined above.

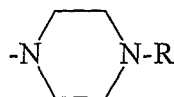
In a further embodiment of the invention, R₁ is a moiety -phenyl-CH₂-A₁' wherein A₁' is an unsubstituted S,S-dioxothiomorpholino group or a moiety



wherein R represents -CO-(C₁-C₄ alkyl), -SO₂-(C₁-C₄ alkyl), -SO₂-(C₁-C₂ haloalkyl) or -SO₂-(C₁-C₂ alkylene)-SO₂-(C₁-C₄ alkyl). Preferably, in this embodiment, R is -SO₂-(C₁-C₄ alkyl). More preferably, in this embodiment, A₁' is other than S,S-dioxothiomorpholino.

Although compounds of the invention in which R₁ is -phenyl-CH₂-A₁' are active compounds, it may be necessary to exclude some such compounds from the scope of the invention. Accordingly, in a further embodiment, the compounds of the invention are

not compounds of the formula (I), as set out above, wherein R_1 is -phenyl-CH₂-A₁' and A₁' is a moiety



wherein R is -SO₂-(C₁-C₄ alkyl).

- 5 More preferably, in this embodiment, the compounds of the invention are not compounds of the formula (I), as set out above, wherein R_1 is -phenyl-CH₂-A₁' and A₁' is a morpholino or piperazinyl group which is unsubstituted or substituted by a -S(O)₂-(C₁-C₄ alkyl) substituent.

10 For the avoidance of doubt, the left hand side of the A and B moieties depicted above are attached to the central biphenyl core. Thus, the right hand side of the depicted moieties are attached to R₁ or R₄.

Typically, A and B are the same or different and each represent -NR'[']-CO-NR''[']-, -CO-NR'[']- or -NR'[']-CO-, wherein R'['] and R''['] are the same or different and represent hydrogen or C₁-C₄ alkyl.

- 15 Typically, A represents -CO-NR'[']- or -NR'[']-CO-, wherein R'['] is hydrogen or C₁-C₄ alkyl. Preferably, A represents -CO-NR'[']-, more preferably -CO-NH-.

Typically, B represents -NR'[']-CO-NR''[']-, -CO-NR'[']- or -NR'[']-CO- wherein R'['] and R''['] are the same or different and represent hydrogen or C₁-C₄ alkyl. Preferably, B represents -NH-CO-NH-, -CO-NH- or -NH-CO-.

- 20 Typically, n and m are the same or different and each represent 0 or 1.

Preferably, n is 0 or 1. Preferably, m is 1. More preferably, m is 1 and R₃ is present on a carbon atom *ortho* to the phenyl ring of the central biphenyl moiety.

- 25 Preferably, R₂ and R₃ are the same or different and each represent halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ alkylthio, hydroxy, thio, -NR'[']R''['], -SO₂R'''['], -NR'[']-COR'''['] or -CO₂R'''['], wherein each R'['] and R''['] are the same or different and represent hydrogen or C₁-C₄ alkyl and R'''['] represents C₁-C₄ alkyl.

- 30 Preferably, each R₂ is the same or different and represents -NR'[']R''['], -NR'[']-CO-R'''['], -SO₂R'''['], -CO₂R'''['], hydroxy or thio, wherein each R'['] and R''['] are the same or different and represent hydrogen or C₁-C₄ alkyl and R'''['] is C₁-C₄ alkyl. More typically, in this embodiment, each R₂ is the same or different and represents -SO₂R'''['], -CO₂R'''['], hydroxy or thio, wherein R'''['] is C₁-C₄ alkyl. More preferably, each R₂ is the same or different and represents -N(R'''['])₂, -NH-CO-R'''['], -SO₂R'''['] or hydroxy, wherein R'''['] is C₁-C₄ alkyl,

preferably CH₃. More preferably, in this embodiment, each R₂ is the same or different and represents -SO₂R^{'''}, in particular -SO₂-CH₃, or hydroxy.

Preferably, each R₃ is the same or different and represents C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₂ haloalkyl, C₁-C₂ haloalkoxy or -NR[']R^{''}, wherein R['] and R^{''} are
 5 the same or different and represent hydrogen or C₁-C₄ alkyl. More preferably, each R₃ is the same or different and represents C₁-C₂ alkyl, C₁-C₂ alkoxy, halogen, C₁-C₂ haloalkoxy, C₁-C₂ haloalkyl or -NR[']R^{''}, wherein R['] and R^{''} are the same or different and each represent C₁-C₂ alkyl.

Typically, R₄ is a moiety -A₄, -A₄-A₄['], -L₄-A₄, -A₄-L₄-A₄['], -A₄-Het₄-L₄-Het₄[']-L₄[']
 10 or -L₄-Het₄-L₄['], wherein A₄, A₄['], L₄, Het₄, Het₄['] and L₄['] are as defined above. In one embodiment, R₄ is a moiety -A₄, -A₄-A₄['], -A₄-L₄-A₄['], -A₄-Het₄-L₄-Het₄[']-L₄['] or -L₄-Het₄-L₄['], wherein A₄, A₄['], L₄, Het₄, Het₄['] and L₄['] are as defined above.

When R₄ is -A₄, it is typically a C₃-C₆ cycloalkyl or 5- to 6- membered heterocyclyl group. Preferably, it is a cyclopropyl, cyclohexyl, piperidiny, piperazinyl
 15 or pyrrolidiny group. Typically, the A₄ moiety is unsubstituted or substituted with 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl and C₁-C₄ haloalkyl substituents. Preferably, these substituents are selected from C₁-C₂ alkyl groups.

When R₄ is -A₄-A₄['], A₄ is typically a phenyl or 5- to 6- membered heteroaryl moiety. Preferably, A₄ is a phenyl or pyridyl group. Typically, A₄ is unsubstituted or
 20 substituted with 1 or 2 unsubstituted substituents selected from halogen, C₁-C₄ alkyl and C₁-C₄ haloalkyl substituents. Preferably, A₄ is unsubstituted.

When R₄ is -A₄-A₄['], A₄['] is typically a 5- to 6- membered heteroaryl or heterocyclyl group. Preferably, A₄['] is a morpholinyl, triazolyl or piperidin-2,6-dionyl group. Preferably, A₄['] is unsubstituted or substituted with 1 or 2 unsubstituted
 25 substituents selected from halogen, C₁-C₄ alkyl and C₁-C₄ haloalkyl substituents. Preferably, A₄['] is unsubstituted or substituted by an unsubstituted C₁-C₂ alkyl group.

Most preferably, when R₄ is -A₄-A₄['], it is an unsubstituted -pyridyl-morpholino, -phenyl-triazolyl or -phenyl-morpholino group or is a -phenyl-piperidin-2,6-dionyl group which is unsubstituted or substituted by a C₁-C₂ alkyl group.

When R₄ is -A₄-L₄-A₄['], A₄ is typically a 5- to 6- membered heterocyclyl group,
 30 in particular a piperidiny group. L₄ is typically C₁-C₂ alkylene, more preferably -CH₂-. A₄['] is typically a phenyl group. Preferably, when R₄ is -A₄-L₄-A₄['], A₄ and A₄['] are unsubstituted.

When R_4 is $-L_4-A_4$, A_4 is typically a 5- to 6- membered heterocyclyl group, in particular a pyrrolidinyl group. L_4 is typically C_1-C_2 alkylene, more preferably $-CH_2-$. Preferably, when R_4 is $-L_4-A_4$, A_4 is unsubstituted.

When R_4 is $-L_4-Het_4-L_4'$, L_4 is typically C_1-C_2 alkylene, more preferably methylene. Het_4 is typically $-NR'$, wherein R' is hydrogen or C_1-C_2 alkyl, and is preferably $-NH-$. L_4' is typically C_1-C_2 alkyl, more preferably methyl.

When R_4 is $-A_4-Het_4-L_4-Het_4'-L_4'$, A_4 is typically a phenyl group. Typically, A_4 is unsubstituted. Het_4 is typically $-NR'$, wherein R' is hydrogen or C_1-C_2 alkyl, and is preferably $-N(CH_3)-$. L_4 is typically C_1-C_2 alkylene. Het_4' is typically $-O-$. L_4' is typically C_1-C_2 alkyl. Most preferably, when R_4 is $-A_4-Het_4-L_4-Het_4'-L_4'$, it is $-phenyl-N(CH_3)-(C_1-C_2 \text{ alkylene})-O-(C_1-C_2 \text{ alkyl})$.

As explained above, it is necessary that, in the present invention, either:

- (a) R_1 is $-A_1-L_1-A_1'-A_1''$ or $-A_1-L_1-A_1'-Y_1-A_1''$; or
- (b) R_1 is $-A_1-L_1-A_1'$ and A_1' is substituted by a $-CO_2R'$, $-SO_2NR''R'''$, $-SO_2-R'$, $-CONR''R'''$, $-COR'''$, $-CO-CO-OR'''$, $-CO-(C_1-C_4 \text{ alkylene})-OR''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''R'''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-CO-R'''$, $-CO-(C_1-C_4 \text{ alkylene})-CO-NR''R'''$, $-CO-(C_1-C_4 \text{ alkylene})-SO_2-R'''$, $-CO-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkylene})-OR''$, $-CO-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkylene})-NR''R'''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-(C_1-C_4 \text{ alkylene})-OR''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-(C_1-C_4 \text{ alkylene})-NR''R'''$, $-SO_2-(C_1-C_4 \text{ alkylene})-OR''$, $-NR''-SO_2-R'''$, $-(C_1-C_4 \text{ alkylene})-CO-(C_1-C_4 \text{ alkylene})-CO_2-R'''$, $-(C_1-C_4 \text{ alkylene})-CO-(C_1-C_4 \text{ alkylene})-CO-NR''R'''$ or $-SO_2-(C_1-C_4 \text{ alkylene})-SO_2-R'$ substituent, wherein each R' is the same or different and represents hydrogen, C_1-C_4 alkyl or C_1-C_4 haloalkyl, each R'' is the same or different and represents hydrogen or C_1-C_4 alkyl and each R''' is the same or different and represents C_1-C_4 alkyl; or
- (c) n is 1 and R_2 is C_1-C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2-R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1-C_4 alkyl and R''' represents C_1-C_4 alkyl; or
- (d) m is 1 and R_3 is C_1-C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2-R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1-C_4 alkyl and R''' represents C_1-C_4 alkyl; or
- (e) R_4 is $-A_4-Het_4-L_4-Het_4'-L_4'$.

Typically, in option (b), A_1' is substituted by a $-CO_2-(C_1-C_4 \text{ haloalkyl})$, $-SO_2(C_1-C_4 \text{ haloalkyl})$, $-COR'''$, $-SO_2-(C_1-C_4 \text{ alkylene})-SO_2-(C_1-C_4 \text{ haloalkyl})$,

-SO₂-(C₁-C₄ alkylene)-SO₂-R^{'''}, -CO-CO-OR^{'''}, -CO-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-CO-R^{'''}, -CO-(C₁-C₄ alkylene)-CO-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-SO₂-R^{'''}, -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-(C₁-C₄ alkylene)-NR^{''}R^{''}, -SO₂-(C₁-C₄ alkylene)-OR^{''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R^{'''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO-NR^{''}R^{''} substituent, wherein each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and R^{'''} is a C₁-C₄ alkyl group.

Preferably, in option (c), n is 1 and R₂ is -SO₂R^{'''}, -NR^{''}R^{''}, -NR^{''}-COR^{'''}, hydroxy, C₁-C₄ alkylthio, thio or -CO₂R^{'''}, wherein R^{'''} is as defined above. More preferably, in option (c), n is 1 and R₂ is -SO₂R^{'''}, -N(R^{'''})₂, -NH-CO-R^{'''} or hydroxy.

Preferably, in option (d), m is 1 and R₃ is -NR[']R^{''}, wherein R['] and R^{''} are as defined above. More preferably, m is 1 and R₃ is -N(CH₃)₂.

In a preferred aspect of this embodiment of the invention, either:

(a) R₁ is -A₁-L₁-A₁[']-A₁^{''} or -A₁-L₁-A₁[']-Y₁-A₁^{''}; or
 (b) R₁ is -A₁-L₁-A['] and A₁['] is substituted by a -CO₂-(C₁-C₄ haloalkyl), -SO₂-(C₁-C₄ haloalkyl), -COR^{'''}, -SO₂-(C₁-C₄ alkylene)-SO₂-(C₁-C₄ haloalkyl), -SO₂-(C₁-C₄ alkylene)-SO₂-R^{'''}, CO-CO-OR^{'''}, -CO-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-CO-R^{'''}, -CO-(C₁-C₄ alkylene)-CO-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-SO₂-R^{'''}, -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-(C₁-C₄ alkylene)-OR^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-(C₁-C₄ alkylene)-NR^{''}R^{''}, -SO₂-(C₁-C₄ alkylene)-OR^{''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R^{'''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO-NR^{''}R^{''} substituent, wherein each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and R^{'''} is a C₁-C₄ alkyl group; or

(c) n is 1 and R₂ is C₁-C₄ alkylthio, hydroxy, thio, -NR[']R^{''}, -SO₂-R^{'''}, -NR[']-COR^{'''} or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl; or

(d) m is 1 and R₃ is C₁-C₄ alkylthio, hydroxy, thio, -NR[']R^{''}, -SO₂-R^{'''}, -NR[']-COR^{'''} or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl; or

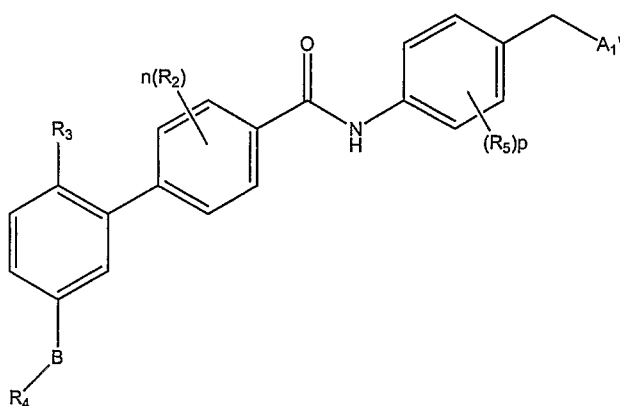
(e) R₄ is -A₄-Het₄-L₄-Het₄[']-L₄['].

Preferred compounds of formula (I) are those wherein:

- R_1 is $-A_1-L_1-A_1'$, $-A_1-L_1-A_1'-A_1''$ or $-A_1-L_1-A_1'-Y_1-A_1''$;
- A and B are the same or different and each represent $-NR'-CO-NR''$ -, $-CO-NR'$ - or $-NR'-CO$ -, wherein R' and R'' are the same or different and each represent hydrogen or C_1 - C_4 alkyl;
- 5 - R_2 and R_3 are the same or different and each represent halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, C_1 - C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein each R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl;
- n and m are the same or different and each represent 0 or 1;
- 10 - R_4 is a moiety $-A_4$, $-A_4-A_4'$, $-L_4-A_4$, $-A_4-L_4-A_4'$, $A_4-Het_4-L_4-Het_4'-L_4'$ or $-L_4-Het_4-L_4'$;
- each A_1 , A_4 , A_1' , A_1'' and A_4' are the same or different and represent a phenyl, 5- to 6- membered heteroaryl, 5- to 6- membered heterocyclyl or C_3 - C_6 cycloalkyl moiety;
- each L_1 and L_4 is the same or different and represents a C_1 - C_4 alkylene group;
- 15 - Y_1 represents $-CO-(C_1-C_2 \text{ alkyl})-$, $-CO-(C_1-C_2 \text{ alkyl})-NR'$ -, $-CO$ -, $-CO-NR'$ - or $-NR'-CO$ -, wherein R' is hydrogen or C_1 - C_4 alkyl;
- L_4' represents a C_1 - C_2 alkyl group; and
- each Het_4 and Het_4' are the same or different and represent $-O$ - or $-NR'$ - wherein R' is hydrogen or C_1 - C_2 alkyl;
- 20 the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4 being unsubstituted or substituted by (a) a single unsubstituted substituent selected from $-S(O)_2-(C_1-C_4 \text{ alkyl})$, $-S(O)_2-(C_1-C_2 \text{ haloalkyl})$, $-CO-NH-R'''$, $-CO-R'''$, $-CO-CO-OR'''$, $-CO-(C_1-C_2 \text{ alkylene})-OR''$, $-CO-(C_1-C_2 \text{ alkylene})-NR''R''$, $-CO-(C_1-C_2 \text{ alkylene})-NH-CO-R'''$, $-CO-(C_1-C_2 \text{ alkylene})-SO_2-R'''$, $-CO-(C_1-C_2 \text{ alkylene})-O-(C_1-C_2 \text{ alkylene})-OR''$,
25 $-SO_2-(C_1-C_4 \text{ alkylene})-OH$, $-(C_1-C_2 \text{ alkylene})-CO-(C_1-C_2 \text{ alkylene})-CO_2-R'''$ and $-SO_2-(C_1-C_2 \text{ alkylene})-SO_2-R'''$ and/or (b) 1 or 2 unsubstituted substituents selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 haloalkyl substituents, wherein each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl.
- 30 Typically, in these preferred compounds of the invention, either:
 - (a) R_1 is $-A_1-L_1-A_1'-A_1''$ or $-A_1-L_1-A_1'-Y_1-A_1''$; or
 - (b) R_1 is $-A_1-L_1-A_1'$ and A_1' is substituted by a $-SO_2-(C_1-C_4 \text{ haloalkyl})$, $-COR'''$, $-SO_2-(C_1-C_2 \text{ alkylene})-SO_2-R'''$, $-CO-CO-OR'''$, $-CO-(C_1-C_4 \text{ alkylene})-OR''$,

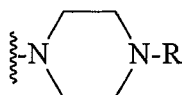
- CO-(C₁-C₄ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₄ alkylene)-NR^{''}-CO-R^{'''}, -CO-(C₁-C₄ alkylene)-SO₂-R^{'''}, -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR^{''}, -SO₂-(C₁-C₄ alkylene)-OR^{''}, -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R^{'''} group, in which each R^{''} is the same or different and represents hydrogen or C₁-C₄ alkyl and R^{'''} is C₁-C₄ alkyl; or
- (c) n is 1 and R₂ is C₁-C₄ alkylthio, hydroxy, thio, -NR[']R^{''}, -SO₂R^{'''} -NR[']-CO-R^{'''} or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl; or
- (d) m is 1 and R₃ is C₁-C₄ alkylthio, hydroxy, thio, -NR[']R^{''}, -SO₂R^{'''}, -NR[']-CO-R^{'''} or -CO₂R^{'''}, wherein R['] and R^{''} are the same or different and represent hydrogen or C₁-C₄ alkyl and R^{'''} represents C₁-C₄ alkyl; or
- (e) R₄ is -A₄-Het₄-L₄-Het₄[']-L₄[']

Further preferred compounds of formula (I) are compounds of formula (Ia), and pharmaceutically acceptable salts thereof,



wherein:

- A₁['] is an unsubstituted S,S-dioxothiomorpholino group, a pyrrolidinyl group substituted with -NH-SO₂-R^{'''} or is, more preferably, a moiety



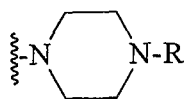
wherein R represents -S(O)₂-(C₁-C₄ alkyl), -S(O)₂-(C₁-C₄ haloalkyl), -CONHR^{'''},

- COR^{'''}, -CO-CO-OR^{'''}, -CO-(C₁-C₂ alkylene)-OR^{''}, -CO-(C₁-C₂ alkylene)-NR^{''}R^{''}, -CO-(C₁-C₂ alkylene)-NH-CO-R^{'''}, -CO-(C₁-C₂ alkylene)-SO₂-R^{'''}, -CO-(C₁-C₂ alkylene)-O-(C₁-C₂ alkylene)-OR^{''}, -SO₂-(C₁-C₄ alkylene)-OH, -NH-SO₂-R^{'''}, -(C₁-C₂ alkylene)-CO-(C₁-C₂ alkylene)-CO₂-R^{'''} and -SO₂(C₁-C₂ alkylene)-SO₂-R^{'''}, wherein each R^{''} is
- 5 the same or different and represents hydrogen or C₁-C₄ alkyl and each R^{'''} is the same or different and represents C₁-C₄ alkyl;
- n is 0 or 1;
 - R₂ represents hydroxy, -N(R^{'''})₂, -NH-CO-R^{'''} or -SO₂-R^{'''}, wherein R^{'''} represents C₁-C₄ alkyl;
- 10 - R₃ represents C₁-C₂ alkyl, C₁-C₂ alkoxy, halogen, C₁-C₂ haloalkoxy, C₁-C₂ haloalkyl or -NR[']R^{''}, wherein R['] and R^{''} are the same or different and each represent C₁-C₂ alkyl;
- B represents -NH-CO-NH-, -CO-NH- or -NH-CO-;
 - R₄ represents -A₄, -A₄-A₄['], -L₄-A₄, -A₄-L₄-A₄['], -A₄-Het₄-L₄-Het₄[']-L₄['] or
- 15 -L₄-Het₄-L₄['];
- R₅ is C₁-C₂ alkoxy, C₁-C₂ haloalkyl or halogen;
 - p is 0 or 1;
 - each A₄ is a phenyl, 5- to 6- membered heteroaryl or C₃-C₆ cycloalkyl group (preferably a phenyl, piperidinyl, pyridyl, piperazinyl, pyrrolidinyl, cyclopropyl or
- 20 cyclohexyl group) which is unsubstituted or substituted by a C₁-C₂ alkyl group;
- each A₄['] moiety is a phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl group (preferably a morpholinyl, phenyl, 2,6-dioxopiperidinyl or triazolyl group) which is unsubstituted or substituted by a C₁-C₂ alkyl group;
 - L₄ is a C₁-C₂ alkylene group;
- 25 - each Het₄ and Het₄['] are the same or different and represent -O- or -NR[']-, wherein R['] represents hydrogen or C₁-C₂ alkyl; and
- L₄['] is a C₁-C₂ alkyl group.

Typically, in these further preferred compounds of the invention, either:

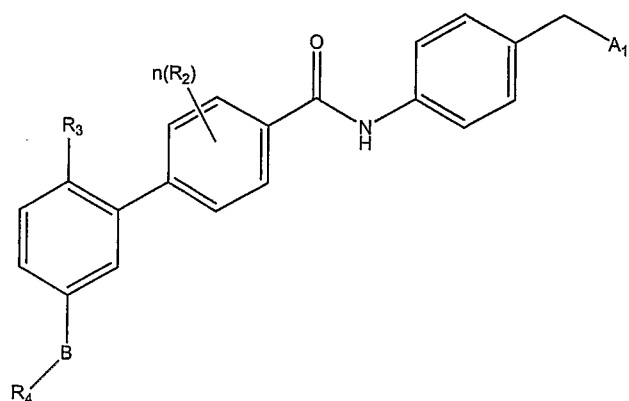
- (a) A₁['] is a moiety

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- wherein R is $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ haloalkyl})$, $-\text{CO}-\text{R}'''$, $-\text{CO}-\text{CO}-\text{OR}'''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{OR}''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{NR}''\text{R}''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{NH}-\text{CO}-\text{R}'''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-\text{R}'''$, $-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{O}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{OR}''$, $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{OH}$, $-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{CO}-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{CO}_2-\text{R}'''$ or $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-\text{R}'''$, wherein each R'' is the same or different and represent hydrogen or C_1-C_4 alkyl and each R''' is the same or different and represents C_1-C_4 alkyl;
- (b) n is 1; or
- (c) R_3 is $-\text{NR}'\text{R}''$, wherein R' and R'' are the same or different and each represent C_1-C_2 alkyl; or
- (d) R_4 represents $-\text{A}_4-\text{Het}_4-\text{L}_4-\text{Het}_4'-\text{L}_4'$.

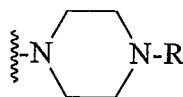
In one embodiment, preferred compounds of formula (I) are compounds of formula (Ia'), and pharmaceutically acceptable salts thereof,



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wherein:

- A_1' is an unsubstituted S,S-dioxothiomorpholino group, or is a moiety

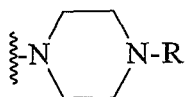


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wherein R represents $-\text{CO}-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ haloalkyl})$ or $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ alkyl})$;

- n is 0 or 1;
- R_2 represents hydroxy or $-\text{SO}_2-\text{R}'''$, wherein R''' represents C_1-C_4 alkyl;

- R_3 represents C_1 - C_2 alkyl, C_1 - C_2 alkoxy, halogen, C_1 - C_2 haloalkoxy, C_1 - C_2 haloalkyl or $-NR'R''$, wherein R' and R'' are the same or different and each represent C_1 - C_2 alkyl;
 - B represents $-NH-CO-NH-$, $-CO-NH-$ or $-NH-CO-$;
 - 5 - R_4 represents $-A_4$, $-A_4-A_4'$, $-A_4-L_4-A_4'$, $-A_4-Het_4-L_4-Het_4'-L_4'$ or $L_4-Het_4-L_4'$;
 - each A_4 is a phenyl, 5- to 6- membered heteroaryl or C_3 - C_6 cycloalkyl group (preferably a phenyl, piperidinyl, pyridyl, piperazinyl, pyrrolidinyl, cyclopropyl or cyclohexyl group) which is unsubstituted or substituted by a C_1 - C_2 alkyl group;
 - each A_4' moiety is a phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered
 - 10 heterocyclyl group (preferably a morpholinyl, phenyl, 2,6-dioxopiperidinyl or triazolyl group) which is unsubstituted or substituted by a C_1 - C_2 alkyl group;
 - L_4 is a C_1 - C_2 alkylene group;
 - each Het_4 and Het_4' are the same or different and represent $-O-$ or $-NR'-$, wherein R' represents hydrogen or C_1 - C_2 alkyl; and
 - 15 - L_4' is a C_1 - C_2 alkyl group.
- Typically, in this embodiment, either:
- (a) A_1' is a moiety

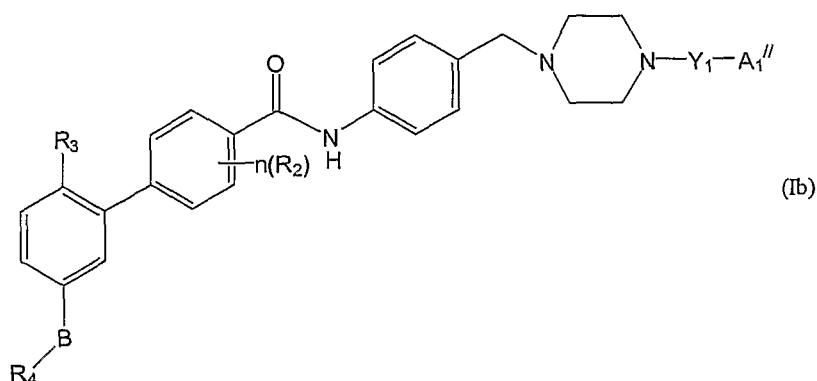


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wherein R is $-CO-(C_1-C_4 \text{ alkyl})$, $-SO_2-(C_1-C_2 \text{ haloalkyl})$ or $-SO_2-(C_1-C_2 \text{ alkylene})-SO_2-(C_1-C_2 \text{ alkyl})$,

- (b) n is 1; or
- (c) R_3 is $-NR'R''$, wherein R' and R'' are the same or different and each
- 25 represent C_1 - C_2 alkyl; or
- (d) R_4 represents $-A_4-Het_4-L_4-Het_4'-L_4'$.

Further preferred embodiments of formula (I) are compounds of formula (Ib), and pharmaceutically acceptable salts thereof



wherein R_4 , B, R_3 , n and R_2 are as defined in the formula (I), Y_1 is $-\text{CO}-\text{CH}_2-$, $-\text{CO}-\text{CH}_2-\text{NH}-$, $-\text{CO}-$, $-\text{CO}-\text{NH}-$ or $-\text{NH}-\text{CO}-$ and A_1'' is a phenyl, 5- to 6- membered heterocyclyl or C_3 - C_6 carbocyclyl group (preferably a phenyl, C_3 - C_6 cycloalkyl, morpholino, S,S-dioxo-thiomorpholino, pyrrolidin-2-onyl, imidazolin-2-onyl or pyrimidin-2,4 (1H, 3H)-dionyl group) which is unsubstituted or substituted by 1 or 2 substituents selected from C_1 - C_4 alkyl, halogen and hydroxy substituents.

The medicaments of the present invention are for use in treating or preventing a hepatitis C viral infection in the human or animal body. Preferably, the medicaments are for use in humans.

Compounds of formula (I) containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers. For the avoidance of doubt, the compounds of formula (I) can, if desired, be used in the form of solvates. Further, for the avoidance of doubt, the compounds of the invention may be used in any tautomeric form.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or *p*-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines and heterocyclic amines.

Especially preferred compounds of the invention include:

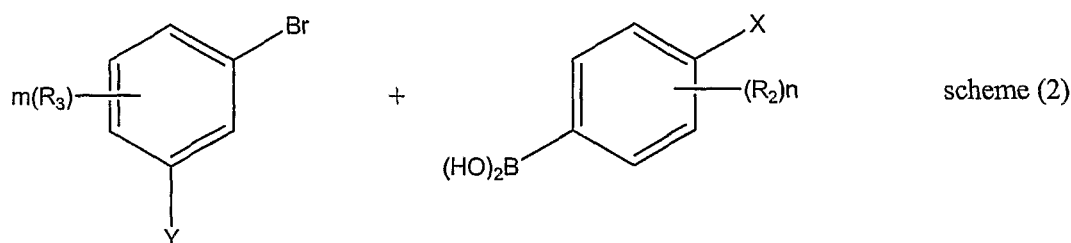
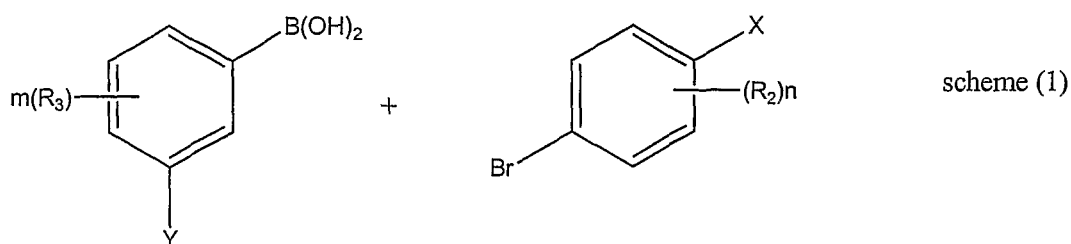
- 1 4-Methyl-piperazine-1-carboxylic acid {4'-[4-(4-acetyl-piperazin-1-ylmethyl)-
phenylcarbamoyl]-6-methyl-biphenyl-3-yl}-amide
- 2 (S)-Pyrrolidine-2-carboxylic acid {4'-[4-(4-acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-
methyl-biphenyl-3-yl}-amide
- 3 (R)-Pyrrolidine-2-carboxylic acid {4'-[4-(4-acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-
6-methyl-biphenyl-3-yl}-amide
- 4 2'-Methyl-5'-(2-methylamino-acetylamino)-biphenyl-4-carboxylic acid[4-(4-acetyl-piperazin-
1-ylmethyl)-phenyl]-amide
- 5 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-
trifluoromethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide
- 6 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-
trifluoromethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide
- 7 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-
methanesulfonylmethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide
- 8 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-
methanesulfonylmethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide
- 9 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-butyryl-
piperazin-1-ylmethyl)-phenyl]-amide
- 10 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-butyryl-
piperazin-1-ylmethyl)-phenyl]-amide
- 11 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-isobutyryl-
piperazin-1-ylmethyl)-phenyl]-amide.
- 12 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-isobutyryl-
piperazin-1-ylmethyl)-phenyl]-amide.
- 13 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-acetyl-
piperazin-1-ylmethyl)-phenyl]-amide.
- 14 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-acetyl-
piperazin-1-ylmethyl)-phenyl]-amide.
- 15 5'-(Cyclopropanecarbonyl-amino)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-
acetyl-piperazin-1-ylmethyl)-phenyl]-amide
- 16 5'-(Cyclohexanecarbonyl-amino)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-
acetyl-piperazin-1-ylmethyl)-phenyl]-amide

- 17 2'-Methyl-5'-(4-morpholin-4-yl-benzoylamino)-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide
- 18 5'-(Cyclopropanecarbonyl-amino)-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-Dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-amide
- 19 5'-(Cyclohexanecarbonyl-amino)-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-Dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-amide
- 20 5'-(Cyclopropanecarbonyl-amino)-2-hydroxy-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-Dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-amide
- 21 6-Trifluoromethoxybiphenyl-3,4'-dicarboxylic acid 4'-{[4-acetylpiperazin-1-yl-methyl)phenyl]amide} 3-[(4-morpholin-4-ylphenyl)amide]
- 22 6-Methoxy-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(1,1-dioxo-1 λ 6-thiomorpholin-4-ylmethyl)phenyl]amide} 3-({4-[(2-methoxyethyl)methylamino]phenyl}-amide)
- 23 6-Methyl-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(6-morpholin-4-yl-pyridin-3-yl)-amide]
- 24 6-Methyl-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(1-benzyl-piperidin-4-yl)-amide]
- 25 (S)-6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-{[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenyl]-amide}
- 26 (R)-6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-{[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenyl]-amide}
- 27 6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(4-[1,2,4]triazol-1-yl-phenyl)-amide]
- 28 6-Fluoro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(4-morpholin-4-yl-phenyl)-amide]
- 29 6-Dimethylamino-biphenyl-3,4'-dicarboxylic acid 3-[(4-morpholin-4-yl-phenyl)-amide 4'-({4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-amide)
- 30 6-Dimethylamino-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(4-morpholin-4-yl-phenyl)-amide]
- 31 (R)-Piperidine-2-carboxylic acid (4'-{4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}carbamoyl}-6-trifluoromethoxy-biphenyl-3-yl)-amide
- 32 5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

- 33 4-(4-{[5'-Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]-amino}-benzyl)-piperazine-1-carboxylic acid tert-butyl amide
- 34 4-(4-{[5'-Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]-amino}-benzyl)-piperazine-1-yl]-oxo-acetic acid ethyl ester
- 35 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-{4-[2-(2-methoxy-ethoxy)-acetyl]-piperazin-1-ylmethyl}-phenyl)-amide
- 36 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-methoxy-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 37 4-[4-(4-{[5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]amino}-benzyl)-piperazin-1-yl]-3-oxo-butyric acid ethyl ester
- 38 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(morpholine-4-carbonyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 39 (S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(5-oxo-pyrrolidin-2-carbonyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 40 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid 4-{4-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-acetyl]-piperazin-1-ylmethyl}-phenyl)-amide
- 41 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-oxo-imidazolin-4-carbonyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 42 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-phenylamino-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 43 (S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-dipropylamino-propionyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 44 (S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-hydroxy-propionyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 45 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-{4-[2-(1,1-dioxo-1 λ 6*-thiomorpholin-4-yl)-acetyl]-piperazin-1-ylmethyl}-phenyl)-amide
- 46 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-amide
- 47 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-amide
- 48 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [3-chloro-4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

- 49 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [3-chloro-4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide
- 50 5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenyl]-amide
- 51 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenyl]-amide
- 52 5'-(Cyclohexanecarbonyl-amino)-3-dimethylamino-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-yl)-phenyl]-amide
- 53 3-Acetylamino-5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-yl)-phenyl]-amide
- 54 (S)-5'-(2-Pyrrolidin-2-yl-acetylamino)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide
- 55 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-methanesulfonyl-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 56 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-hydroxy-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 57 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-acetylamino-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 58 5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide
- 59 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(3-hydroxy-propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-amide
- 60 (S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[3-(propane-1-sulfonylamino)-pyrrolidin-1-ylmethyl]-phenyl}-amide
- and pharmaceutically acceptable salts thereof.

The compounds of formula (I) may be prepared by analogy with known methods. For example, they can be prepared by the following reactions:

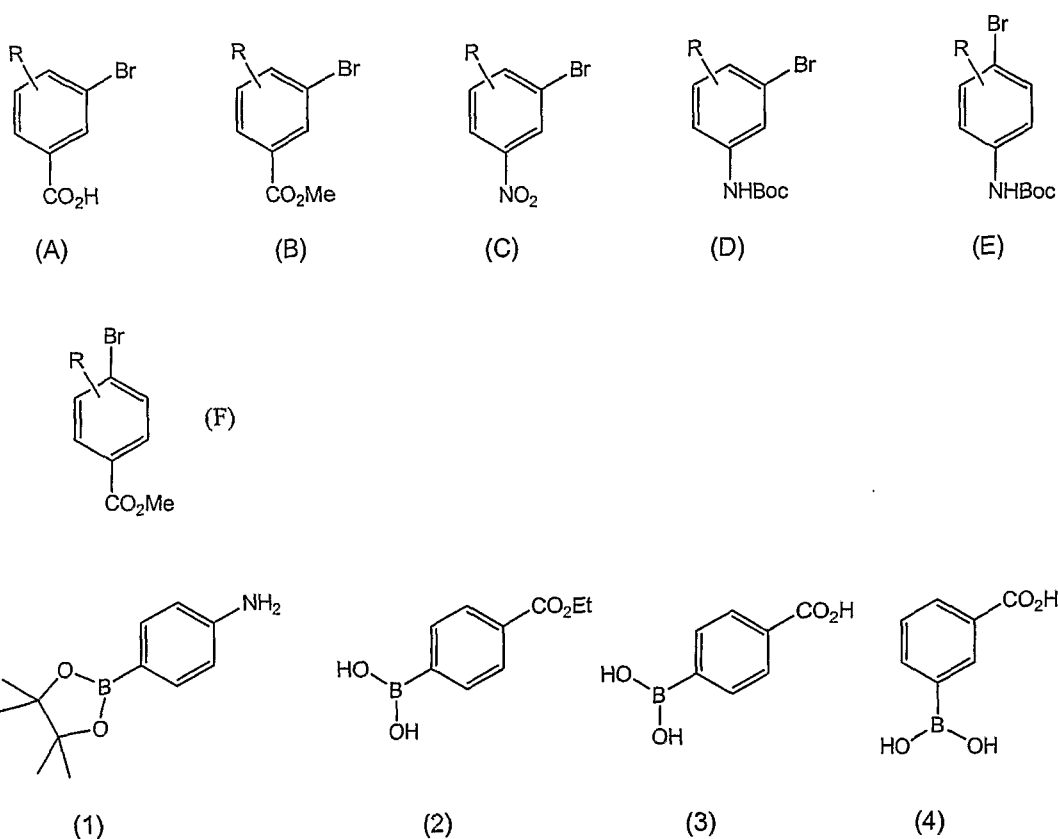


wherein R_2 , R_3 , n and m are as defined above, and either X and Y are,
 respectively, $-A-R_1$ or $-B-R_4$, wherein A , B , R_1 and R_4 are as defined above, or X and Y
 5 represent groups which can be further reacted by standard techniques to yield the
 moieties $-A-R_1$ or $-B-R_4$, for example amino groups or carbocyclic acid groups.

The coupling reactions shown in schemes (1) and (2) can be effected by known
 methods, for example cesium carbonate and palladium catalyst in aqueous DMF at
 reflux. The starting materials used in schemes (1) and (2) are known compounds or can
 10 be prepared by analogy with known methods.

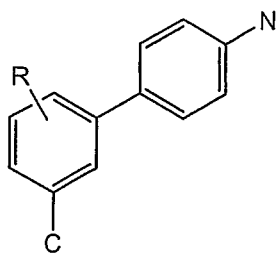
Methods for converting the moieties X and Y into moieties $-A-R_1$ and $-B-R_4$,
 and for converting moieties $-A-R_1$ and $-B-R_4$ into other moieties set out in the
 definitions of $-A-R_1$ and $-B-R_4$, are known to those of skill in the art. By way of
 example, some representative techniques are set out below.

15 Examples of Suzuki Coupling reaction.

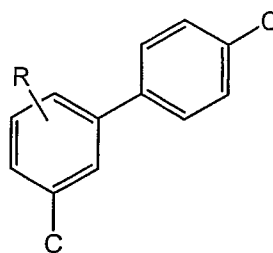


5 The above aryl bromides and boronic acids/esters can be coupled under standard conditions (cesium carbonate and palladium catalyst in aqueous DME at reflux) to provide a number of diverse biphenyl cores. These may have two carbonyl functionalities, two amino functionalities or one of both types. Some products from these reactions are shown below (for the sake of brevity, a substituent on the aromatic

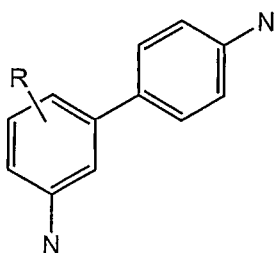
10 ring is either shown as "C" or "N" and the R_2 and R_3 substituents are simply shown as 'R').



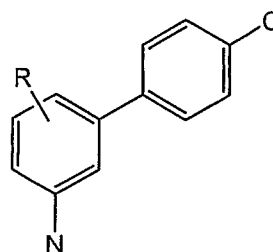
Product of: A/B1



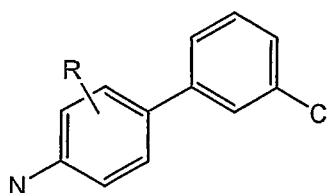
A/B2/3



Product of: C/D1,

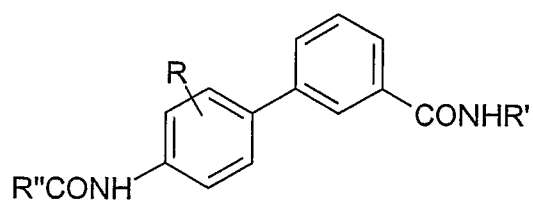
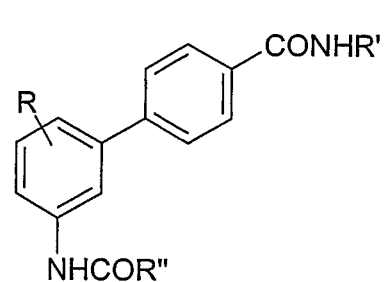
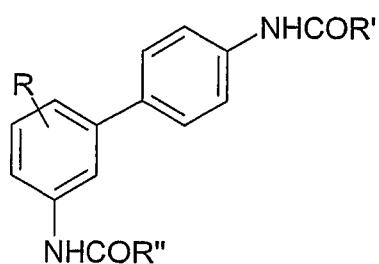
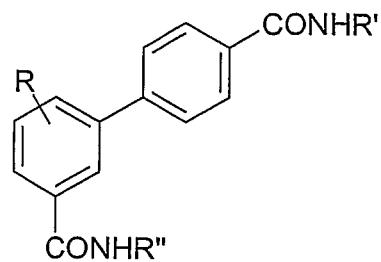
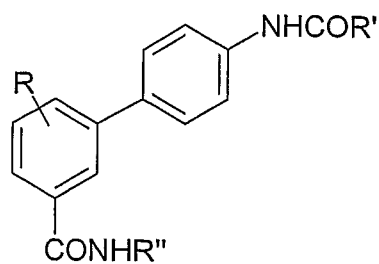


C/D2/3

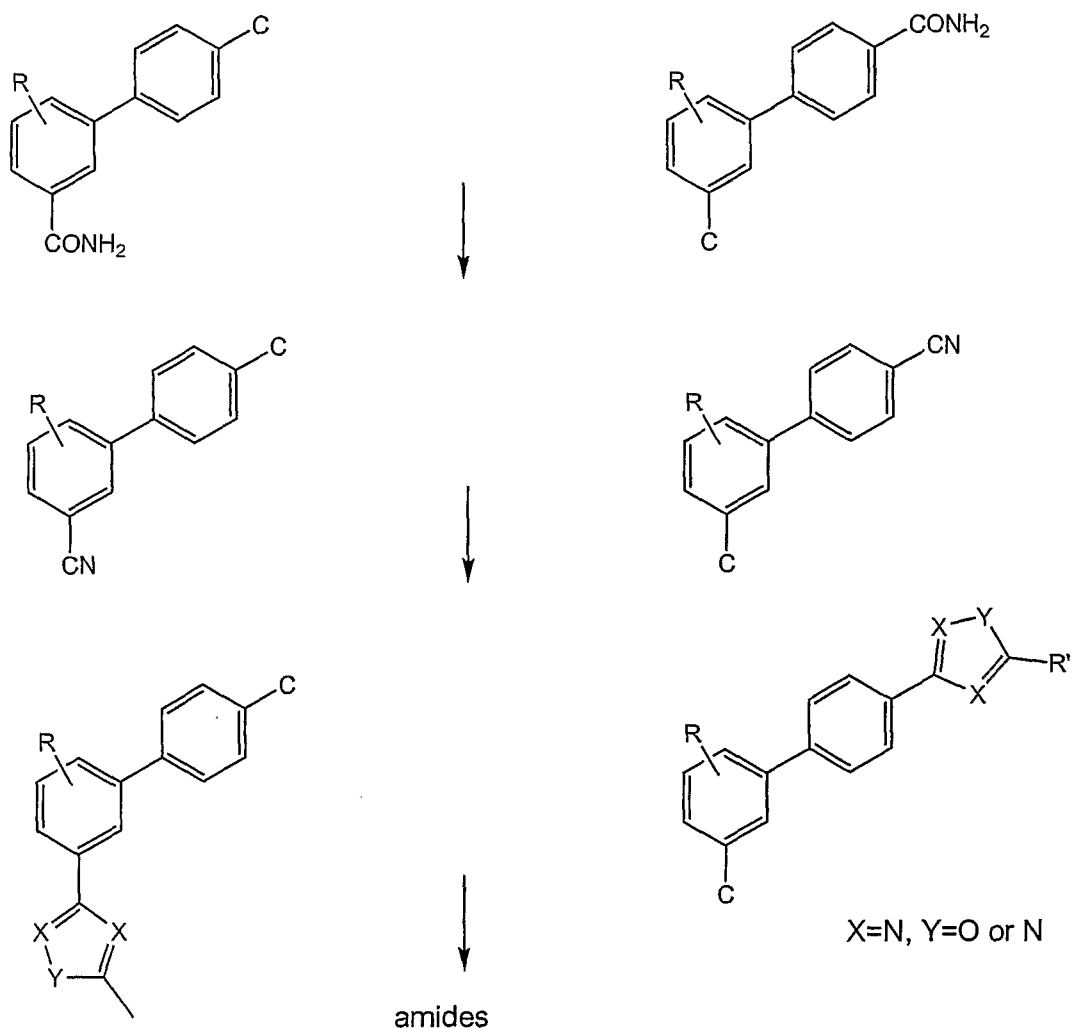


Product of: E4

- 5 By careful usage of monomers i.e. esters vs. acids and nitro groups vs. protected amines it can be seen that amide and reverse amide groups may be placed selectively at either end of the biphenyl core. The initial amide coupling reactions may be carried out by reaction of amines with acid chlorides, or by reaction with carboxylic acids and a suitable coupling reagent e.g. HBTU or EDAC/HOBT. Subsequent to this and
- 10 dependent on the second functionality to be converted to the second amide, a hydrolysis of an ester, a deprotection of a protected amine, or a hydrogenation of a nitro-group will then furnish intermediates which are readily coupled as described above to give the final compounds shown below.

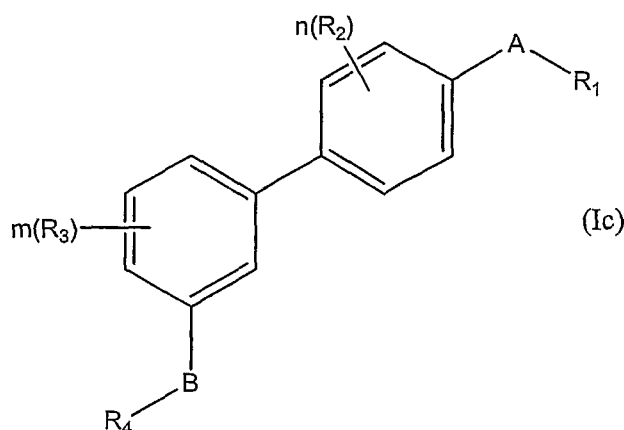


- 5 Analogues in which one of the amides has been replaced by a ring structure may be prepared, for example, via dehydration of a primary amide into a nitrile. Suitable adaptation of the nitrile furnishes compounds with heteroaromatic rings, e.g. 1,2,4-oxadiazoles or 1,2,4-triazoles. Replacement of the amide with aryl, carbocyclyl and heterocyclyl groups may be performed by analogy.



As explained above, the compounds of the invention are active against the hepatitis C virus. The present invention therefore provides a method for ameliorating a hepatitis C infection in a patient, which method comprises administering to said patient an effective amount of a biphenyl derivative of formula (I), as defined above, or a pharmaceutically acceptable salt thereof. Also provided is a method for alleviating or reducing the incidence of a hepatitis C infection in a patient, which method comprises administering to said patient an effective amount of a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof.

The present invention also provides a biphenyl derivative of formula (Ic) or a pharmaceutically acceptable salt thereof, for the treatment of the human or animal body,



wherein R_1 , R_2 , R_3 , R_4 , A , B , n and m are as defined for formula (I),

provided that either (i) when R_1 is $-A_1-L_1-A_1'$, the moiety A_1' carries a

5 substituent which is other than an alkyl group or (ii) R_3 is other than halogen or alkyl.

Preferably, in option (i), the substituent on A_1' is a single unsubstituted substituent selected from $-\text{CO}_2\text{R}'$, $-\text{SO}_2\text{NR}''\text{R}''$, $-\text{S}(\text{O})_2\text{-R}'$, $-\text{CONR}''\text{R}''$, $-\text{COR}'''$, $-\text{CO-CO-OR}'''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{R}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{-CO-R}'''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-CO-NR}''\text{R}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-SO}_2\text{-R}'''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{R}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{R}''$, $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{NR}''\text{-SO}_2\text{-R}'''$, $-\text{(C}_1\text{-C}_4\text{ alkylene)-CO-(C}_1\text{-C}_4\text{ alkylene)-CO}_2\text{-R}'''$, $-\text{(C}_1\text{-C}_4\text{ alkylene)-CO-(C}_1\text{-C}_4\text{ alkylene)-CO-NR}''\text{R}''$ and $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkylene)-SO}_2\text{-R}'$.

15 More preferably, in option (i) the substituent on A_1' is a single unsubstituted substituent selected from $-\text{SO}_2\text{NR}''\text{R}''$, $-\text{S}(\text{O})_2\text{-R}'$, $-\text{CONR}''\text{R}''$, $-\text{COR}'''$, $-\text{CO-CO-OR}'''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{R}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{-CO-R}'''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-CO-NR}''\text{R}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-SO}_2\text{-R}'''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{R}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{CO-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{-(C}_1\text{-C}_4\text{ alkylene)-NR}''\text{R}''$, $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkylene)-OR}''$, $-\text{NR}''\text{-SO}_2\text{-R}'''$, $-\text{(C}_1\text{-C}_4\text{ alkylene)-CO-(C}_1\text{-C}_4\text{ alkylene)-CO}_2\text{-R}'''$, $-\text{(C}_1\text{-C}_4\text{ alkylene)-CO-(C}_1\text{-C}_4\text{ alkylene)-CO-NR}''\text{R}''$ and $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkylene)-SO}_2\text{-R}'$.

Further, in the formula (Ic), A_1' is preferably other than cycloalkyl. Other preferred substituent definitions for the formula (Ic) of the invention are those set out above in connection with the definition of the compounds of formula (I) and in particular the substituent definitions in the formula (Ia) and (Ib).

5 Certain compounds of formula (Ic) are also believed to be novel. The present invention therefore also provides a biphenyl derivative of formula (Ic), as defined above, or a pharmaceutically acceptable salt thereof. In one embodiment, in the compounds of formula (Ic) A and B are the same or different and each represent $-NR'$ -CO-NR'', $-CO-NR'$ - or $-NR'-CO-$, wherein R' and R'' are the same or different and each
10 represent hydrogen or C_1 - C_4 alkyl.

Yet further the present invention provides a pharmaceutical composition comprising a biphenyl derivative of formula (Ic) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier. Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More
15 typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free. Further, the pharmaceutical compositions of the invention typically contain a compound of the invention which is a substantially pure optical isomer.

The compounds of the invention may be administered in a variety of dosage
20 forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

25 The compounds of the invention are typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g.
30 starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive

substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and
5 suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together
10 with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

15 Compounds of the present invention may be used in conjunction with known anti-viral agents. Preferred known anti-viral agents in this regard are interferon and ribavirin, which are known for the treatment of hepatitis C (Clinical Microbiology Reviews, Jan. 2000, 67-82). The said medicament therefore typically further comprises interferon and/or ribavirin. Further, the present invention provides a pharmaceutical
20 composition comprising:

- (a) a biphenyl derivative of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof;
- (b) interferon and/or ribavirin; and
- (c) a pharmaceutically acceptable carrier or diluent.

25 Also provided is a product comprising:

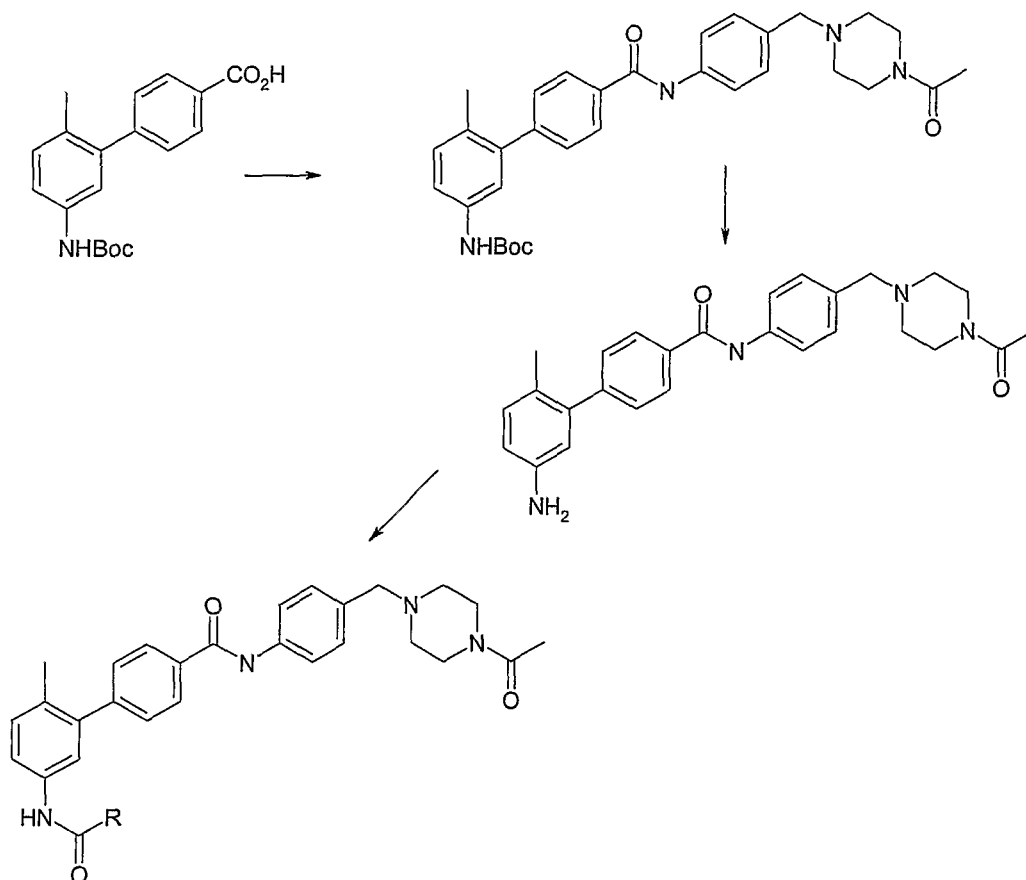
- (a) a biphenyl derivative of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof; and
- (b) interferon and/or ribavirin,

for separate, simultaneous or sequential use in the treatment of the human or
30 animal body.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.01 to 100 mg per kg of body weight, according to the activity of the specific compound, the age, weight and

conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 0.05 to 16 mg per kg of body weight, more preferably, from 0.05 to 1.25 mg per kg of body weight.

- 5 The following Examples illustrate the invention. They do not however, limit the invention in any way. In this regard, it is important to understand that the particular assay used in the Examples section is designed only to provide an indication of anti-hepatitis C activity. There are many assays available to determine such activity, and a negative result in any one particular assay is therefore not determinative.

EXAMPLES

5 **{4'-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-methyl-biphenyl-3-yl}-carbamic acid tert-butyl ester**

A mixture of 5'-tert-butoxycarbonylamino-2'-methyl-biphenyl-4-carboxylic acid (350mg), 1-[4-(4-Amino-benzyl)-piperazin-1-yl]-ethanone (236mg), HBTU (608mg) and N-methyl morpholine (0.3ml) in dry DMF (5ml) was stirred at room temperature for 18h. Water (10ml) was then added and the resulting colourless precipitate collected by filtration and dried (576mg).

5'-Amino-2'-methyl-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide (Intermediate Z)

15 {4'-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-methyl-biphenyl-3-yl}-carbamic acid tert-butyl ester (572mg) in dioxan (10ml) was treated with conc. hydrochloric acid (8ml) and the mixture stirred at room temperature for 1h. The

mixture was then basified and extracted with DCM. The dried organic layer was evaporated and the residue purified on a silica gel SPE cartridge. Elution with DCM:EtOH:ammonia; 200:8:1 gave a colourless gum (300mg).

5 Example 1

4-Methyl-piperazine-1-carboxylic acid {4'-[4-(4-acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-methyl-biphenyl-3-yl}-amide

Intermediate Z (60mg) and 4-methyl-piperazine-1-carbonyl chloride,
10 hydrochloride (54mg) were stirred at room temperature in dry DMF (3ml) containing N-methyl morpholine (0.1ml) for 18h. Water (10ml) was then added and the mixture was then extracted with DCM. The dried organic layer was evaporated and the residue purified on a silica gel SPE cartridge. Elution with DCM:EtOH:ammonia; 200:8:1 gave a colourless foam (28mg).
15 ¹H-NMR (CDCl₃, δ) 2.08 (s+m, 4H) 2.22 (s+m, 4H) 2.38-2.48 (m, 5H) 3.02 (s, 7H) 3.44-3.48 (m, 2H) 3.52 (s, 2H) 3.58-3.66 (m, 3H) 6.85 (d, 1H) 6.92 (dd, 1H) 7.18 (d, 1H) 7.33 (d, 2H) 7.44 (d, 2H) 7.56 (s, 1H) 7.67 (d, 2H) 7.92 (d, 2H) 8.33 (s, 1H)

20 Example 2

(S)-Pyrrolidine-2-carboxylic acid {4'-[4-(4-acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-methyl-biphenyl-3-yl}-amide

Intermediate Z (60mg) and (S)-pyrrolidine-1,2-dicarboxylic acid 1 tert-butyl ester
25 (29mg) were stirred at room temperature in dry DMF (3ml) containing HBTU (76mg) and N-methyl morpholine (0.03ml) for 18h. Water (10ml) was then added and the resulting colourless precipitate collected by filtration and dried (52mg).

This material was dissolved in dioxan (4ml) and was treated with conc.
30 hydrochloric acid (8ml) and the mixture stirred at room temperature for 4h. The mixture was then basified and extracted with DCM. The dried organic layer was evaporated and the residue purified on a silica gel SPE cartridge. Elution with DCM:EtOH:ammonia; 200:8:1 gave a colourless foam (16mg).

¹H-NMR (CDCl₃, δ) 1.62-1.74 (m, 2H) 1.84-2.01 (m+s, 6H) 2.04-2.18 (m+s, 5H) 2.29-2.38 (m, 4H) 2.84-3.06 (m, 2H) 3.36 (t, 2H) 3.43 (s, 2H) 3.53 (t, 2H) 3.72-3.80 (m, 1H) 7.15 (d, 1H) 7.24 (d, 2H) 7.31 (d, 2H) 7.41-7.47 (m, 2H) 7.59 (d, 2H) 7.82 (d, 2H) 8.22 (s, 1H) 9.67 (s, 1H)

5

Example 3

(R)-Pyrrolidine-2-carboxylic acid {4'-[4-(4-acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-methyl-biphenyl-3-yl}-amide

Example 3 was prepared as described for Example 2 except that (R)-pyrrolidine-1,2-dicarboxylic acid 1 tert-butyl ester was used. The title compound was isolated as a colourless foam (22mg)

¹H-NMR (CDCl₃, δ) 1.62-1.74 (m, 2H) 1.84-2.01 (m+s, 6H) 2.04-2.18 (m+s, 5H) 2.29-2.38 (m, 4H) 2.84-3.06 (m, 2H) 3.36 (t, 2H) 3.43 (s, 2H) 3.53 (t, 2H) 3.72-3.80 (m, 1H) 7.15 (d, 1H) 7.24 (d, 2H) 7.31 (d, 2H) 7.41-7.47 (m, 2H) 7.59 (d, 2H) 7.82 (d, 2H) 8.28 (s, 1H) 9.67 (s, 1H)

15

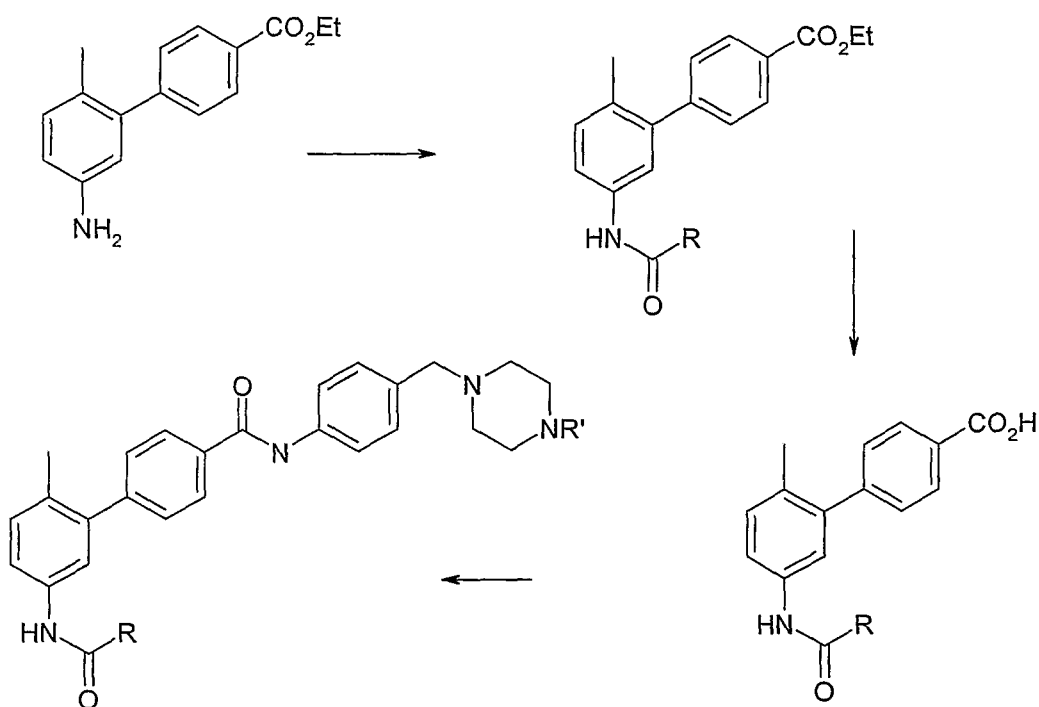
Example 4

2'-Methyl-5'-(2-methylamino-acetyl-amino)-biphenyl-4-carboxylic acid[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide

Example 4 was prepared as described for Example 2 except that (tert-butoxycarbonyl-methyl-amino)-acetic acid was used. The title compound was isolated as a colourless foam (29mg)

¹H-NMR (CDCl₃, δ) 1.98 (s, 3H) 2.13 (s, 3H) 2.30-2.37 (m, 5H) 2.40 (s, 3H) 3.24 (s, 2H) 3.36 (t, 2H) 3.42 (s, 2H) 3.53 (t, 2H) 7.15 (d, 1H) 7.23 (d, 2H) 7.29 (d, 2H) 7.39-7.46 (m, 2H) 7.60 (d, 2H) 7.82 (d, 2H) 8.35 (s, 1H) 9.20 (s, 1H).

25



5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid ethyl ester

5'-Amino-2'-methyl-biphenyl-4-carboxylic acid ethyl ester (737mg) and
 5 triethylamine (0.81ml) in dry THF (30ml) was treated with cyclopropane
 carbonyl chloride (0.26ml). The mixture was stirred at room temperature for 18h
 and then the solvent was evaporated. The residue was partitioned between
 water and DCM. The dried organic layer was then evaporated giving a beige
 solid (820mg).

10

**5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid
 (Intermediate Y)**

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid ethyl
 ester (620mg) in ethanol (30ml) and 2M NaOH (15ml) was stirred at room
 15 temperature for 18h. The mixture was then acidified and the ethanol
 evaporated. The resulting precipitate was collected by filtration and dried
 (560mg).

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid ethyl ester

20 5'-Amino-2'-methyl-biphenyl-4-carboxylic acid ethyl ester (737mg) and

triethylamine (0.81ml) in dry THF (30ml) was treated with cyclohexane carbonyl chloride (0.46ml). The mixture was stirred at room temperature for 18h and then the solvent was evaporated. The residue was partitioned between aqueous potassium carbonate and DCM. The dried organic layer was then evaporated
5 giving a sticky brown foam (1.1g).

**5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid
(Intermediate X)**

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid ethyl
10 ester (crude, 1.1g) in ethanol (30ml) and 2M NaOH (15ml) was stirred at room temperature for 18h. The mixture was then acidified and the ethanol evaporated. The resulting precipitate was collected by filtration and dried (640mg).

15 Example 5.

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-trifluoromethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

Intermediate Y (50mg) and 4-(4-trifluoromethanesulfonyl-piperazin-1-ylmethyl)-
phenylamine (52mg) were stirred at room temperature for 18h in the presence
20 of EDAC (29mg), HOBt (21mg) and N-methyl morpholine (0.035ml) in dry DMF (1ml). Water (6ml) was then added and the resulting colourless precipitate collected by filtration. This material was then purified via prep HPLC method A. Pure fractions combined and reduced in vacuo to yield 50mg of a tan solid.

¹H NMR (DMSO, δ) 0.98-1.00 (d,4H) 1.94-1.96 (m,1H) 2.40 (s,3H) 3.55 (m,2H)
25 3.73-3.84 (m,8H) 7.46-7.52 (m,3H) 7.68-7.75 (m,4H) 7.95-7.99 (d,2H) 8.20-8.23 (d,2H) 10.43 (s,1H) 10.52 (s,1H)

LCMS- ES+ = 643

Example 6

30 **5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-trifluoromethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide**

This material was prepared as Example 5 except that Intermediate X was used. The title compound was isolated as a tan solid (90mg)

¹H NMR (DMSO, δ) 1.24-1.43 (m, 5H) 1.65-1.77 (m, 5H) 2.20-2.22 (s, 3H) 2.32 (t, 1H) 3.37 (s, 2H) 3.50-3.53 (m, 8H) 7.26-7.33 (m, 3H) 7.48-7.59 (m, 4H) 7.77-7.80 (d, 2H) 8.01-8.05 (d, 2H) 9.85 (s, 1H) 10.34 (s, 1H)

LCMS- ES+ = 601

5

Example 7

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonylmethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

Intermediate Y (50mg) and 4-(4-methanesulfonylmethanesulfonyl-piperazin-1-ylmethyl)-phenylamine (59mg) were stirred at room temperature for 18h in the presence of EDAC (33mg), HOBT (23mg) and N-methyl morpholine (0.040ml) in dry DMF (1ml). Water (6ml) was then added and the resulting colourless precipitate collected by filtration. This material was then purified via prep HPLC method A. Pure fractions combined and reduced in vacuo to yield a yellow solid (17mg).

15

¹H NMR (DMSO, δ) 0.78-0.81 (d, 4H) 1.75-1.80 (m, 1H) 2.21 (s, 1H) 2.46-2.51 (m, 4H) 3.19 (m, 4H) 3.28 (m, 3H) 3.51 (s, 2H) 5.28 (s, 2H) 7.27-7.32 (m, 3H) 7.54-7.60 (m, 4H) 7.76-7.80 (d, 2H) 8.01-8.05 (d, 2H) 10.24 (s, 1H) 10.33 (s, 1H)

LCMS- ES+ = 625

20

Example 8

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonylmethanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

This material was prepared as Example 7 except that Intermediate X was used.

25 The title compound was isolated as a yellow solid (18mg)

¹H NMR (DMSO, δ) 1.04-1.74 (m, 5H) 1.74-1.82 (m, 5H) 2.20-2.22 (s, 3H) 2.35 (t, 1H) 2.46-2.51 (m, 4H) 2.71 (s, 3H) 3.19-3.31 (m, 4H) 3.51 (s, 2H) 5.28 (s, 2H) 7.29-7.32 (m, 2H) 7.48-7.59 (m, 4H) 7.77-7.80 (d, 2H) 8.01-8.05 (d, 2H) 8.36 (s, 1H) 9.88 (s, 1H) 10.35 (s, 1H)

30 LCMS- ES+ = 667

Example 9

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-butyl-1-piperazin-1-ylmethyl)-phenyl]-amide

Intermediate Y (50mg) and 4-(4-butyl-1-piperazin-1-ylmethyl)-phenylamine (45mg) were stirred at room temperature for 18h in the presence of EDAC (35mg), HOBT (23mg) and N-methyl morpholine (0.037ml) in dry DMF (1ml). Water (6ml) was then added and the resulting colourless precipitate collected by filtration. This material was then purified on silica gel. Gradient elution of 20% DCM:EtOH:ammonia;20:8:1 in DCM over 30mins gave the title compound as a tan solid (66mg).

¹H NMR (DMSO, δ) 0.78-0.81 (m,4H) 0.86-0.92 (t,3H) 1.47-1.56 (q,2H) 1.75-1.78 (m,1H) 2.21 (s,3H) 2.24-2.27 (m,2H) 2.30-2.36 (m,4H) 3.33 (m,2H) 3.48 (m,4H) 7.23-7.32 (m,3H) 7.48-7.56 (m,4H) 7.75-7.79 (d,2H) 8.02-8.05 (d,2H) 10.21 (s,1H) 10.30 (s,1H)

LCMS- ES+ = 539

Example 10

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-butyl-1-piperazin-1-ylmethyl)-phenyl]-amide

This material was prepared as Example 9 except that Intermediate X was used. The title compound was isolated as a tan solid (80mg)

¹H NMR (DMSO, δ) 0.90-0.96 (t,3H) 1.28-1.50 (m,4H) 1.53-1.56 (m,2H) 1.59 (t,1H) 1.78-1.86 (m,4H) 2.24 (s,3H) 2.28-2.34 (m,2H) 2.36-2.56 (m,4H) 3.37 (s,2H) 3.51 (m,4H) 7.26-7.36 (m,3H) 7.51-7.62 (m,4H) 7.79-7.83 (d,2H) 8.05-8.08 (d,2H) 9.85 (s,1H) 10.34 (s,1H)

LCMS- ES+ = 581

Example 11

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-isobutyl-1-piperazin-1-ylmethyl)-phenyl]-amide.

Intermediate Y (50mg) and 4-(4-isobutyl-1-piperazin-1-ylmethyl)-phenylamine (45mg) were stirred at room temperature for 18h in the presence of EDAC

(35mg), HOBT (23mg) and N-methyl morpholine (0.037ml) in dry DMF (1ml). Water (6ml) was then added and the resulting colourless precipitate collected by filtration. This material was then purified on silica gel. Gradient elution of 0-20% DCM:EtOH:ammonia;20:8:1 in DCM over 30mins gave the title compound
5 as an off-white solid (28mg).

¹H NMR (DMSO, δ) 0.63-0.66 (m,4H) 0.83-0.85 (d,6H) 1.62 (m,1H) 2.06 (s,3H) 2.19 (m,4H) 2.70 (m,1H) 3.18 (s,2H) 3.33 (m,4H) 7.08-7.17 (m,3H) 7.33-7.41 (m,4H) 7.60-7.64 (d,2H) 7.86-7.90 (d,2H) 10.05 (s,1H) 10.15 (s,1H)
10 LCMS- ES+ = 539

Example 12

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-isobutyryl-piperazin-1-ylmethyl)-phenyl]-amide.
15

This material was prepared as Example 11 except that Intermediate X was used. The title compound was isolated as an off-white solid (64mg)
¹H NMR (DMSO, δ) 1.02-1.05 (d,6H) 1.29-1.48 (m,6H) 1.79-1.87 (m,5H) 2.25 (s,3H) 2.55-2.57 (m,4H) 2.90 (m,1H) 2.35-2.38 (s,2H) 3.52 (m,4H) 7.27-7.37 (m,3H) 7.52-7.63 (m,4H) 7.80-7.83 (d,2H) 8.06-8.09 (d,2H) 9.86 (s,1H) 10.35 (s,1H)
20 LCMS- ES+ = 581

Example 13

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide.
25

Intermediate Y (50mg) and 4-(4-acetyl-piperazin-1-ylmethyl)-phenylamine (40mg) were stirred at room temperature for 18h in the presence of HBTU (64mg) and N-methyl morpholine (0.040ml) in dry DMF (1ml). Water (6ml) was then added and the resulting colourless precipitate collected by filtration. This material was then purified via prep HPLC method A. Pure fractions combined and reduced in vacuo to yield 24mg of an off-white solid.
30

¹H NMR (DMSO, δ) 0.78-0.80 (m,4H) 1.75-1.77 (m,1H) 1.99 (s,3H) 2.21 (s,3H)
 2.31-2.37 (m,4H) 3.18 (s,2H) 3.44 (m,4H) 7.28-7.32 (m,2H) 7.49-7.56 (m,4H)
 7.76-7.79 (d,2H) 8.01-8.04 (d,2H) 8.24 (s,1H) 10.25 (s,1H) 10.33 (s,1H)
 LCMS- ES+ = 511

5

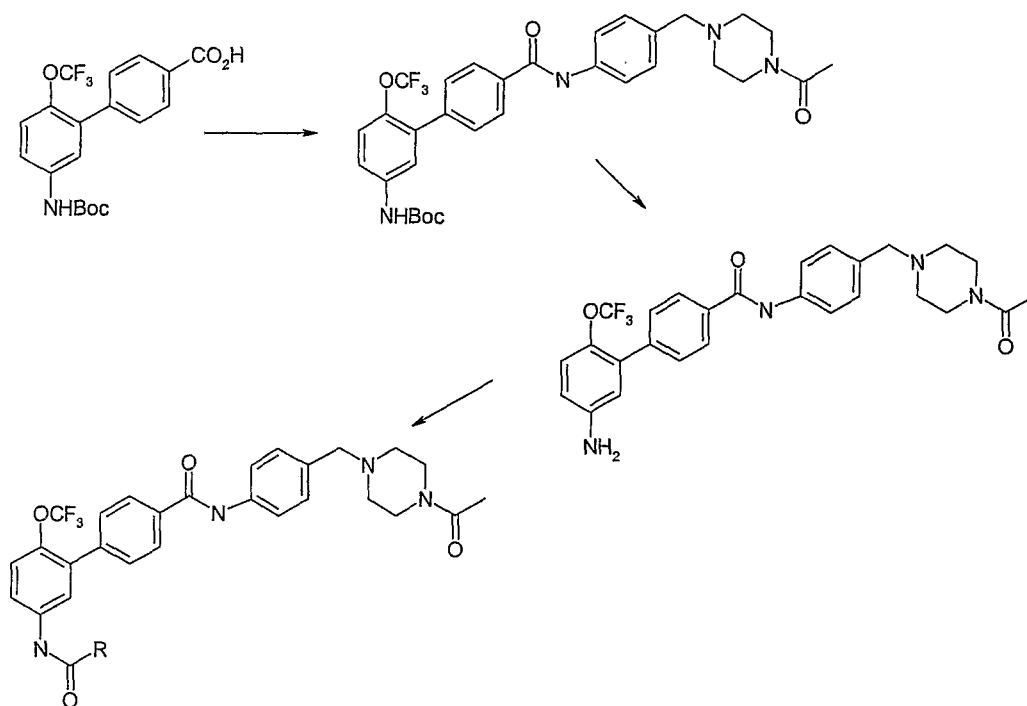
Example 14

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide.

- 10 This material was prepared as Example 13 except that Intermediate X was used. The title compound was isolated as an off-white solid (25mg)

¹H NMR (DMSO, δ) 1.24-1.43 (m,5H) 1.67-1.82 (m,5H) 1.99 (s,3H) 2.20 (s,3H)
 2.31 (t,1H) 2.32-2.37 (m,4H) 3.43 (m,4H) 3.48 (s,2H) 7.26-7.32 (m,3H) 7.48-
 7.58 (m,4H) 7.76-7.79 (d,2H) 8.01-8.05 (d,2H) 9.85 (s,1H) 10.33 (s,1H)

- 15 LCMS- ES+ = 553.



{4'-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-trifluoromethoxy-biphenyl-3-yl}-carbamic acid tert-butyl ester

A mixture of 5'-tert-butoxycarbonylamino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid (300mg), 1-[4-(4-Amino-benzyl)-piperazin-1-yl]-ethanone (176mg), EDAC (144mg), HOBt (102mg) and N-methyl morpholine (0.016ml) in dry DMF (3ml) was stirred at room temperature for 18h. Water (6ml) was then added and the resulting tan solid collected by filtration (462mg)

LCMS- ES+ = 613

10 5'-Amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide

{4'-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-trifluoromethoxy-biphenyl-3-yl}-carbamic acid tert-butyl ester (462mg) was dissolved in DCM (4ml) and trifluoroacetic acid (4ml) and was stirred at room temperature for 2h.

15 The mixture was then evaporated and the residue partitioned between aq sodium bicarbonate and ethyl acetate. The dried extracts were then evaporated giving a beige foam (316mg)

LCMS- ES+ = 513

20

Example 15

5'-(Cyclopropanecarbonyl-amino)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide

25 5'-Amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide (35mg) in dry THF (1ml) was treated with cyclopropanecarbonylchloride (0.015ml) and diisopropylethylamine (0.048ml). The mixture was stirred at room temperature for 18h and was then evaporated. The residue was then purified on silica gel. Gradient elution of 0-20% DCM:EtOH:ammonia;20:8:1 in DCM over 30mins gave the title compound as an off-white solid (11mg).

30

¹H NMR (DMSO, δ) 0.83-0.85 (d,4H) 1.79-1.81 (m,1H) 1.99 (s,3H) 2.31-2.38 (m,4H) 3.43-3.48 (m,4H) 3.48 (s,2H) 7.29-7.32 (m,2H) 7.46-7.49 (d,1H) 7.63-

7.71 (m,2H) 7.72-7.79 (m,3H) 7.86-7.87 (d,1H) 8.05-8.08 (d,2H) 10.35 (s,1H)
10.53 (s,1H)
LCMS- ES+ = 581

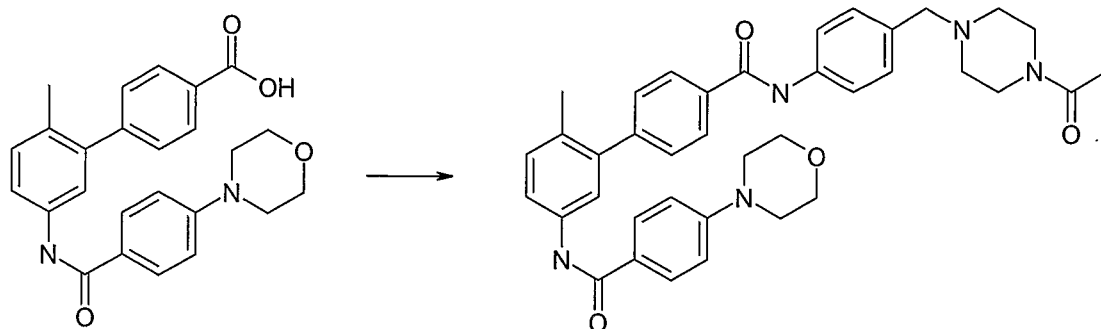
5 Example 16

**5'-(Cyclohexanecarbonyl-amino)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid
[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide**

This material was prepared as Example 15 except that
10 cyclohexanecarbonylchloride was used. The title compound was isolated as an
off-white solid (28mg)
¹H NMR (DMSO, δ) 0.99-1.24 (m,2H) 1.26-1.45 (m,4H) 1.68-1.85 (m,4H) 1.99
(s,3H) 2.31-2.51 (m,4H) 3.43 (m,4H) 3.48 (s,2H) 7.29-7.32 (d,2H) 7.44-7.45
(d,1H) 7.59-7.63 (d,2H) 7.73-7.79 (m,3H) 7.88-7.89 (d,1H) 8.05-8.08 (d,2H)
15 10.13 (s,1H) 10.35 (s,1H)
LCMS- ES+ = 623

2'-Methyl-5'-(4-morpholin-4-yl-benzoylamino)-biphenyl-4-carboxylic acid ethyl ester
5'-Amino-2'-methyl-biphenyl-4-carboxylic acid ethyl ester (2.15g), 4-morpholin-
20 4-yl benzoic acid (1.27g), N-methylmorpholine (2.05ml), 1-hydroxybenzotriazole
(826mg) and 1-ethyl-3-(3-(dimethylaminopropyl)carbodiimide hydrochloride
(1.17g) in dry DMF (30ml) was stirred at 20C for 18h. Then the DMF was
evaporated and the residue partitioned between water and dichloromethane.
The dried extracts were evaporated and the residue purified on silica gel.
25 Elution with 1-2% methanol in dichloromethane gave a colourless solid (2.4g)

2'-Methyl-5'-(4-morpholin-4-yl-benzoylamino)-biphenyl-4-carboxylic acid
(Intermediate W)
2'-Methyl-5'-(4-morpholin-4-yl-benzoylamino)-biphenyl-4-carboxylic acid ethyl
30 ester (2.4g) was stirred in a mixture of THF (25ml) and 1M sodium hydroxide
(50ml) at 100C for 4h. The mixture was allowed to cool and the THF was
evaporated. The residue was acidified and the resultant colourless precipitate
collected by filtration and dried (1.98g).



5

Example 17

2'-Methyl-5'-(4-morpholin-4-yl-benzoylamino)-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide

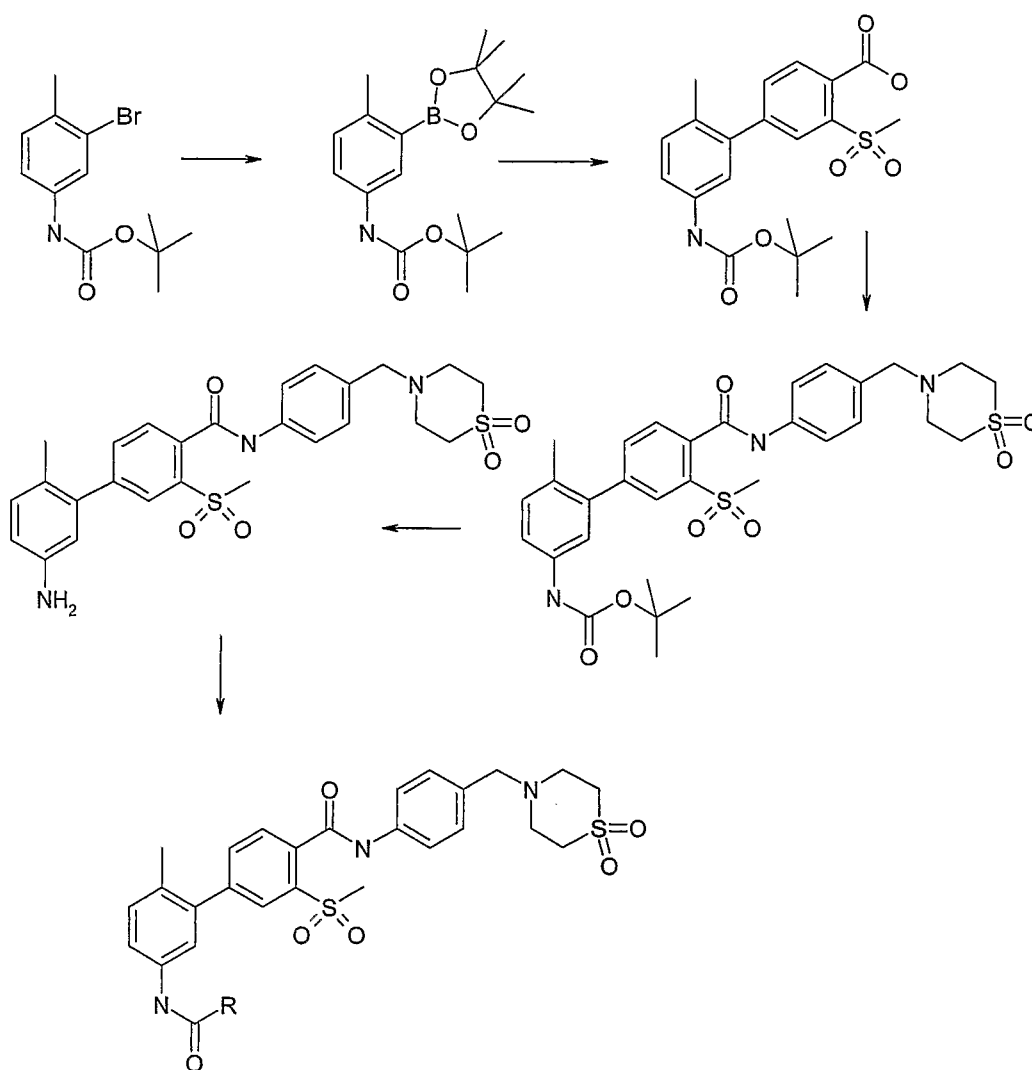
10 A mixture of Intermediate W (42mg), EDAC (19mg), HOBT (14mg) and N-methyl morpholine (20mg) in dry DMF (2ml) was treated with 1-[4-(4-Amino-benzyl)-piperazin-1-yl]-ethanone (23mg) and was stirred at room temperature for 18h. Water (6ml) was then added and the resulting colourless precipitate collected by filtration. This material was then purified via prep HPLC method A.

15 Pure fractions combined and reduced in vacuo to yield an off-white solid (28mg).

¹H NMR (DMSO, δ) 1.99 (s, 3H) 2.25 (s, 3H) 2.31-2.38 (m, 4H) 3.25-3.28 (m, 4H) 3.43-3.48 (m, 6H) 3.74-3.76 (m, 4H) 7.02-7.05 (d, 2H) 7.29-7.32 (d, 3H) 7.52-7.55 (d, 2H) 7.74-7.80 (m, 4H) 7.89-7.93 (d, 2H) 8.04-8.07 (d, 2H) 10.01 (s,

20 1H) 10.34 (s, 1H)

LCMS- ES+ = 632



**[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-carbamic acid
5 tert-butyl ester**

A solution of (3-bromo-4-methyl-phenyl)-carbamic acid tert-butyl ester (3.4g) and 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaboralanyl] (4.5g) in dry DMF (55ml) was treated with potassium acetate (5.8g) and (diphenylphosphinoferrocene) palladium dichloride (650mg) and was heated to 80C, under nitrogen, for 16h. The mixture was evaporated and the residue purified on silica. Gradient elution with 1-20% (4EtOAc:1Hexane) in Hexane over 40 mins gave an off-white solid (2.5g).

¹H NMR (DMSO, δ) 1.020-1.040 (s,6H) 1.165 (s,9H) 1.330 (s,6H) 2.370-2.377 (s,3H) 6.90 (d,1H) 7.20 (s,1H) 7.65 (s,1H) 9.05 (s,1H)

5'-tert-Butoxycarbonylamino-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid.

- 5 [4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-carbamic acid tert-butyl ester (200mg), 4-bromo-2-methanesulfonyl-benzoic acid (167mg), cesium carbonate (390mg) and tetrakis(triphenylphosphine)palladium (70mg) in water (2ml) and DME (5ml) was heated to 165C for 25mins in the microwave.
- 10 The mixture was evaporated and the residue purified on silica. Gradient elution of 35-100% DCM:EtOH:ammonia;20:8:1 in DCM over 35mins gave a tan foam (180mg).
- LCMS- ES+ = 406

- 15 **{4'-[4-(1,1-Dioxo-1λ⁶-thiomorpholin-4-ylmethyl)-phenylcarbamoyl]-3'-methanesulfonyl-6-methyl-biphenyl-3-yl}-carbamic acid tert-butyl ester**

- A mixture of 5'-tert-butoxycarbonylamino-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid (180mg), 4-(1,1-dioxo-1λ⁶-thiomorpholin-4-ylmethyl)-phenylamine (120mg), EDAC (90mg), HOBt (62mg) and N-methyl morpholine
- 20 (0.14ml) in dry DMF (1ml) was stirred at room temperature for 18h. The mixture was evaporated and the residue purified on silica. Gradient elution of 0-30% DCM:EtOH:ammonia;20:8:1 in DCM over 35mins gave a tan solid (120mg).
- LCMS- ES+ = 628

- 25 **5'-Amino-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-dioxo-1λ⁶-thiomorpholin-4-ylmethyl)-phenyl]-amide**

- {4'-[4-(1,1-Dioxo-1λ⁶-thiomorpholin-4-ylmethyl)-phenylcarbamoyl]-3'-methanesulfonyl-6-methyl-biphenyl-3-yl}-carbamic acid tert-butyl ester (120mg) was dissolved in DCM (2ml) and trifluoroacetic acid (2ml) and was stirred at
- 30 room temperature for 2h. The mixture was then evaporated and the residue partitioned between aq sodium bicarbonate and DCM. The dried extracts were then evaporated giving a yellow oil (95mg)
- LCMS- ES+ = 528

Example 18

5'-(Cyclopropanecarbonyl-amino)-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-Dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-amide

A mixture of 5'-Amino-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid 4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenylamine (47mg) and N-methyl morpholine (0.02ml) was treated with cycpropanecarbonylchloride (0.010ml) and was stirred at room temperature for 18h. The mixture was then evaporated and the residue purified via prep HPLC method A. Pure fractions combined and reduced in vacuo to yield a white solid (12mg).

¹H NMR (DMSO, δ) 0.79-0.81 (d,4H) 1.76-1.81 (m,1H) 2.24 (s,3H) 2.88 (m,4H) 3.12 (m,4H) 3.46 (s,3H) 3.65 (s,2H) 7.28-7.35 (m,3H) 7.54-7.61 (m,2H) 7.68-7.72 (m,2H) 7.78-7.92 (m,4H) 10.31 (s,1H) 10.74 (s,1H)

LCMS- ES+ = 596

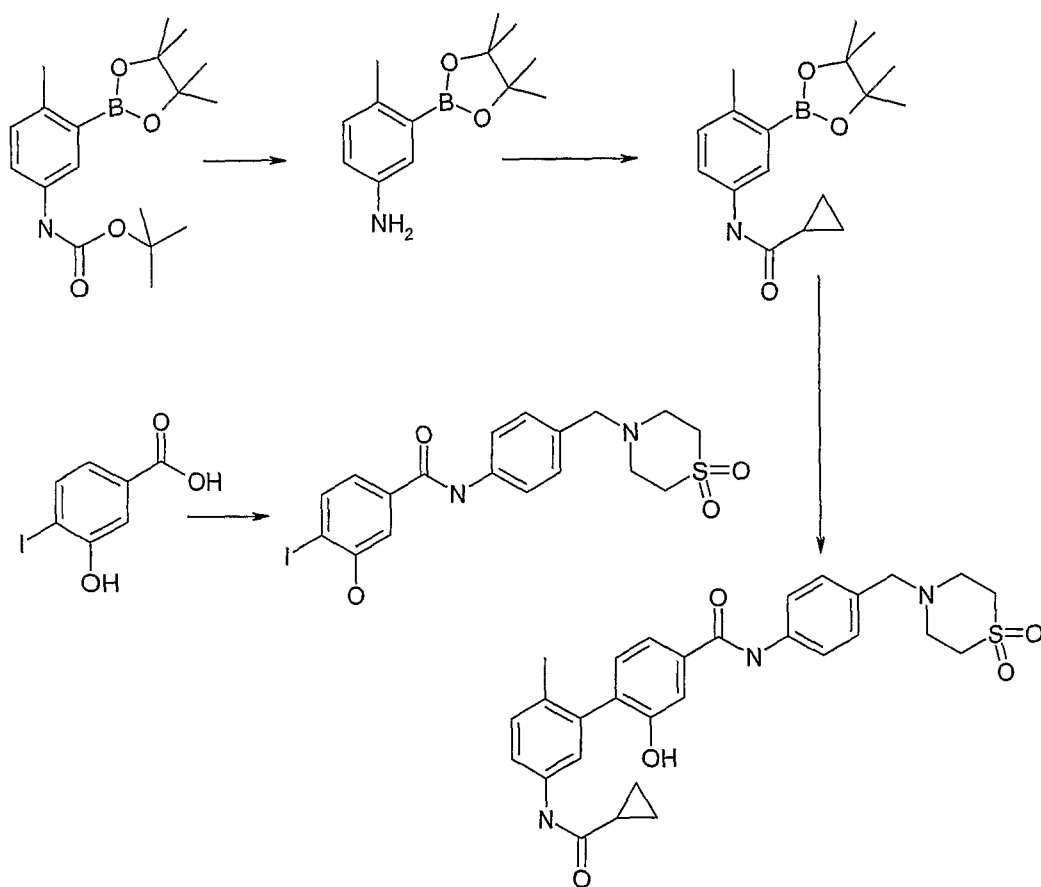
Example 19

5'-(Cyclohexanecarbonyl-amino)-3-methanesulfonyl-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-Dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-amide

This material was prepared as for Example 18 except that cyclohexanecarbonylchloride was used. The title compound was isolated as a pale yellow solid (14mg).

¹H NMR (DMSO, δ) 1.12-1.40 (m,6H) 1.64-1.79 (m,4H) 2.20 (s,3H) 2.25-2.30 (m,1H) 2.86-2.87 (m,4H) 3.09 (m,4H) 3.43 (s,3H) 3.62 (s,2H) 7.24-7.29 (m,3H) 7.51-7.69 (m,4H) 7.75-7.88 (m,3H) 9.88 (s,1H) 10.71 (s,1H)

LCMS- ES+ = 638



4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine

[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-carbamic acid
 5 tert-butyl ester (78mg) was dissolved in DCM (2ml) and trifluoroacetic acid (2ml)
 and was stirred at room temperature for 2h. The mixture was then evaporated
 and the crude trifluoroacetate salt used crude in the following step (yellow oil,
 81mg)

LCMS- ES+ = 234

10

Cyclopropanecarboxylic acid [4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide

4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (80mg) in
 dry DCM (2ml) was treated with N-methyl morpholine (0.08ml) and
 15 cyclopropanecarbonylchloride (0.025ml) and was stirred at room temperature for
 72h. The mixture was then evaporated and the residue partitioned between aq

sodium bicarbonate and ethyl acetate. The dried extracts were then evaporated giving a yellow oil (70mg) which was used crude in the final step.

LCMS- ES+ = 302

5 **N-[4-(1,1-Dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-3-hydroxy-4-iodo-benzamide**

A mixture of 4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenylamine (90mg), 3-hydroxy-4-iodo-benzoic acid (100mg), EDAC (80mg), HOBT (60mg) and N-methyl morpholine (0.09ml) in dry DMF was stirred at room temperature
10 for 18h. The mixture was evaporated and the residue purified on silica. Gradient elution of 0-30% DCM:EtOH:ammonia;20:8:1 in DCM over 35mins gave a yellow solid (50mg).

Example 20

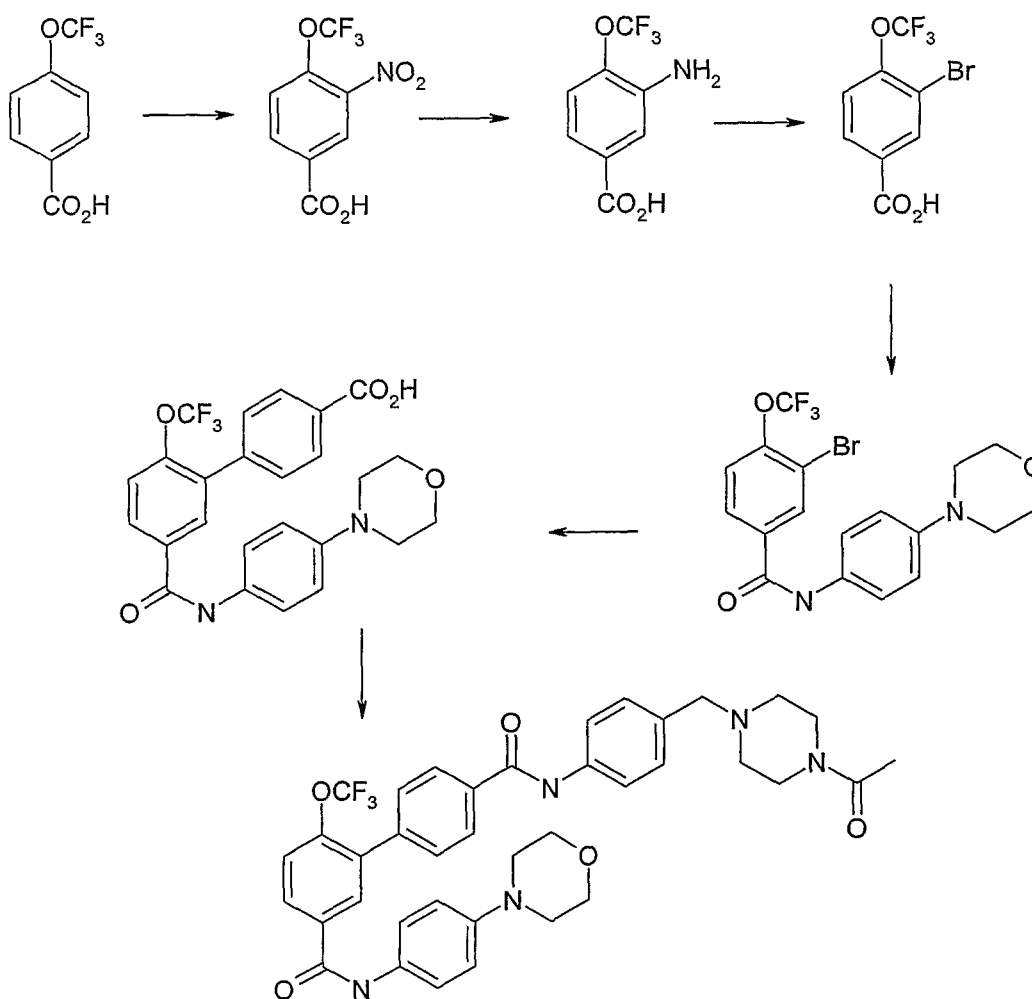
15 **5'-(Cyclopropanecarbonyl-amino)-2-hydroxy-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-Dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-amide**

A mixture of cyclopropanecarboxylic acid [4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (70mg), N-[4-(1,1-Dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-3-hydroxy-4-iodo-benzamide (50mg), cesium
20 carbonate (33mg) and tetrakis(triphenylphosphine)palladium (10mg) in water (5ml) and DME (10ml) was heated to reflux for 16h. The mixture was then partitioned between saturated potassium carbonate solution and ethyl acetate. The dried extracts were evaporated and the residue purified on silica.

Gradient elution of 0-30% DCM:EtOH:ammonia;20:8:1 in DCM over 35mins
25 gave a tan solid (6mg).

¹H NMR (DMSO, δ) 0.82-0.84 (m,4H) 1.79-1.82 (m,1H) 2.13 (s,3H) 2.93-2.94 (m,4H) 3.15-3.17 (m,4H) 3.70 (s,2H) 7.21-7.24 (d,2H) 7.35-7.38 (d,2H) 7.47-7.54 (m,4H) 7.80-7.83 (d,2H) 9.82 (s,1H) 10.18 (s,1H) 10.29 (s,1H)

LCMS- ES+ = 534



3-Nitro-4-trifluoromethoxybenzoic acid

To a stirred solution of 4-trifluoromethoxybenzoic acid (2.96g) in concentrated sulphuric acid (19mL) at room temperature was added a mixture of concentrated nitric acid (8.5mL) and concentrated sulphuric acid (8.5mL) dropwise. After 15 min a white precipitate had formed. The reaction was slowly poured onto ice (approx. 100mL). Once the ice had melted the resulting suspension was filtered, and the residue washed with water (3 x 10mL) and then dried *in vacuo* to give the title compound as a white solid (3.41g).

^1H NMR (DMSO, δ) 7.87 (dd, 1H), 8.36 (dd, 1H), 8.59 (d, 1H), 14.05 (br. s).

LCMS- ES- = 250

3-Amino-4-trifluoromethoxybenzoic acid

A solution of 3-nitro-4-trifluoromethoxybenzoic acid (3g) in methanol (240mL) was hydrogenated at 50°C and 50 bar using H-cube apparatus. The methanol solution was evaporated giving the title compound as a white solid (2.58g).

- 5 ¹H NMR (DMSO, δ) 5.63 (br. s, 2H), 7.13 (dd, 1H), 7.20 (dd, 1H), 7.42 (d, 1H), 12.85 (br. s).

3-Bromo-4-trifluoromethoxybenzoic acid

- 10 To a stirred solution of 3-amino-4-trifluoromethoxybenzoic acid (2g) in a mixture of water (16mL) and 48% HBr (12mL) at 0°C was added a solution of sodium nitrite (0.64g) in water (8mL) drop-wise. After 15 min at 0°C the reaction mixture was diluted with water (12mL) and carefully poured onto a stirred solution of copper (I) bromide (1.32g) in 48% HBr (8mL) at room temperature. The resulting suspension was filtered, and the residue washed with water (3 x
- 15 5mL) and dried *in vacuo* to give the title compound as a beige solid (2.08g).
¹H NMR (DMSO, δ) 7.87 (dd, 1H), 8.26 (dd, 1H), 8.46 (d, 1H), 13.70 (br. s, 1H).
LCMS- ES- = 284.

3-Bromo-N-(4-morpholin-4-ylphenyl)-4-trifluoromethoxy-benzamide

- 20 A solution of 3-bromo-4-trifluoromethoxybenzoic acid (515mg), N-(4-aminophenyl)morpholine (323mg), EDAC (763mg), HOBt (538mg) and N-methylmorpholine (597μL) in DMF (5mL) was stirred at room temperature. After 1h, water (10mL) was added and the resulting suspension filtered. The residue was dried *in vacuo* and then purified by flash column chromatography,
- 25 eluting with 2 : 1 petroleum ether : ethyl acetate. The title compound was isolated as an off-white solid (532mg).
¹H NMR (DMSO, δ) 3.07 (t, 4H), 3.80 (t, 4H), 6.84 (d, 2H), 7.31 (dd, 1H), 7.42 (d, 2H), 7.68 (s, 1H), 7.76 (dd, 1H), 8.07 (s, 1H).
LCMS- ES+ = 446.

30

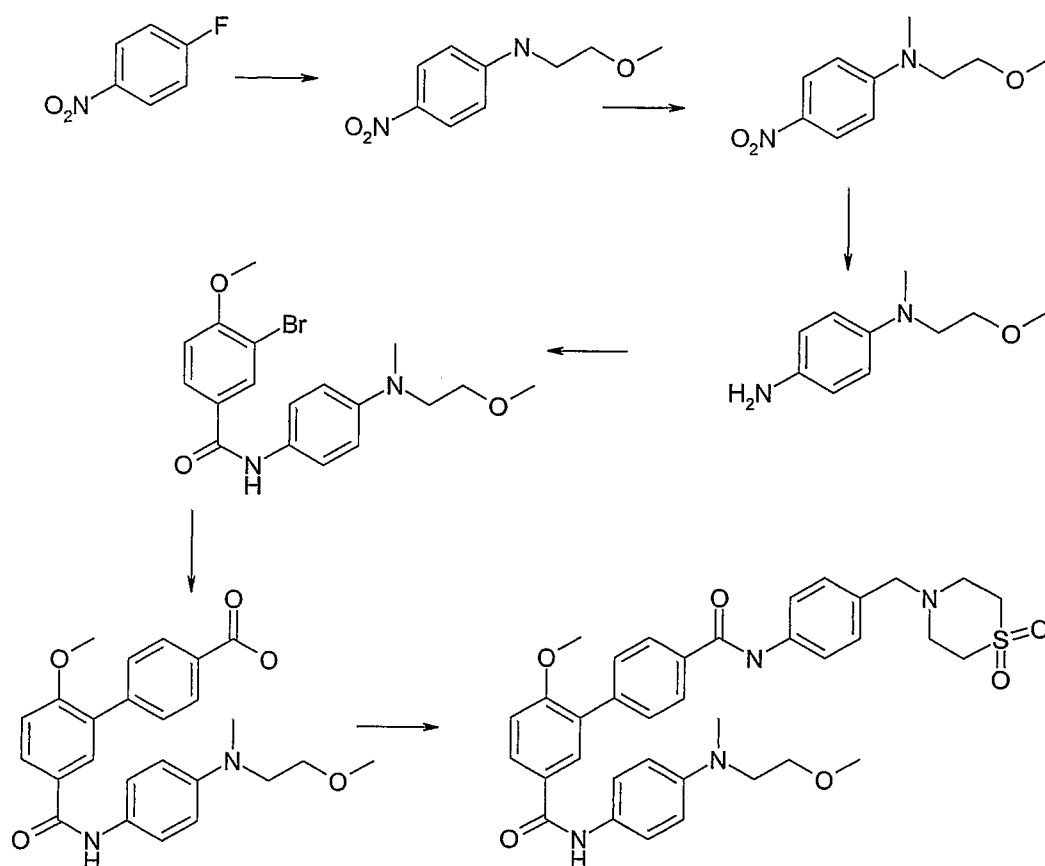
5'-(4-Morpholino-4-ylphenylcarbamoyl)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid

A mixture of 3-bromo-*N*-(4-morpholin-4-ylphenyl)-4-trifluoromethoxybenzamide (505mg), 4-carboxyphenylboronic acid (207mg) and tetrakis(triphenylphosphine)palladium (65mg) in DME (5mL) and a saturated aqueous solution of Na₂CO₃ (2.5mL) was heated to reflux. After 16h the reaction was allowed to cool to room temperature and then concentrated to dryness to yield a brown residue. The residue was taken up in water (10mL) and treated with a 2M aqueous solution of HCl until no further effervescence occurred. The resulting suspension was filtered and the residue washed with water (3 x 3mL) and dried *in vacuo* to give the title compound as a light brown solid (565mg).
¹H NMR (DMSO, δ) 3.14 (t, 4H), 3.80 (t, 4H), 7.01 (d, 2H), 7.68 (m, 6H), 8.12 (d, 2H), 8.21 (s, 1H).
LCMS- ES+ = 487.

Example 21

6-Trifluoromethoxybiphenyl-3,4'-dicarboxylic acid 4'-{[4-acetyl]piperazin-1-yl-methyl)phenyl]amide} 3-[(4-morpholin-4-ylphenyl)amide]

A solution of 5'-(4-morpholino-4-ylphenylcarbonyl)-2'-trifluoromethoxybiphenyl-4-carboxylic acid (100mg), 1-[4-(4-amino-benzyl)-piperazin-1-yl]ethanone (50mg), EDAC (86mg), HOBt (61mg) and N-methylmorpholine (68μL) in DMF (1mL) was stirred at room temperature. After 16h, water (5mL) was added and the resulting suspension filtered. The residue was dried *in vacuo* and then purified by flash column chromatography, eluting with 400 : 8 : 1 CH₂Cl₂ : EtOH : NH₃. The title compound was isolated as an off-white solid (73mg).
¹H NMR (DMSO, δ) 1.99 (s, 3H), 2.32 (m, 2H), 2.38 (m, 2H), 3.09 (t, 3H), 3.43 (m, 4H), 3.48 (s, 2H), 3.76 (t, 4H), 6.97 (d, 2H), 7.31 (d, 2H), 7.64 (d, 2H), 7.71 (m, 5H), 8.13 (m, 4H), 10.26 (s, 1H), 10.37 (s, 1H).
LCMS- ES+ = 703.



(2-Methoxyethyl)-(4-nitrophenyl)amine

A mixture of 1-fluoro-4-nitrobenzene (1g), 2-methoxyethylamine (639mg) and potassium carbonate (1.17g) in acetonitrile (5mL) was heated at 80°C. After 16h the reaction was allowed to cool to room temperature and then filtered. The residue was washed with acetonitrile (3 x 5mL) and the combined filtrate and washings were concentrated in vacuo to give the title compound as a yellow solid (1.37g).

¹H-NMR (CDCl₃, δ) 3.40 (t, 2H), 3.44 (s, 3H), 3.66 (t, 2H), 4.88 (br. s, 1H), 6.58 (d, 2H), 8.12 (d, 2H).

LCMS- ES⁺ = 197.

(2-Methoxy-ethyl)-methyl-(4-nitrophenyl)amine

A mixture of (2-methoxy-ethyl)-(4-nitrophenyl)amine (1g), formaldehyde (5mL), formic acid (5mL) and water (10mL) was heated at reflux. After 1h the reaction was allowed to cool to room temperature and then concentrated *in vacuo* to

give an oily yellow residue. The residue was treated with a saturated aqueous solution of Na_2CO_3 until effervescence ceased. The resulting suspension was filtered and the collected solid washed with water (3 x 10mL) and dried *in vacuo* to give the title compound as a yellow solid (0.92g).

- 5 ^1H NMR (DMSO, δ) 3.05 (s, 3H), 3.29 (s, 3H), 3.52 (t, 2H), 3.56 (t, 3H), 6.57 (d, 2H), 8.04 (d, 2H).
LCMS- ES+ = 211.

N-(2-Methoxy-ethyl)-N-methyl-benzene-1,4-diamine

- 10 A solution of (2-methoxy-ethyl)-methyl-(4-nitrophenyl)amine (850mg) in methanol (80mL) was hydrogenated at 25°C and 40 bar using H-cube apparatus. The methanol solution was concentrated *in vacuo* to give the title compound as a viscous deep red oil (658mg).
 ^1H -NMR (CDCl_3 , δ) 2.90 (s, 3H), 3.40 (m, 7H), 6.69 (m, 4H).
15 LCMS- ES+ = 181.

Example 22

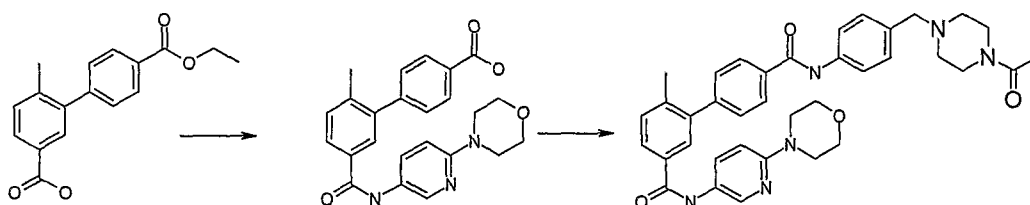
6-Methoxy-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(1,1-dioxo-1 λ ⁶-thiomorpholin-4-ylmethyl)phenyl]amide} 3-{[4-[(2-methoxyethyl)methylamino]phenyl]-amide}

- 20 A solution of 3-bromo-4-methoxybenzoic acid (130mg), N-(2-methoxyethyl)-N-methylbenzene-1,4-diamine (101mg), EDAC (238mg), HOBt (168mg) and N-methylmorpholine (185 μ L) in DMF (1mL) was stirred at room temperature. After 16h, water (5mL) was added and the resulting suspension filtered to give a
25 tacky brown solid that was used without further manipulation.
The above solid taken up in DME (3mL) and to the resulting solution was added 4-carboxyphenylboronic acid (103mg), tetrakis(triphenylphosphine)-palladium (32mg) and a saturated aqueous solution of sodium carbonate (1.5mL). The mixture was heated to reflux. After 16h the reaction was allowed to cool to
30 room temperature and concentrated to dryness. To the residue was added water (10mL) followed by the drop-wise addition of a 2M solution of HCl until no further precipitate was formed. Upon filtration the isolated solid became tacky in nature and was used without further manipulation.

The above solid was dissolved in DMF (2mL) and to this solution was added 4-(1,1-dioxo-1 λ^6 -thiomorpholin-4-ylmethyl)phenylamine (167mg), EDAC (215mg), HOBT (151mg) and N-methylmorpholine (185 μ L). The reaction was stirred at room temperature for 16h and then concentrated to dryness. The residue was purified by flash column chromatography, eluting with 400 : 8 : 1 CH₂Cl₂ : EtOH : NH₃ to give the title compound as an off-white solid (158mg).

¹H NMR (DMSO, δ) 2.91 (m, 5H), 3.13 (m, 4H), 3.27 (m, 2H), 3.49 (m, 4H), 3.67 (s, 2H), 3.89 (s, 3H), 6.72 (d, 2H), 7.34 (d, 2H), 7.61 (m, 4H), 7.74 (d, 2H), 7.77 (d, 2H), 8.01 (m, 2H), 8.06 (s, 1H), 9.92 (s, 1H), 10.31 (s, 1H).

LCMS- ES+ = 658.



2'-Methyl-5'-(6-morpholin-4-yl-pyridin-3-ylcarbamoyl)-biphenyl-4-carboxylic acid

To a solution of 6-methyl-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester (200mg)

in DMF (4ml) was added 6-morpholin-4-ylpyridin-3-ylamine (163mg), HOBT (123mg), EDAC (174mg) and N-methylmorpholine (200 μ L). The mixture was stirred at room temperature overnight and was then poured into water (40ml) and the resulting precipitate filtered under vacuum. Column chromatography (gradient elution with 0-20% 20:8:1 DCM:EtOH:NH₄OH in DCM) yielded the ethyl ester of the desired product.

This was dissolved in ethanol (4ml) and 2N NaOH (2ml) and the solution stirred at room temperature overnight.

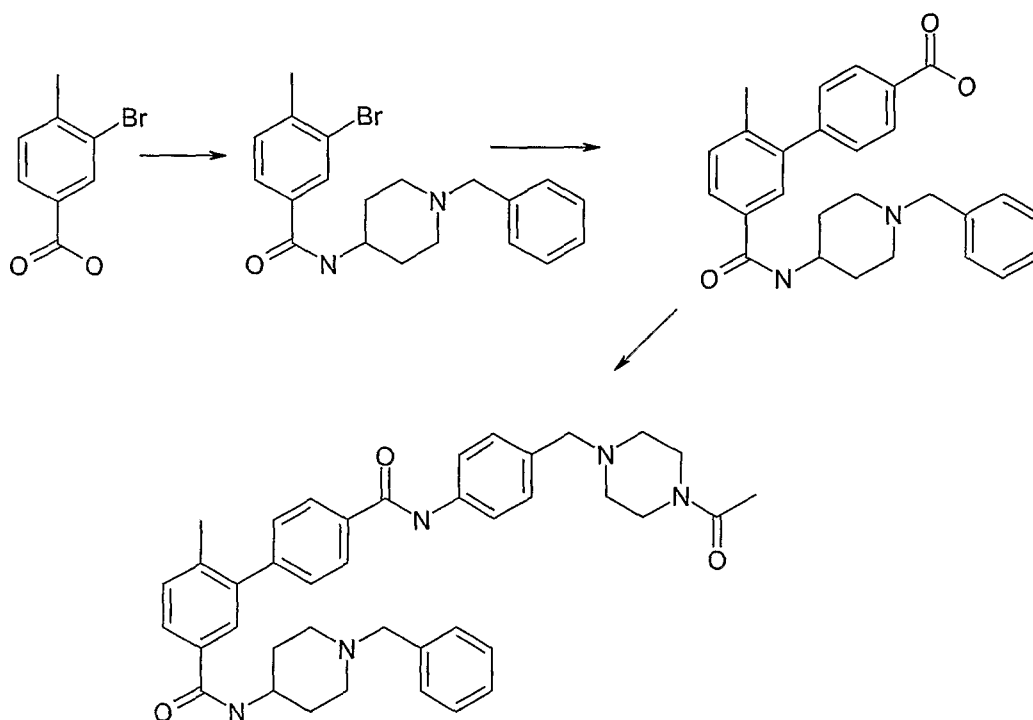
The mixture was evaporated under vacuum and the residues treated with 2N HCl (10ml). The resulting precipitate was filtered under vacuum and dried giving a yellow solid (173mg).

LCMS- ES+ = 418

Example 23

6-Methyl-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(6-morpholin-4-yl-pyridin-3-yl)-amide]

- To a solution of 2'-Methyl-5'-(6-morpholin-4-yl-pyridin-3-ylcarbamoyl)-biphenyl-4-carboxylic acid (50mg) in DMF (1ml) was added 1-[4-(4-amino-benzyl)-piperazin-1-yl]ethanone (37mg), HOBT (22mg), EDAC (31mg) and N-methylmorpholine (35ul). This mixture was stirred at room temperature overnight and was then poured into water (10ml) and the resulting precipitate filtered under vacuum. This material was then purified via prep HPLC method A.
- 10 Pure fractions combined and reduced in vacuo to yield a yellow solid (32mg).
¹H NMR (DMSO, δ) 2.10 (3H, s) 2.47 (7H, m) 3.54 (8H, m) 3.83 (4H, m) 5.88 (1H, s) 7.01 (1H, d) 7.44 (2H, d) 7.64 (1H, d) 7.74 (2H, d) 7.88 (2H, d) 8.01 (3H, m) 8.22 (2H, d) 8.35 (1H, s) 8.61 (1H, d) 10.28 (1H, s) 10.45 (1H, s)
 LCMS- ES+ = 633.

**5'-(1-Benzyl-piperidin-4-yl)-3-bromo-4-methyl-benzamide**

- To a solution of 3-bromo-4-methylbenzoic acid (1g) in DMF (10ml) was added 1-benzyl-piperidin-4-ylamine (1.05ml), HOBT (692mg), EDAC (982mg) and N-methylmorpholine (1.13ml). The mixture was stirred at room temperature overnight and was then poured into water (70ml). The resulting precipitate was
- 20

filtered under vacuum. The resulting solid was washed with water and dried *in vacuo* then used without purification (off-white solid, 1.771g)

LCMS- ES+ = 387,389.

5 5'-(1-Benzyl-piperidin-4-ylcarbamoyl)-2'-methyl-biphenyl-4-carboxylic acid

To a suspension of 5'-(1-Benzyl-piperidin-4-yl)-3-bromo-4-methyl-benzamide (1g) and 4-carboxyphenylboronic acid (428mg) in DME (20ml) and water (10ml) was added cesium carbonate (841mg) and tetrakis(triphenylphosphine)-palladium (149mg). The mixture was stirred at 80°C overnight and was then
10 evaporated and the residue diluted with water and extracted with ethyl acetate. The aqueous portion was acidified with 2N HCl and the resulting precipitate was filtered under vacuum and the solid washed with water and dried giving an off white solid (935mg)
LCMS- ES+ = 429.

15

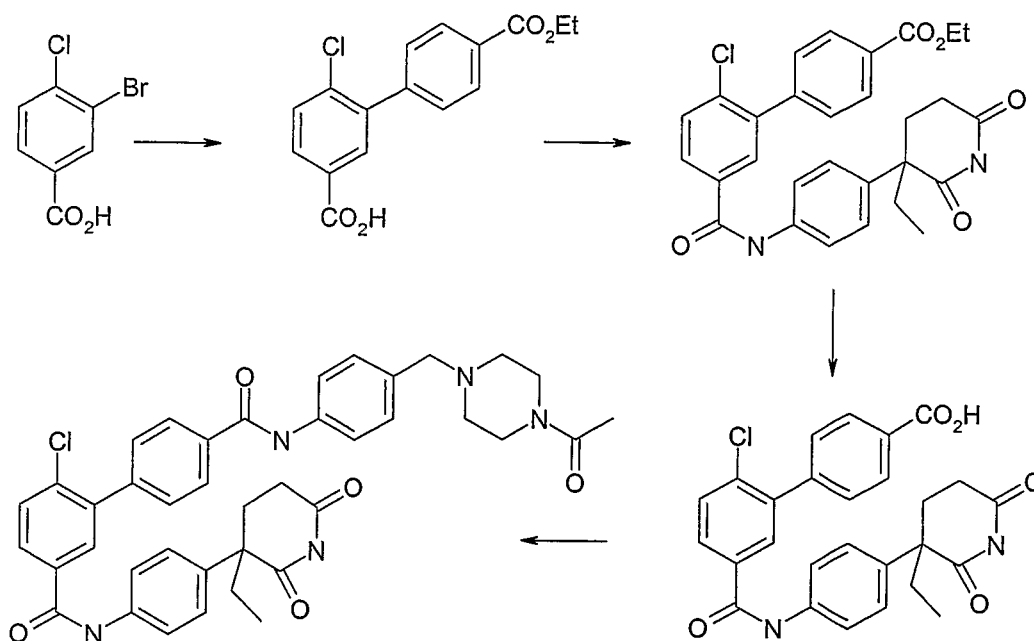
Example 24

6-Methyl-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-yl)methyl]-phenyl]-amide} 3-[(1-benzyl-piperidin-4-yl)-amide]

To a solution of 5'-(1-Benzyl-piperidin-4-ylcarbamoyl)-2'-methyl-biphenyl-4-carboxylic acid (50mg) in DMF (1ml) was added 1-[4-(4-amino-benzyl)-
20 piperazin-1-yl]ethanone (28mg), HOBT (22mg), EDAC (31mg) and N-methylmorpholine (35ul). The mixture was stirred at room temperature overnight and was then poured into water (10ml) and the resulting precipitate was filtered under vacuum This material was then purified via prep HPLC
25 method A. Pure fractions combined and reduced in *vacuo* to yield a yellow solid (50mg).

¹H NMR (DMSO, δ) 1.60 (2H, m) 1.76 (2H, m) 1.99 (6H, m) 2.38 (7H, m) 2.56 (3H, s) 2.81 (2H, d) 3.43 (4H, m) 3.48 (1H, m) 3.78 (1H, m) 7.32 (7H m) 7.44 (1H, d) 7.58 (2H, d) 7.97 (2H, d) 8.05 (2H, d) 8.36 (3H, m) 10.36 (1H, s)

30 LCMS- ES+ = 644.



6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester

- 5 To a suspension of 3-bromo-4-chlorobenzoic acid (1g) and 4-ethoxycarbonyl-phenylboronic acid (825mg) in DME (20ml) and water (10ml) was added cesium carbonate (2.07g) and tetrakis(triphenylphosphine)-palladium (246mg). The mixture was stirred at 80°C overnight and was then evaporated and the residue diluted with water and extracted with ethyl acetate. The aqueous portion was
- 10 acidified with 2N HCl and the resulting precipitate was filtered under vacuum and the solid washed with water and dried giving an off white solid (1.17g)
- ¹H-NMR (CDCl₃, δ) 1.36 (3H, t) 4.37 (2H, q) 7.19 (1H, m) 7.48 (3H, m) 8.06 (3H, m)
- LCMS- ES - = 303

15

(S)-2'-Chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid ethyl ester.

- To a solution of 6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester (300mg) and (S)-3-(4-amino-phenyl)-3-ethyl-piperidin-2,6-dione (250mg) in DMF (3ml)
- 20 was added HOBt (146mg), EDAC (200mg) and N-methylmorpholine (237ul).

The mixture was stirred at room temperature overnight and was poured into water (30ml) and the resulting precipitate filtered under vacuum.

Column chromatography (gradient elution with 50-100% EtOAc in pet. Ether) yielded an off-white solid (356mg)

5 LCMS- ES+ = 519, 521

(S)-2'-Chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid

(S)-2'-Chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid ethyl ester (356mg) was dissolved in EtOH (2ml) and 2N NaOH (1ml) and stirred at room temperature overnight. The reaction mixture was evaporated under vacuum and the residues treated with 2N HCl. The precipitate was filtered and the resulting tan solid dried and then used without purification (284mg)

15 LCMS- ES+ = 507, 509.

Example 25

(S)-6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-{[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenyl]-amide}

20 To a solution of (S)-2'-chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid (50mg) in DMF (1ml) was added 1-[4-(4-amino-benzyl)-piperazin-1-yl]ethanone (30mg), HOBt (18mg), EDAC (25mg) and N-methylmorpholine (30ul). The mixture was stirred at room temperature overnight and was poured into water (10ml) and the resulting precipitate was collected by filtration. This material was then purified via prep HPLC method A. Pure fractions combined and reduced in vacuo to yield a tan solid (7mg).

25 ¹H NMR (DMSO, δ) 0.79 (3H, t) 1.86 (2H, q) 1.99 (3H, s) 2.19 (2H, m) 2.31 (4H, m) 2.51 (2H, s) 3.41 (4H, m) 3.47 (2H, s) 7.32 (4H, d) 7.78 (7H, m) 8.09 (4H, m) 10.38 (2H, d)

30

LCMS- ES+ = 706

(R)-2'-Chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid ethyl ester.

To a solution of 6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester (300mg) and (R)-3-(4-amino-phenyl)-3-ethyl-piperidin-2,6-dione (250mg) in DMF (3ml) was added HOBT (146mg), EDAC (200mg) and N-methylmorpholine (237ul). The mixture was stirred at room temperature overnight and was poured into water (30ml) and the resulting precipitate filtered under vacuum. Column chromatography (gradient elution with 50-100% EtOAc in pet. Ether) yielded an off-white solid (320mg)

LCMS- ES+ = 519

(R)-2'-Chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid

(R)-2'-Chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid ethyl ester (320mg) was dissolved in EtOH (2ml) and 2N NaOH (1ml) and stirred at room temperature overnight. The reaction mixture was evaporated and the residues treated with 2N HCl. The precipitate was filtered and the resulting tan solid dried *in vacuo*, then used without purification (295mg)

LCMS- ES+ = 509

Example 26

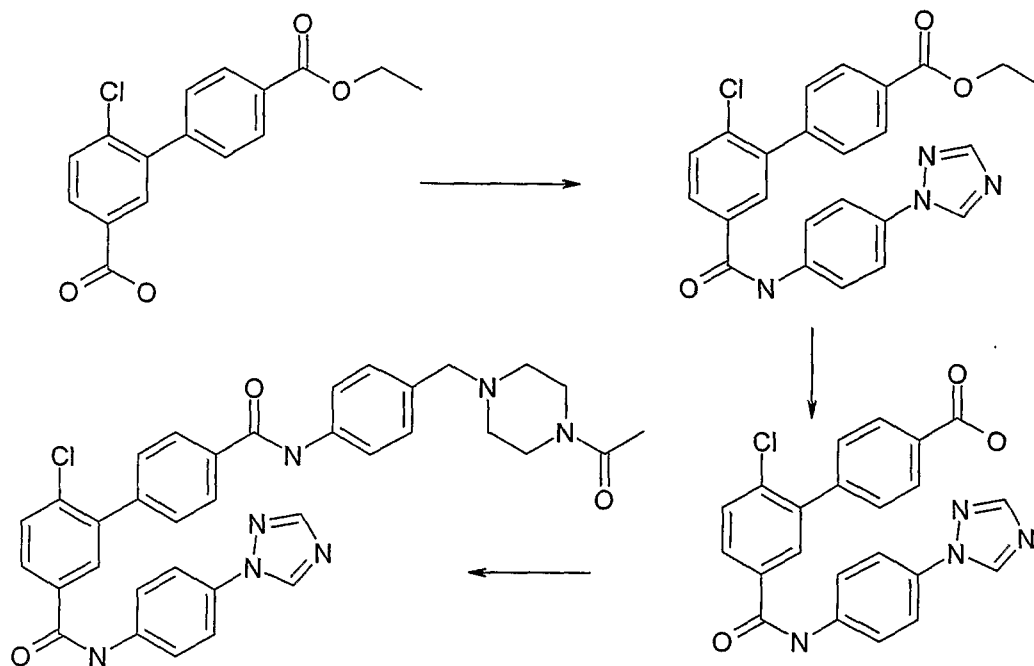
(R)-6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-{[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenyl]-amide}

To a solution of (R)-2'-chloro-5'-[4-(3-ethyl-2,6-dioxo-piperidin-3-yl)-phenylcarbamoyl]-biphenyl-4-carboxylic acid (50mg) in DMF (1ml) was added 1-[4-(4-amino-benzyl)-piperazin-1-yl]ethanone (30mg), HOBT (18mg), EDAC (25mg) and N-methylmorpholine (30ul). The mixture was stirred at room temperature overnight and was poured into water (10ml) and the resulting precipitate was collected by filtration. This material was then purified via prep HPLC method A. Pure fractions combined and reduced *in vacuo* to yield a tan solid (4mg).

^1H NMR (DMSO, δ) 0.79 (3H, t) 1.86 (2H, q) 1.99 (3H, s) 2.19 (2H, m) 2.31 (4H, m) 2.51 (2H, s) 3.41 (4H, m) 3.47 (2H, s) 7.32 (4H, d) 7.78 (7H, m) 8.09 (4H, m) 10.38 (2H, d)

LCMS- ES+ = 706.

5



2'-Chloro-5'-(4-[1,2,4]triazol-1-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester

- 10 To a solution of 6-chloro-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester (300mg) and 4-[1,2,4]triazol-1-yl-phenylamine (250mg) in DMF (3ml) was added HOBt (146mg), EDAC (200mg) and N-methylmorpholine (237ul). The mixture was stirred at room temperature overnight and was poured into water (30ml) and the resulting precipitate was collected by filtration
- 15 Column chromatography (gradient elution with 50-100% EtOAc in pet. Ether) yielded an off-white solid (121mg)
- LCMS- ES+ = 447

2'-Chloro-5'-(4-[1,2,4]triazol-1-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid

- 20 2'-Chloro-5'-(4-[1,2,4]triazol-1-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester (121mg) was dissolved in EtOH (2ml) and 2N NaOH (1ml) and

stirred at room temperature overnight. The reaction mixture was evaporated and the residue treated with 2N HCl. The precipitate was filtered and the resulting tan solid dried *in vacuo*, then used without purification (106mg)
LCMS- ES+ = 419

5

Example 27

6-Chloro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(4-[1,2,4]triazol-1-yl-phenyl)-amide]

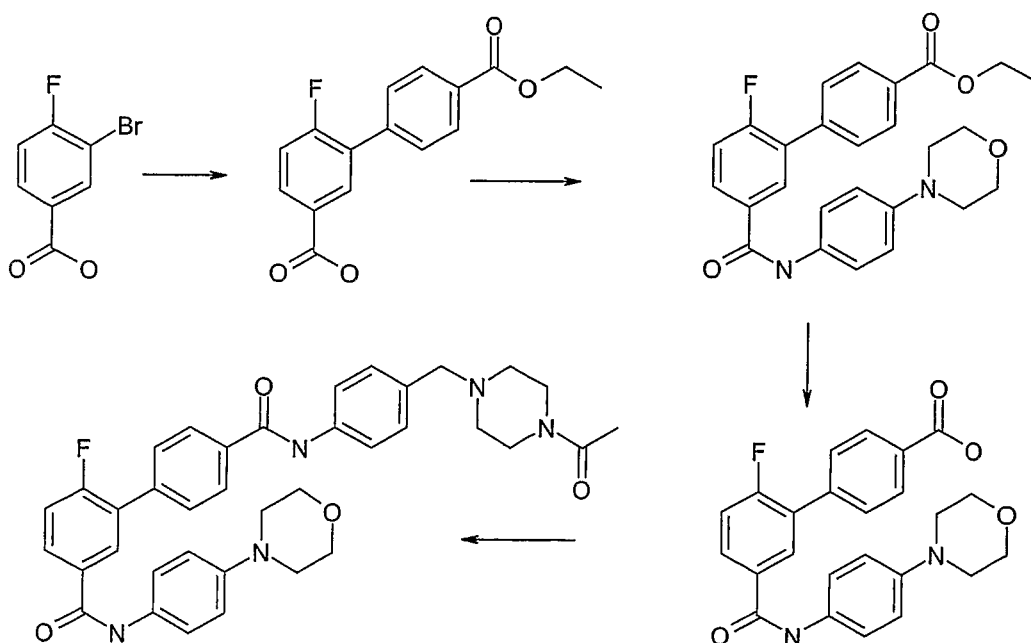
To a solution of 2'-Chloro-5'-(4-[1,2,4]triazol-1-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid (50mg) in DMF (1ml) was added 1-[4-(4-amino-benzyl)-piperazin-1-yl]ethanone (30mg), HOBt (18mg), EDAC (25mg) and N-methylmorpholine (30ul). The mixture was stirred at room temperature overnight and was poured into water (10ml) and the resulting precipitate was collected by filtration. This material was then purified via prep HPLC method A.

15

Pure fractions combined and reduced *in vacuo* to yield a tan solid (29mg).
¹H NMR (DMSO, δ) 1.97 (3H, s) 2.36 (4H, m) 3.41 (4H, m) 3.47 (2H, s) 7.31 (2H, d) 7.78 (7H, m) 7.94 (2H, d) 8.08 (4H, m) 8.22 (1H, s) 9.24 (1H, s) 10.36 (1H, s) 10.58 (1H, s)

LCMS- ES+ = 634

20



6-Fluoro-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester

To a suspension of 3-bromo-4-fluorobenzoic acid (500mg) and 4-ethoxycarbonyl-phenylboronic acid (442mg) in DME (10ml) and water (5ml) was added cesium carbonate (743mg) and tetrakis(triphenylphosphine)-palladium (132mg). The mixture was stirred at 80°C overnight and was then evaporated and the residue diluted with water and extracted with ethyl acetate. The aqueous portion was acidified with 2N HCl and the resulting precipitate was filtered under vacuum and the solid washed with water and dried giving an off white solid (432mg)

¹H-NMR (CDCl₃, δ) 1.34 (3H, t) 4.34 (2H, q) 7.50 (2H, m) 7.76 (2H, d) 8.06 (3H, m) 13.25 (1H, s)

LCMS- ES - = 287

2'-Fluoro-5'-(4-morpholin-4-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester

To a solution of 6-Fluoro-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester (300mg) and 4-morpholin-4-yl-phenylamine (203mg) in DMF (5ml) was added HOBt (156mg), EDAC (219mg) and N-methylmorpholine (251ul). The mixture was stirred at room temperature overnight and was poured into water (50ml) and the resulting precipitate filtered under vacuum giving an off-white solid (350mg)

LCMS- ES+ = 449

2'-Fluoro-5'-(4-morpholin-4-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid

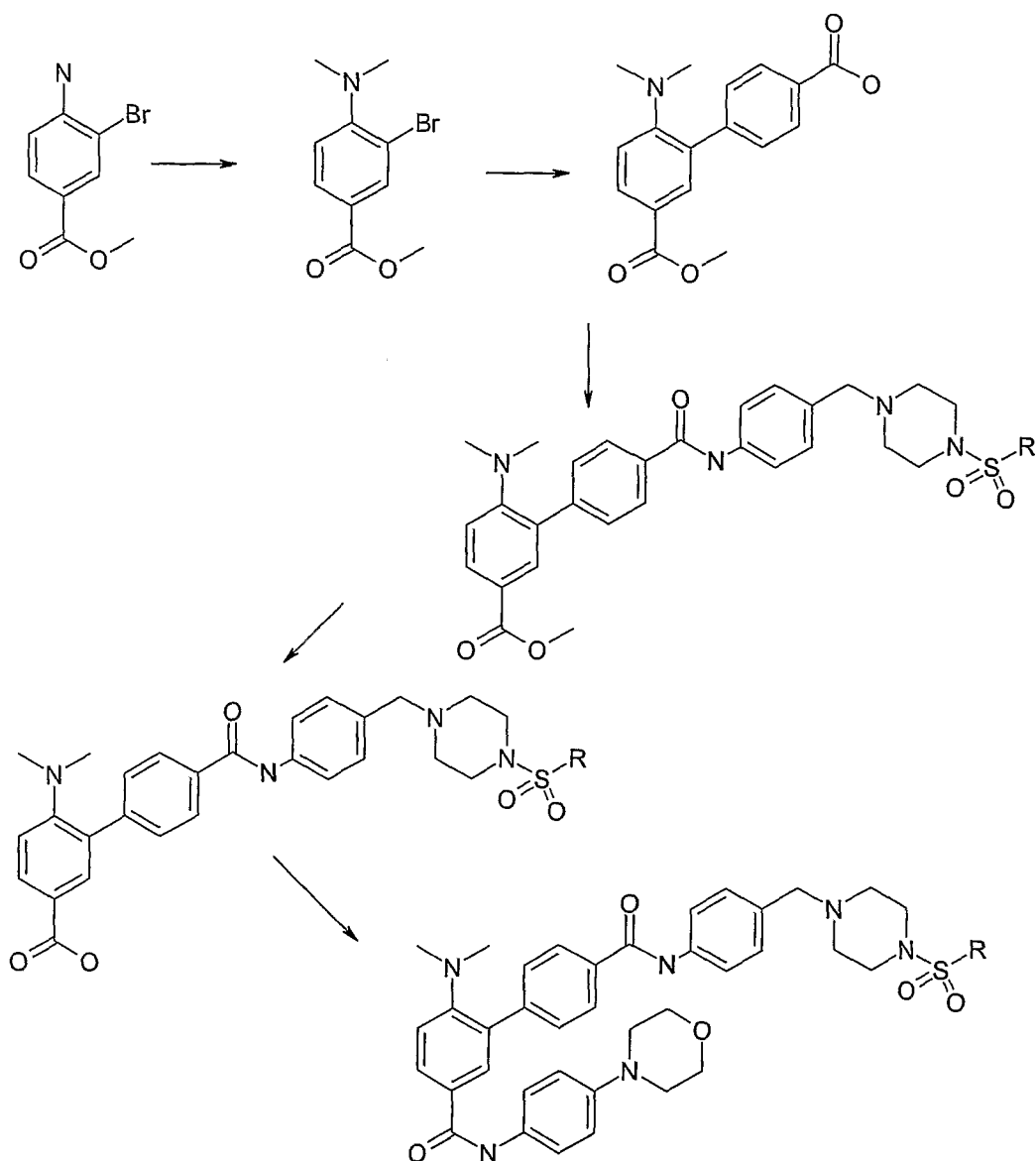
2'-Fluoro-5'-(4-morpholin-4-yl-phenylcarbamoyl)-biphenyl-4-carboxylic acid ethyl ester (350mg) was dissolved in EtOH (20ml) and 2N NaOH (10ml) and stirred at room temperature overnight. The reaction mixture was evaporated under vacuum and the residues treated with 2N HCl. The residue was purified by column chromatography. Elution with 50:8 DCM:EtOH followed by DMF gave a tan solid (190mg).

LCMS- ES+ = 421

Example 28

6-Fluoro-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(4-morpholin-4-yl-phenyl)-amide]

- To a solution of 2'-Fluoro-5'-(4-morpholin-4-yl-phenylcarbonyl)-biphenyl-4-
- 5 carboxylic acid (40mg) in DMF (1ml) was added 1-[4-(4-amino-benzyl)-piperazin-1-yl]ethanone (30mg), HOBT (18mg), EDAC (25mg) and N-methylmorpholine (30ul). The mixture was stirred at room temperature overnight and was poured into water (10ml) and the resulting precipitate was filtered under vacuum. This material was then purified via prep HPLC method A.
- 10 Pure fractions combined and reduced in vacuo to yield a tan solid (14mg).
- ¹H NMR (DMSO, δ) 1.97 (3H, s) 2.36 (4H, m) 3.08 (4H, m) 3.41 (4H, m) 3.47 (2H, s) 3.74 (4H, m) 6.97 (2H, d) 7.31 (2H, d) 7.61 (3H, m) 7.75 (5H, m) 8.09 (3H, m) 10.19 (1H, s) 10.34 (1H, s)
- LCMS- ES+ = 636



3-Bromo-4-dimethylamino-benzoic acid methyl ester

- 4-Amino-3-bromo-benzoic acid methyl ester (500mg) was dissolved in formic acid (2.5ml), 37% w/v formaldehyde (2.5ml) and water (5ml) and stirred at reflux overnight. The reaction mixture was made basic with sat. aq. Na_2CO_3 and extracted with DCM. The dried extracts were evaporated and purified by silica gel column chromatography. Elution with pet. ether then 5% EtOAc in pet. Ether gave a yellow oil (416mg)
- $^1\text{H-NMR}$ (CDCl_3 , δ) 2.90 (6H, s) 3.80 (3H, s) 6.95 (1H, d) 7.85 (1H, dd) 8.15 (1H, d)

LCMS- ES+ = 258, 260

6-Dimethylamino-biphenyl-3,4'-dicarboxylic acid 3-methyl ester

To a suspension of 3-Bromo-4-dimethylamino-benzoic acid methyl ester
5 (416mg) and 4-carboxy-phenyl boronic acid (266mg) in DME (10ml) and water
(5ml) was added cesium carbonate (521mg) and tetrakis(triphenylphosphine)-
palladium (92mg). The mixture was stirred at 80°C overnight and the solvent
was evaporated. The residue was then diluted with water and washed with ethyl
acetate. The aqueous portion was acidified with 2N HCl and the resulting
10 precipitate was filtered under vacuum and the off-white solid washed with water
(273mg).

LCMS- ES+ = 300

**6-Dimethylamino-4' {4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-
15 phenylcarbamoyl}-biphenyl-3-carboxylic acid methyl ester**

To a solution of 6-Dimethylamino-biphenyl-3,4'-dicarboxylic acid 3-methyl ester
(90mg) and 4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]- phenylamine
(134mg) in DMF (2ml) was added HOBt (61mg), EDAC (86mg) and N-
methylmorpholine (99ul). The mixture was stirred at room temperature
20 overnight and was poured into water (20ml) and the resulting white solid
collected by filtration and dried (167mg).

LCMS- ES+ = 579

**6-Dimethylamino-4' {4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-
25 phenylcarbamoyl}-biphenyl-3-carboxylic acid**

6-Dimethylamino-4' {4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-
phenylcarbamoyl}-biphenyl-3-carboxylic acid methyl ester (167mg) was
dissolved in EtOH (2ml) and 2N NaOH (1ml) and stirred at room temperature
overnight.

30

Reaction mixture evaporated under vacuum and the residues treated with 2N
HCl, then evaporated completely. This material was then purified via prep HPLC

method A. Pure fractions combined and reduced in vacuo to yield an off-white solid (38mg).

LCMS- ES+ = 565

5 Example 29

6-Dimethylamino-biphenyl-3,4'-dicarboxylic acid 3-[(4-morpholin-4-yl-phenyl)-amide 4'-({4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-amide)

To a solution of 6-Dimethylamino-4'({4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenylcarbamoyl}-biphenyl-3-carboxylic acid (38mg) and 4-morpholin-10 4-yl-phenylamine (16mg) in DMF (1ml) was added HOBT (12mg), EDAC (17mg) and N-methylmorpholine (20ul). The mixture was stirred at room temperature overnight and was poured into water (10ml) and the resulting tan solid collected by filtration and dried (50mg).

¹H NMR (DMSO, δ) 0.98 (3H, t) 1.67 (2H, m) 2.44 (4H, m) 2.60 (6H, s) 3.04 15 (6H, m) 3.16 (4H, m) 3.49 (2H, s) 3.73 (4H, m) 6.90 (2H, d) 7.13 (1H, d) 7.31 (2H, d) 7.59 (2H, d) 7.75 (3H, t) 7.89 (3H, m) 8.04 (2H, d) 9.91 (1H, s) 10.28 (1H, s)

LCMS- ES+ = 725

20 **6-Dimethylamino-4'[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-biphenyl-3-carboxylic acid methyl ester**

To a solution of 6-dimethylamino-biphenyl-3,4'-dicarboxylic acid 3-methyl ester (90mg) and 4-(4-methanesulfonyl-piperazin-1-ylmethyl)- phenylamine (121mg) in DMF (2ml) was added HOBT (61mg), EDAC (86mg) and N-methylmorpholine 25 (99ul). The mixture was stirred at room temperature overnight and was poured into water (20ml) and the resulting white solid collected by filtration and dried (155mg).

LCMS- ES+ = 551

30 **6-Dimethylamino-4'[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-biphenyl-3-carboxylic acid**

6-Dimethylamino-4'[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-biphenyl-3-carboxylic acid methyl ester (155mg) was

dissolved in EtOH (2ml) and 2N NaOH (1ml) and stirred at room temperature overnight.

Reaction mixture evaporated under vacuum and the residues treated with 2N HCl, then evaporated again. This material was then purified via prep HPLC

- 5 method A. Pure fractions combined and reduced in vacuo to yield an off-white solid (44mg).

LCMS- ES+ = 537

Example 30

- 10 **6-Dimethylamino-biphenyl-3,4'-dicarboxylic acid 4'-{[4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide} 3-[(4-morpholin-4-yl-phenyl)-amide]**

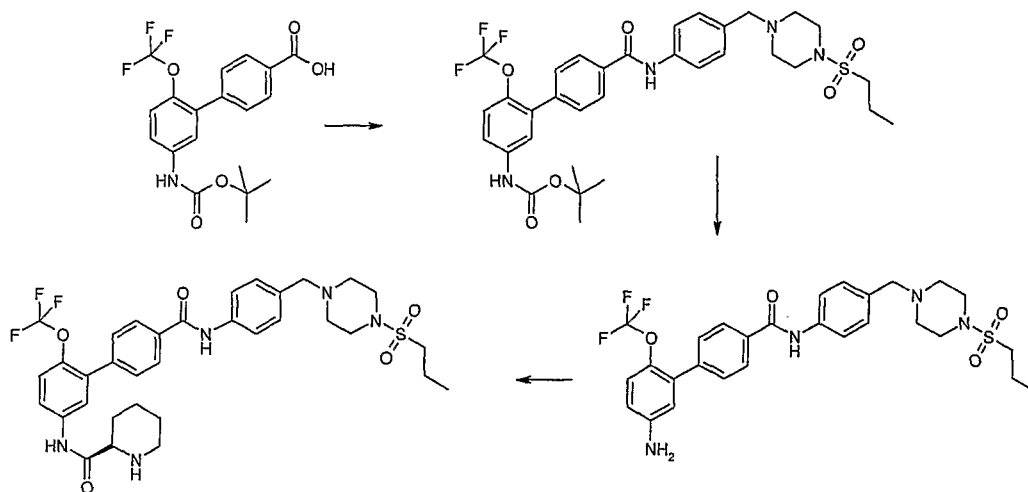
To a solution of 6-Dimethylamino-4' [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-biphenyl-3-carboxylic acid (44mg) and 4-morpholin-4-yl-phenylamine (18mg) in DMF (1ml) was added HOBT (14mg), EDAC (19mg)

15 and N-methylmorpholine (22ul). The mixture was stirred at room temperature overnight and was poured into water (10ml) and the resulting tan solid collected by filtration and dried (54mg).

¹H NMR (DMSO, δ) 2.46 (4H, m) 2.60 (6H, s) 2.87 (3H, s) 3.08 (8H, m) 3.80 (2H, s) 3.74 (4H, m) 6.94 (2H, d) 7.13 (1H, d) 7.31 (2H, d) 7.59 (2H, d) 7.75 (3H, t) 7.84 (3H, m) 8.04 (2H, d) 9.91 (1H, s) 10.28 (1H, s)

20

LCMS- ES+ = 697



(4'-{4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenylcarbamoyl}-6-trifluoromethoxy-biphenyl-3-yl)-carbamic acid tert-butyl ester.

- 5 A mixture of 5'-tert-butoxycarbonylamino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid (300mg), 4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenylamine (224mg), EDAC (144mg), HOBT (102mg) and N-Methylmorpholine (166ul) in dry DMF (3ml) was stirred for 16hrs.

This mixture was the diluted with water (12ml) and the tan solid produced collected and
10 dried (459mg).

LCMS- ES+ = 677

5'-Amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid {4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-amide

- 15 (4'-{4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenylcarbamoyl}-6-trifluoromethoxy-biphenyl-3-yl)-carbamic acid tert-butyl ester (459mg) in DCM (4ml) and Trifluoroacetic Acid (4ml) was stirred for 2hrs. The mixture was evaporated and the residue partitioned between EtOAc and saturated potassium carbonate. The dried extracts were then evaporated giving the title compound as a tan foam (374mg).

20 LCMS- ES+ = 577

Example 31

(R)-Piperidine-2-carboxylic acid (4'-{4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenylcarbamoyl}-6-trifluoromethoxy-biphenyl-3-yl)-amide.

25

- A cold (-10) stirred solution of (R)-N-Boc-2-piperidinecarboxylic acid (39.7mg) in dry THF (4ml) and N,N-Diisopropylethylamine (60.4ul) was treated dropwise with isobutylchloroformate (22.5ul) for 10 minutes. 5'-Amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid {4-[4-(propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-amide
30 (50mg) in dry THF (1ml) was then added and the reaction mixture allowed to warm to room temperature, stirring under nitrogen for 16 hours.

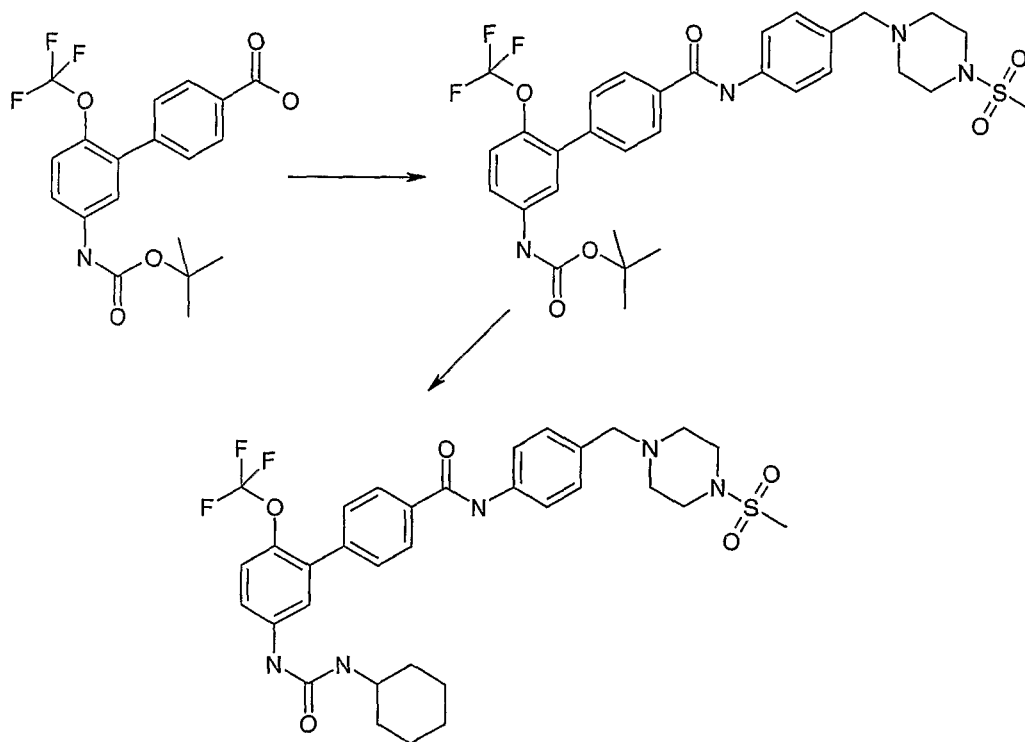
The mixture was then evaporated and the residue purified on silica gel. Gradient elution with 0%-20% 20DCM:8EtOH:1NH3 in DCM over 35 mins gave a tan solid (45mg).

LCMS- ES+ = 788

The above material (45mg) was dissolved in DCM (2ml) and was then treated with trifluoroacetic acid (2ml) and the mixture stirred for 2 hours. The mixture was
5 evaporated and the residue partitioned between EtOAc and saturated potassium carbonate. The dried extracts were then evaporated and the residue purified on silica gel. Gradient elution with 0%-35% 20DCM:8EtOH:1NH₃ in DCM over 30 mins. Gave the title compound as an off-white solid (35mg).

LCMS- ES+ = 688

- 10 ¹H NMR (DMSO, δ) 0.97-1.03 (t,3H) 1.38-1.48 (m,4H) 1.66-1.78 (m,4H) 2.45 (m,4H) 2.52-2.63 (m,1H) 2.99-3.01 (m,2H) 3.18 (m,4H) 3.26 (m,2H) 3.51 (m,2H) 7.29-7.32 (d,2H) 7.45-7.49 (d,1H) 7.60-7.64 (d,2H) 7.76-7.87 (m,3H) 7.93-7.94 (m,1H) 8.05-8.08 (d,2H) 9.95 (s,1H) 10.35 (s,1H)



{4'-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-trifluoromethoxy-biphenyl-3-yl}-carbamic acid tert-butyl ester.

A mixture of 5'-tert-butoxycarbonylamino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid (50mg), 4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylamine (35.2mg), HBTU (49.6mg) and N-Methylmorpholine (30ul) in dry DMF (3ml) was stirred for 16hrs.

The reaction mixture was then diluted with water (6ml) and the resulting solid collected by filtration and dried to giving a tan solid (80mg).

LCMS- ES+ = 649

Example 32

5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

15

{4'-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-trifluoromethoxy-biphenyl-3-yl}-carbamic acid tert-butyl ester (80mg) in DCM (3ml) and trifluoroacetic acid (3ml) was stirred for 2hrs. The reaction mixture was then evaporated giving a brown oil which was used without further purification in the next step.

20

LCMS- ES+ = 549

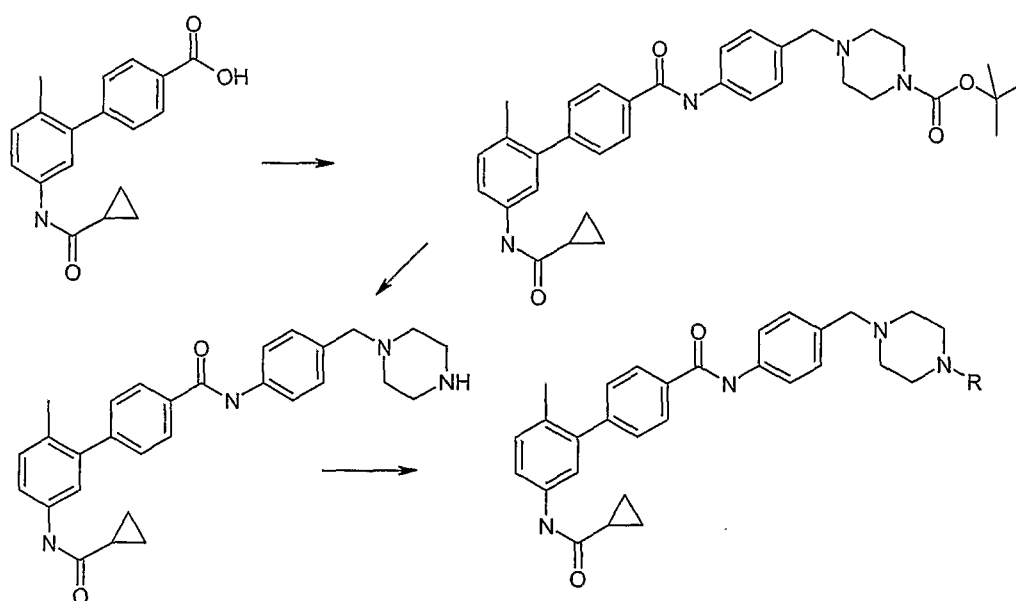
The crude amine (95mg), cyclohexylisocyanate (62mg) and N-Methylmorpholine (60ul) in dry DMF (3ml) was stirred at room temperature for 48 hours. The reaction mixture was then diluted with water (6ml) and the solid formed collected by filtration. This material was then purified on silica gel. Gradient elution with 0%-30% 20DCM:8EtOH:1NH3 in DCM over 35 mins gave the title compound as an off-white solid (26mg).

25

LCMS- ES+ = 674

¹H NMR (DMSO, δ) 1.16-1.34 (m,6H) 1.55-1.83 (m,5H) 2.47-2.51 (m,4H) 2.89 (s,3H) 3.13 (m,4H) 3.51 (m,2H) 6.21-6.24 (d,1H) 7.29-7.75 (m,4H) 7.59-7.66 (m,3H) 7.76-7.79 (m,2H) 8.03-8.66 (d,2H) 8.66 (s,1H) 10.37 (s,1H)

30



5 **4-(4-{[5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]-amino}-benzyl)-piperazine-1-carboxylic acid tert-butyl ester**

A mixture of 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (1.82g), 4-(4-amino-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (1.8g), HBTU (3.51g) and N-methylmorpholine (1.8ml) in dry DMF (50ml) was stirred at room temperature for 18h. The mixture was partitioned between water and DCM. The dried extracts were evaporated and the residue purified on silica gel. Elution with DCM:EtOH:ammonia;400 to 200:8:1 gave the title compound as a beige foam (2.64g)

15 **5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-piperazin-1-ylmethyl-phenyl)-amide**

4-(4-{[5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]-amino}-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (2.63g) in ethanol (50ml) and conc hydrochloric acid (20ml) was stirred at room temperature for 3h. The mixture was carefully basified with potassium carbonate and then extracted with DCM. The dried extracts were evaporated giving the title compound as a cream foam (2.25g).

Example 33

4-(4-{[5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxyl]-amino}-benzyl)-piperazine-1-carboxylic acid tert-butyl amide

A mixture of 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid
5 (4-piperazin-1-ylmethyl-phenyl)-amide (40mg) and 2-isocyanato-2-methyl-propane
(0.011ml) in dry DMF (3ml) was stirred at room temperature for 18h. The mixture was
partitioned between water and DCM. The dried extracts were evaporated and the
residue purified on silica gel. Elution with DCM:EtOH:ammonia;150:8:1 gave the title
compound as a colourless foam (48mg)
10 ¹H NMR (CDCl₃, δ) 0.72-0.80 (m, 2H) 0.97-1.04 (m, 2H) 1.34 (2x s, 12H) 1.58-1.64
(m, 1H) 2.18 (s, 3H) 2.35-2.42 (m, 4H) 3.26-3.33 (m, 4H) 3.48 (s, 2H) 4.41 (s, 1H)
7.14-7.30 (m, 5H) 7.40-7.72 (m, 2H) 7.68 (d, 2H) 7.83 (d, 2H) 8.57 (s, 1H) 8.77 (s, 1H)

Example 34

4-(4-{[5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxyl]-amino}-benzyl)-piperazine-1-yl]-oxo-acetic acid ethyl ester

A mixture of 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid
(4-piperazin-1-ylmethyl-phenyl)-amide (40mg) and chloro-oxo-acetic acid ethyl ester
(0.011ml) in dry DMF (3ml) containing N-methylmorpholine (0.01ml) was stirred at
20 room temperature for 18h. The mixture was partitioned between water and DCM. The
dried extracts were evaporated and the residue purified on silica gel. Elution with
DCM:EtOH:ammonia;150:8:1 gave the title compound as a colourless foam (40mg)
¹H NMR (CDCl₃, δ) 0.73-0.82 (m, 2H) 1.00-1.05 (m, 2H) 1.35 (t, 3H) 1.54-1.61 (m,
1H) 2.18 (s, 3H) 3.41-3.45 (m, 4H) 3.51 (s, 2H) 3.61-3.65 (m, 4H) 4.32 (q, 2H) 7.17 (d,
25 1H) 7.27-7.31 (m, 4H) 7.39-7.43 (m, 2H) 7.68 (d, 2H) 7.83 (d, 2H) 8.31 (s, 1H) 8.63 (s,
1H)

Example 35

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-{4-[2-(2-methoxy-ethoxy)-acetyl]-piperazin-1-ylmethyl}-phenyl)-amide

This material was prepared as for Example 34 except that (2-methoxy-ethoxy)-acetyl
chloride (14.3mg) was used. The title compound was obtained as a colourless gummy
foam (9mg)

¹H NMR (CDCl₃, δ) 0.78-0.85 (m, 2H) 1.03-1.09 (m, 2H) 1.47-1.56 (m, 1H) 2.20 (s, 3H) 2.39-2.46 (m, 4H) 3.37 (s, 3H) 3.46-3.69 (m, 10H) 4.19 (s, 2H) 7.18-7.44 (m, 7H) 7.64 (d, 2H) 7.68 (s, 1H) 7.86 (d, 2H) 8.11 (s, 1H)

5 Example 36

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-methoxy-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide

This material was prepared as for Example 34 except that methoxy-acetyl chloride (0.008ml) was used. The title compound was obtained as a colourless foam (41mg)

10 ¹H NMR (CDCl₃, δ) 0.67-0.74 (m, 2H) 0.93-0.98 (m, 2H) 1.44-1.54 (m, 1H) 2.10 (s, 3H) 2.29-2.38 (m, 4H) 3.32 (s, 3H) 3.36-3.42 (m+s, 4H) 3.50-3.56 (m, 2H) 4.00 (s, 2H) 7.07-7.11 (m, 1H) 7.19-7.23 (m, 4H) 7.31-7.34 (m, 2H) 7.58 (d, 2H) 7.74 (d, 2H) 8.05 (s, 1H) 8.39 (s, 1H)

15 Example 37

4-[4-(4-{[5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]amino}-benzyl)-piperazin-1-yl]-3-oxo-butyric acid ethyl ester

This material was prepared as for Example 34 except that 4-chloro-3-oxo-butyric acid ethyl ester (0.015ml) was used. The title compound was obtained as an orange gum

20 (10mg)

Example 38

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(morpholine-4-carbonyl)-piperazin-1-ylmethyl]-phenyl}-amide

25 This material was prepared as for Example 34 except morpholine-4-carbonyl chloride(12.7mg) was used. The title compound was obtained as a yellow gum (43mg)

¹H NMR (CDCl₃, δ) 0.79-0.86 (m, 2H) 1.04-1.10 (m, 2H) 1.52-1.60 (m, 1H) 2.22 (s, 3H) 2.43-2.47 (m, 4H) 3.24-3.33 (m, 8H) 3.52 (s, 2H) 3.67-3.72 (m, 4H) 7.20 (d, 1H) 7.31-7.44 (m, 6H) 7.67 (d, 2H) 7.87 (d, 2H) 8.03 (s, 1H) 8.33 (s, 1H)

30

Example 39

(S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(5-oxo-pyrrolidin-2-carbonyl)-piperazin-1-ylmethyl]-phenyl}-amide

A mixture of 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-piperazin-1-ylmethyl-phenyl)-amide (40mg) and (S)-5-oxo-pyrrolidine-2-carboxylic acid (11mg) in dry DMF (3ml) containing N-methylmorpholine (0.05ml) and HBTU (49mg) was stirred at room temperature for 18h. The mixture was partitioned between
5 water and DCM. The dried extracts were evaporated and the residue purified on silica gel. Elution with DCM:EtOH:ammonia;100:8:1 gave the title compound as an off-white solid (27mg)

¹H NMR (DMSO, δ) 0.78-0.84 (m, 4H) 1.75-1.84 (m, 1H) 2.12 (t, 2H) 2.22 (s, 3H)
2.33-2.43 (m, 2H) 2.52-2.56 (m, 4H) 3.44-3.56 (m, 6H) 4.52-4.60 (m, 1H) 7.25-7.35
10 (m, 3H) 7.50-7.59 (m, 4H) 7.71-7.80 (m, 3H) 8.04 (d, 2H) 10.24 (s, 1H) 10.33(s, 1H)

Example 40

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid 4-{4-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-acetyl]-piperazin-1-ylmethyl}-phenyl)-amide
15

This material was prepared as for Example 39 except that (5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-acetic acid (15.7mg) was used. The title compound was obtained as a pale orange solid (10mg)

¹H NMR (DMSO, δ) 0.77-0.83 (m, 4H) 1.76-1.82 (s+m, 4H) 2.21 (s, 3H) 2.37-2.45 (m,
20 4H) 3.44-3.53 (m, 6H) 4.57 (s, 2H) 7.23-7.38 (m, 3H) 7.48-7.58 (m, 4H) 7.77 (d, 2H)
8.03 (d, 2H) 10.22 (s, 1H) 10.32 (s, 1H) 11.29 (s, 1H)

Example 41

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-oxo-imidazolin-4-carbonyl)-piperazin-1-ylmethyl]-phenyl}-amide
25

This material was prepared as for Example 39 except that 2-oxo-imidazolin-4-carboxylic acid (11mg) was used. The title compound was obtained as a colourless solid (37mg)

¹H NMR (DMSO, δ) 0.55-0.61 (m, 4H) 1.51-1.59 (m, 1H) 1.99 (s, 3H) 2.06-2.19 (m,
30 2H) 2.28-2.32 (m, 4H) 3.18-3.40 (m, 6H) 4.31-4.36 (m, 1H) 6.05 (s, 1H) 6.14 (s, 1H)
7.01-7.11 (m, 3H) 7.27-7.36 (m, 4H) 7.56 (d, 2H) 7.82 (d, 2H) 10.01 (s, 1H) 10.11 (s,
1H)

Example 42

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-phenylamino-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide

This material was prepared as for Example 39 except that phenylamino-acetic acid

- 5 (13mg) was used. The title compound was obtained as a colourless glass (14mg)
¹H NMR (DMSO, δ) 0.76-0.82 (m, 4H) 1.73-1.81 (m, 1H) 2.21 (s, 3H) 2.32-2.44 (m, 4H) 3.47-3.56 (m, 6H) 3.89 (d, 2H) 5.53 (t, 1H) 6.54-6.67 (m, 3H) 7.04-7.12 (m, 2H) 7.23-7.34 (m, 3H) 7.48-7.58 (m, 4H) 7.78 (d, 2H) 8.03 (d, 2H) 10.21 (s, 1H) 10.31 (s, 1H)

10

Example 43

(S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-dipropylamino-propionyl)-piperazin-1-ylmethyl]-phenyl}-amide

This material was prepared as for Example 39 except that (S)-2-dipropylamino-

- 15 propionic acid (15mg) was used. The title compound was obtained as an orange foam (35mg)

¹H NMR (CDCl₃, δ) 0.76-0.88 (m, 10H) 1.02-1.05 (m, 2H) 1.12-1.15 (m, 2H) 1.34-1.48 (m, 4H) 2.19 (s, 3H) 2.29-2.49 (m, 7H) 2.81 (s, 2H) 3.50-3.58 (m, 4H) 3.69-3.84 (m, 2H) 7.17 (d, 1H) 7.28-7.45 (m, 6H) 7.69 (d, 2H) 7.85 (d, 2H) 8.35 (s, 1H) 8.61 (s, 1H)

20

Example 44

(S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-hydroxy-propionyl)-piperazin-1-ylmethyl]-phenyl}-amide

This material was prepared as for Example 39 except that (S)-2-hydroxy-propionic acid

- 25 (9mg of an 85% aqueous solution) was used. The title compound was obtained as a pale yellow foam (25mg)

¹H NMR (CDCl₃, δ) 0.78-0.85 (m, 2H) 1.03-1.07 (m, 2H) 1.33 (d, 3H) 1.49-1.60 (m, 1H) 2.21 (s, 3H) 2.42-2.48 (m, 4H) 3.39-3.45 (m, 2H) 3.53 (s, 3H) 3.60-3.73 (m, 1H) 3.88 (brs, 1H) 4.44-4.48 (m, 1H) 7.20 (d, 1H) 7.29-7.44 (m, 6H) 7.68 (d, 2H) 7.97 (d,

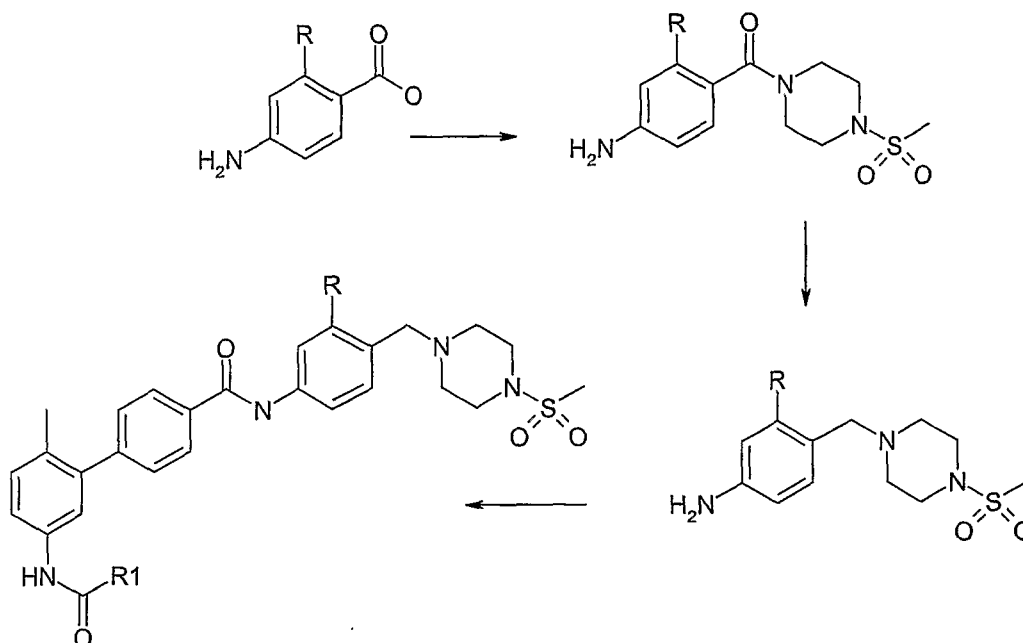
- 30 2H) 7.97 (s, 1H) 8.39 (s, 1H)

Example 45

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-{4-[2-(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-acetyl]-piperazin-1-ylmethyl}-phenyl)-amide

- 5 This material was prepared as for Example 39 except that (1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-acetic acid (16.5mg) was used. The title compound was obtained as a pale yellow foam (38mg)

¹H NMR (CDCl₃, δ) 0.72-0.79 (m, 2H) 0.96-1.02 (m, 2H) 1.42-1.51 (m, 1H) 2.14 (s, 3H) 2.31-2.39 (m, 4H) 2.96-3.05 (m, 8H) 3.27 (s, 2H) 3.36-3.45 (m, 4H) 3.52-3.59 (m, 2H) 7.11-7.39 (m, 7H) 7.59 (d, 2H) 7.66 (s, 1H) 7.79 (d, 2H) 8.14 (s, 1H)



15 **(4-Amino-2-trifluoromethyl-phenyl)-(4-methanesulfonyl-piperazin-1-yl)-methanone**

- A mixture of 4-amino-2-trifluoromethyl-benzoic acid (400mg) and 1-methanesulfonyl-piperazine (383mg) in dry DMF (3ml) containing N-methylmorpholine (0.51ml) and HBTU (887mg) was stirred at room temperature for 18h. The mixture was evaporated and the residue partitioned between aq. sodium bicarbonate and ethyl acetate. The dried organic layer was evaporated giving a tan solid (600mg). This material was used without purification in the following synthetic step.
- 20

4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine

A mixture of (4-Amino-2-trifluoromethyl-phenyl)-(4-methanesulfonyl-piperazin-1-yl)-methanone and borane THF complex (10ml) was heated to 80C for 18h. The mixture was cooled and quenched with methanol. The solvents were then evaporated and the residue partitioned between aq. sodium bicarbonate and ethyl acetate. The dried organic layer was evaporated and the residue was then purified on silica gel. Gradient elution of 0-30% DCM:EtOH:ammonia; 20:8:1 in DCM over 40mins gave the title compound as a white solid (210mg).

Example 46**5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-amide**

A mixture of 5'-(cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (50mg) and 4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine (50mg) in dry DMF (1ml) containing N-methylmorpholine (0.033ml) and HBTU (65mg) was stirred at room temperature for 18h. Water was then added and the solid collected by filtration. This material was then purified on silica gel. Gradient elution of 0-20% DCM:EtOH:ammonia; 20:8:1 in DCM over 45mins gave the title compound as a tan solid (43mg).

¹H NMR (DMSO, δ) 1.41-1.60 (m,5H) 1.81-1.94 (m,5H) 2.37 (s,3H) 2.49(m,1H) 2.68 (m,4H) 3.07 (s,3H) 3.32 (m,4H) 3.83 (m,2H) 7.39-7.42 (d,1H) 7.67-7.76 (m,4H) 7.89-7.93 (d,1H) 8.21-8.29 (m,3H) 8.44 (s,1H) 9.99 (s,1H) 10.76 (s,1H)

LCMS- ES+ = 658

Example 47**5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-amide**

A mixture of 5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (50mg) and 4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine (57mg) in dry DMF (1ml) containing N-methylmorpholine (0.038ml) and HBTU (65mg) was stirred at room temperature for 18h. Water was then added and the solid collected by filtration. This material was then purified on silica gel. Gradient elution of

0-20% DCM:EtOH:ammonia; 20:8:1 in DCM over 45mins gave the title compound as a tan solid (57mg).

¹H NMR (DMSO, δ) 0.55-0.57 (d,4H) 1.51-1.53 (m,1H) 1.97 (s,3H) 2.66 (s,3H) 2.28 (m,4H) 2.91 (m,4H) 3.42 (m,2H) 7.00-7.03 (d,1H) 7.27-7.33 (m,4H) 7.49-7.52 (1H)

5 7.80-7.88 (m,3H) 8.03 (s,1H) 9.98 (s,1H) 10.35 (s,1H)

LCMS- ES+ = 616

(4-Amino-2-chloro-phenyl)-(4-methanesulfonyl-piperazin-1-yl)-methanone

This material was prepared as described above for the corresponding trifluoromethyl
10 analogue except that 4-amino-2-chloro-benzoic acid was used. The title compound was obtained as a tan solid (638mg) which was used without purification in the following synthetic step.

3-Chloro-4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylamine

15 The amide described above was reduced with borane as for the trifluoromethyl analogue. The title compound was isolated as a colourless solid (401mg).

Example 48

**5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [3-chloro-
20 4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide**

This material was prepared as described for Example 46 except that 3-chloro-4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylamine (22.5mg) was used. The title compound was isolated as an off-white solid (6mg).

¹H NMR (DMSO, δ) 1.24-1.43 (m,5H) 1.67-1.82 (m,5H) 2.20 (s,3H) 2.33 (m,1H) 2.52
25 (m,4H) 2.89 (s,3H) 3.14 (m,4H) 3.61 (m,2H) 3.80 (s,3H) 7.22-7.26 (d,1H) 7.45-7.59 (m,5H) 7.74-7.77 (d,1H) 8.02-8.05 (m,3H) 9.84 (s,1H) 10.48 (s,1H)

LCMS- ES+ = 624

Example 49

30 **5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [3-chloro-4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide**

This material was prepared as described for Example 47 except that 3-chloro-4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenylamine (22.5mg) was used. The title compound was isolated as an off-white solid (20mg).

¹H NMR (DMSO, δ) 0.78-0.81 (d,4H) 1.75-1.77 (m,1H) 2.18-2.21 (s,3H) 2.52 (m,4H)
 5 2.89 (s,3H) 3.14 (m,4H) 3.61 (m,2H) 7.24-7.27 (d,1H) 7.45-7.56 (m,5H) 7.73-7.77
 (m,1H) 8.02-8.05 (m,3H) 10.23 (s,1H) 10.47 (s,1H)
 LCMS- ES+ = 582

(4-Amino-2-methoxy-phenyl)-(4-methanesulfonyl-piperazin-1-yl)-methanone

10 A mixture of 2-methoxy-4-nitro-benzoic acid (500mg) and 1-methanesulfonyl-piperazine (416mg) in dry DMF (3ml) containing N-methylmorpholine (0.56ml) and HBTU (962mg) was stirred at room temperature for 18h. Water (50ml) was then added and the resulting tan solid collected by filtration and dried (747mg). This material
 (200mg) was then heated to 120C in 4:1 aqueous acetic acid (2.5ml) in the presence of
 15 iron powder. The cooled mixture was filtered through celite and the residue partitioned between aq sodium bicarbonate and ethyl acetate. The dried extracts were evaporated giving a white foam which was used in the following step without purification.

4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenylamine

20 The amide described above was reduced with borane as for the trifluoromethyl analogue. The title compound was isolated as a colourless oil (63mg).

Example 50

5'-(Cyclohexanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenyl]-amide

25 This material was prepared as described for Example 46 except that 4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenylamine (30mg) was used. The title compound was isolated as a tan solid (19mg).

¹H NMR (DMSO, δ) 1.16-1.43 (m,5H) 1.68-1.78 (m,5H) 2.20 (s,3H) 2.32 (m,1H) 2.88
 30 (s,3H) 3.12 (m,4H) 3.33-3.36 (m,4H) 3.51 (m,2H) 3.80 (s,3H) 7.22-7.28 (m,2H) 7.42-
 7.59 (m,6H) 8.02-8.05 (d,2H) 9.84 (s,1H) 10.31 (s,1H)

LCMS- ES+ = 620

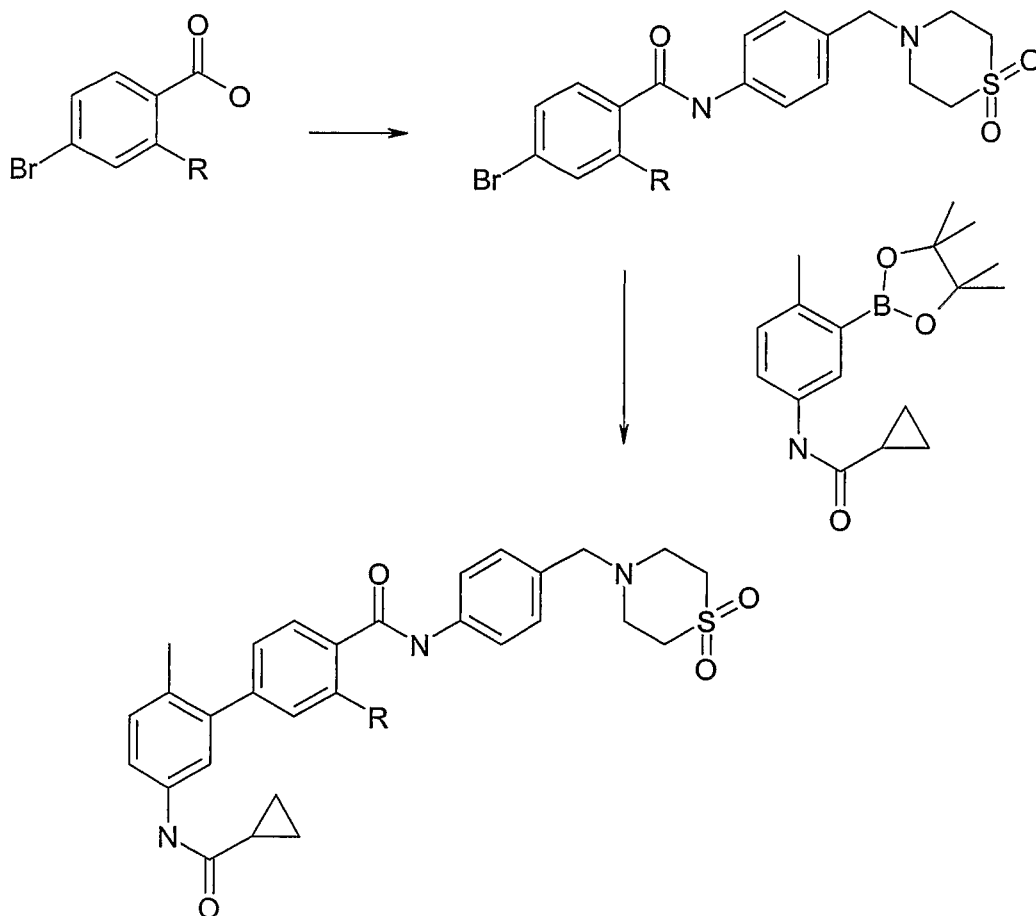
Example 51

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenyl]-amide

- 5 This material was prepared as described for Example 47 except that 4-(4-methanesulfonyl-piperazin-1-ylmethyl)-3-methoxy-phenylamine (30mg) was used. The title compound was isolated as a tan solid (35mg).

¹H NMR (DMSO, δ) 0.83-0.86 (d,4H) 1.80-1.82 (m,1H) 2.26 (s,3H) 2.93 (s,3H) 3.17 (m,4H) 3.41 (m,4H) 3.56 (m,2H) 3.85 (s,3H) 7.29-7.32 (m,2H) 7.46-7.62 (m,6H) 8.07-8.10 (d,2H) 10.28 (s,1H) 10.36 (s,1H)

LCMS- ES+ = 578



4-Bromo-N-[4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-2-fluoro-benzamide

A mixture of 4-bromo-2-fluoro-benzoic acid (100mg) and 4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenylamine (131mg) in dry DMF (2ml) containing N-methylmorpholine (0.12ml) and HBTU (208mg) was stirred at room temperature for 18h. Water (10ml) was then added and the resulting tan solid collected by filtration and dried (298mg).

4-Bromo-2-dimethylamino-N-[4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-benzamide

A mixture of 4-Bromo-N-[4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-2-fluoro-benzamide (55mg) and dimethylamine (2M soln in THF, 2ml) was heated in a sealed tube in a microwave at 180C for 30mins. The solvent was then evaporated and the residue used crude in the following step.

15

Example 52

5'-(Cyclohexanecarbonyl-amino)-3-dimethylamino-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-yl)-phenyl]-amide

A mixture of cyclohexanecarboxylic acid [4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (21mg) and 4-bromo-2-dimethylamino-N-[4-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-phenyl]-benzamide (29mg) in 2:1 DME:water (6ml) containing cesium carbonate (20mg) and tetrakis(triphenylphosphine)palladium⁰ (7mg) was heated to 160C in a microwave for 15mins. The solvents were evaporated and the residue purified on silica gel. Gradient elution of 0-30% DCM:EtOH:ammonia; 20:8:1 in DCM over 35mins gave the title compound as a tan solid (7mg).

25

¹H NMR (DMSO, δ) 1.24-1.43 (m,5H) 1.78 (m,5H) 2.21 (s,3H) 2.31(m,1H) 2.80 (s,6H) 2.88 (m,4H) 3.12 (m,4H) 3.65 (m,2H) 7.02-7.11 (m,2H) 7.21-7.24 (d,1H) 7.31-7.34 (d,2H) 7.52-7.55 (m,2H) 7.72-7.75 (m,3H) 9.82 (s,1H) 11.28 (s,1H)

30 LCMS- ES+ = 604

2-Acetylamino-4-bromo-benzoic acid methyl ester

A mixture of 2-amino-4-bromo-benzoic acid methyl ester (514mg), triethylamine (0.23ml) and acetic anhydride (0.35ml) in dry DCM (5ml) was stirred at room temperature for 18h. The mixture was then washed with sodium bicarbonate solution and the dried organic layer evaporated giving the title compound as a grey solid (580mg).

2-Acetylamino-4-bromo-benzoic acid

The above material was then stirred in ethanol (10ml) and 2M sodium hydroxide (5ml) for 2h at room temperature. The ethanol was then evaporated and the residue acidified with 2M HCl. The solid thus formed was collected by filtration and dried yielding a tan solid (475mg).

2-Acetylamino-4-bromo-N-[4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-benzamide

A mixture of 2-Acetylamino-4-bromo-benzoic acid (100mg) and 4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenylamine (93mg) in dry DMF (2ml) containing N-methylmorpholine (0.09ml) and HBTU (147mg) was stirred at room temperature for 18h. Water (10ml) was then added and the resulting tan solid collected by filtration and dried (178mg).

Example 53**3-Acetylamino-5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-yl)-phenyl]-amide**

A mixture of cyclopropanecarboxylic acid [4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (32mg) and 2-acetylamino-4-bromo-N-[4-(1,1-dioxo-1 λ 6*-thiomorpholin-4-ylmethyl)-phenyl]-benzamide (50mg) in 2:1 DME:water (6ml) containing cesium carbonate (34mg) and tetrakis(triphenylphosphine)palladium⁰ (12mg) was heated to 140C in a microwave for 15mins. The solvents were evaporated and the residue purified on silica gel. Gradient elution of 0-30% DCM:EtOH:ammonia; 20:8:1 in DCM over 35mins gave the title compound as a white solid (16mg).

¹H NMR (DMSO, δ) 0.75-0.77 (d,4H) 1.71-1.74 (m,1H) 2.11 (s,3H) 2.18 (s,3H) 2.91 (m,4H) 3.30 (m,4H) 3.76 (m,2H) 7.22-7.25 (m,1H) 7.39-7.58 (m,9H) 8.10-8.13 (d,1H) 10.22 (s,1H)
LCMS- ES+ = 558

5

5'-Amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

Was prepared as described previously.

10 **(S)-2-({4'-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenylcarbamoyl]-6-trifluoromethoxy-biphenyl-3-ylcarbamoyl}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

A mixture of (S)-2-carboxymethyl-pyrrolidin-1-carboxylic acid tert-butyl ester (21mg) and 5'-amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-

15 piperazin-1-ylmethyl)-phenyl]-amide (50mg) in dry DMF (1ml) containing N-methylmorpholine (0.02ml) and HBTU (35mg) was stirred at room temperature for 18h. Water (10ml) was then added and the resulting residue purified on silica gel. Gradient elution of 0-25% DCM:EtOH:ammonia; 20:8:1 in DCM over 35mins gave the title compound as a tan solid (40mg).

20

Example 54

(S)-5'-(2-Pyrrolidin-2-yl-acetylamino)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-amide

The above Boc-protected amine was stirred in DCM (2ml) and trifluoroacetic acid (2ml) for 3h. The mixture was then evaporated and the residue partitioned between DCM and aq sodium bicarbonate. The dried organic layer was evaporated and the residue purified on silica gel. Gradient elution of 0-30% DCM:EtOH:ammonia; 20:8:1 in DCM over 35mins gave the title compound as a white solid (33mg).

25 ¹H NMR (DMSO, δ) 1.22-1.41 (m,1H) 1.66-1.68 (m,2H) 1.81-1.96 (m,1H) 2.48-2.51 (m, 4H) 2.76-2.82 (m, 2H) 2.89 (s,3H) 3.13 (m,4H) 3.33-3.41 (m,2H) 3.51 (m, 2H) 7.29-7.33 (d,2H) 7.46-7.49 (d,1H) 7.60-7.63 (d,2H) 7.70-7.79 (m,3H) 7.85-7.86 (d,1H) 8.05-8.08 (d,2H) 10.36 (s,1H)
LCMS- ES+ = 661

Example 55

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-methanesulfonyl-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide

- 5 This material was prepared as for Example 39 except that methanesulfonyl-acetic acid (12mg) was used. The title compound was obtained as a colourless solid (33mg)
- ¹H NMR (DMSO, δ) 0.76-0.79 (m, 4H) 1.71-1.80 (m, 1H) 2.19 (s, 3H) 2.32-2.41 (m, 4H) 3.09 (s, 3H) 3.46-3.54 (m, 6H) 4.44 (s, 2H) 7.22-7.31 (m, 3H) 7.46-7.55 (m, 4H) 7.76 (d, 2H) 8.02 (d, 2H) 10.19 (s, 1H) 10.29 (s, 1H)

10

Example 56

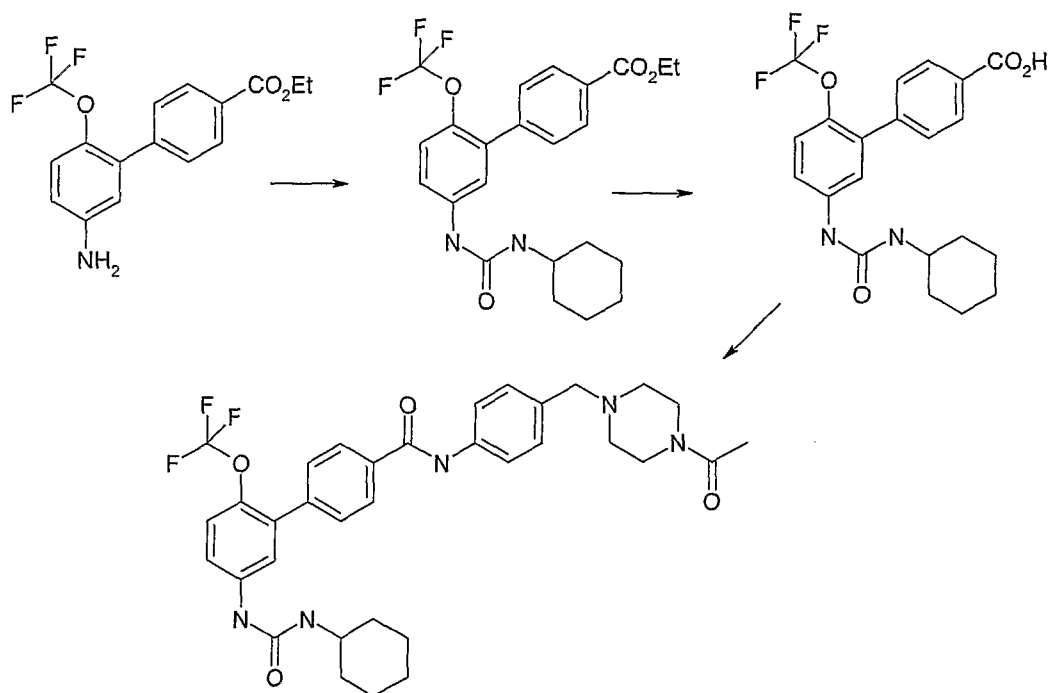
5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-hydroxy-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide

- This material was prepared as for Example 39 except that hydroxy-acetic acid (6.5mg)
- 15 was used. The title compound was obtained as a colourless solid (31mg)
- ¹H NMR (DMSO, δ) 0.74-0.81 (m, 4H) 1.72-1.82 (m, 1H) 2.20 (s, 3H) 2.31-2.42 (m, 4H) 3.39-3.51 (m, 6H) 4.07 (d, 2H) 4.35 (t, 1H) 7.21-7.36 (m, 3H) 7.47-7.57 (m, 4H) 7.78 (d, 2H) 8.02 (d, 2H) 10.22 (s, 1H) 10.31 (s, 1H)

20 Example 57

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(2-acetylamino-acetyl)-piperazin-1-ylmethyl]-phenyl}-amide

- This material was prepared as for Example 39 except that acetylamino-acetic acid (10mg) was used. The title compound was obtained as an off-white solid (36mg)
- 25 ¹H NMR (DMSO, δ) 0.77-0.82 (m, 4H) 1.74-1.80 (m, 1H) 1.87 (s, 3H) 2.21 (s, 3H) 2.32-2.41 (m, 4H) 3.40-3.50 (m, 6H) 3.92 (d, 2H) 7.23-7.32 (m, 3H) 7.47-7.56 (m, 4H) 7.77 (d, 2H) 7.94 (t, 1H) 8.03 (d, 2H) 10.20 (s, 1H) 10.30 (s, 1H)



5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid ethyl ester

A mixture of 5'-amino-2'-trifluoromethoxy-biphenyl-4-carboxylic acid ethyl ester (250mg) and isocyanato-cyclohexane (0.29ml) in dry DMF (2ml) was stirred at room temperature for 16h. The mixture was then evaporated and the residue purified on silica gel. Gradient elution of 0-30% DCM:EtOH:ammonia; 20:8:1 in DCM over 30mins gave the title compound as a white solid (411mg).

5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid

The material described above was stirred in ethanol (30ml) and 2M sodium hydroxide (15ml) at room temperature for 3h. The ethanol was then evaporated and the residue acidified with 2M hydrochloric acid. The resulting white solid was collected by filtration and dried (340mg).

15

Example 58

5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid [4-(4-acetyl-piperazin-1-ylmethyl)-phenyl]-amide

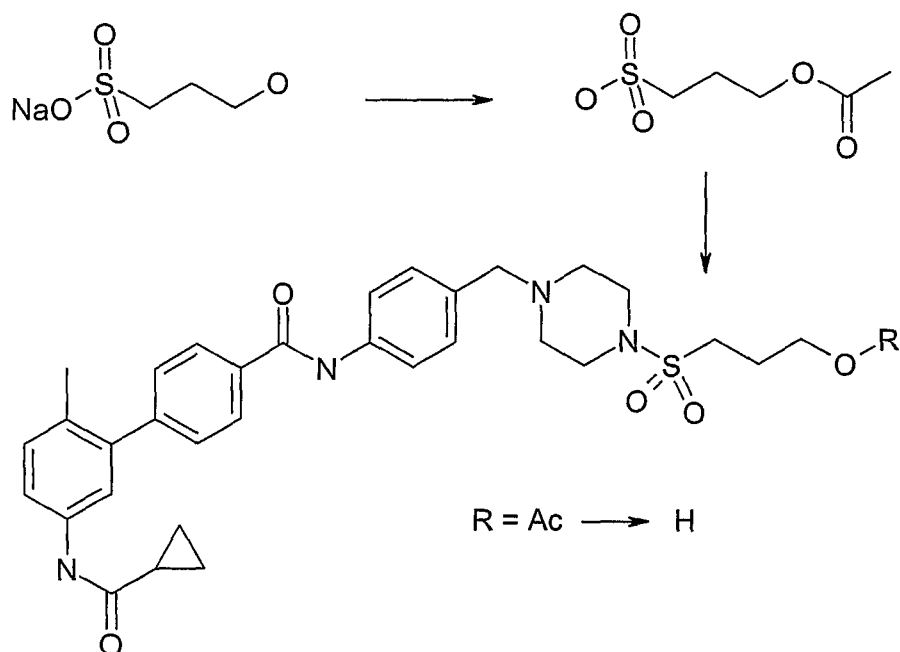
A mixture of 5'-(3-Cyclohexyl-ureido)-2'-trifluoromethoxy-biphenyl-4-carboxylic acid (50mg) 1-[4-(4-amino-benzyl)-piperazin-1-yl]-ethanone (28mg), HBTU (45mg) and N-

20

methyl morpholine (0.03ml) in dry DMF (1ml) was stirred at room temperature for 18h. Water (10ml) was then added and the resulting precipitate collected by filtration and dried. The residue was then purified on silica gel. Gradient elution of 0-20% DCM:EtOH:ammonia; 20:8:1 in DCM over 30mins gave the title compound as a tan solid (15mg).

¹H NMR (DMSO, δ) 1.04-1.34 (m,5H) 1.65-1.84 (m,5H) 1.99 (s,3H) 2.31-2.38 (m,4H) 3.43-3.45 (m,4H) 3.48 (s,2H) 6.21-6.24 (d,1H) 7.29-7.49 (m,4H) 7.59-7.66 (m,3H) 7.75-7.79 (d,2H) 8.04-8.07 (d,2H) 8.66 (s,1H) 10.34 (s,1H)

LCMS- ES+ = 639



Acetic acid 3-sulfo-propyl ester

The commercially available propane sulfonic acid salt (1g) was sonicated for 20 min in DMF (20 ml) to ensure dissolution. Triethylamine (0.5ml) was added to the stirred solution under N₂, followed by acetyl chloride (1.1ml). The resulting mixture was allowed to stir overnight under N₂ before being evaporated to give an orange slurry. DMF (5ml) was added and the mixture then filtered through a pad of celite. The pad was washed with DMF (2 x 10ml) and the filtrate then evaporated to give the title compound as an orange oil which was used in the next stage without further purification.

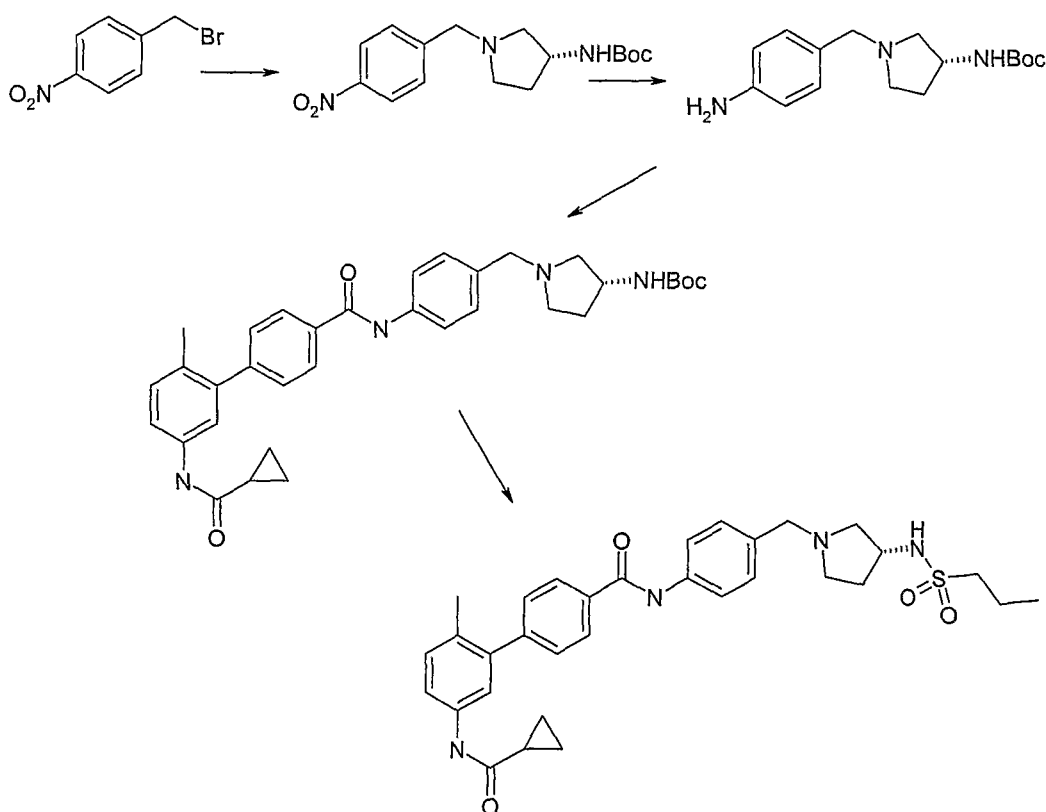
Acetic acid 3-[4-(4-{{5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]-amino}-benzyl)-piperazine-1-sulfonyl]-propyl ester

- The material described previously (200mg) was heated in thionyl chloride (2ml) at 50°C for 12hrs. The resulting orange solution was evaporated to dryness to afford a yellow solid. This material was dissolved in DCM (3ml) and added dropwise to a stirred, cooled (0°C) solution of 5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (4-piperazin-1-ylmethyl-phenyl)-amide (300mg) and triethylamine (0.11ml) in DCM (5ml). The reaction was allowed to warm to room temperature and left to stir for 18hrs, before being quenched via the addition of water (5ml). The organic layer was separated, passed through a hydrophobic frit and evaporated. The crude product was purified on silica gel. Elution with 3:1 EtOAc/petrol gave the title compound as a brown solid (69mg).

Example 59

5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[4-(3-hydroxy-propane-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-amide

- Acetic acid 3-[4-(4-{{5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl]-amino}-benzyl)-piperazine-1-sulfonyl]-propyl ester (69mg) and potassium carbonate (32mg) were stirred for 1hr in 1:1 aqueous methanol (5ml). The solution was then acidified to pH 3 via the addition of HCl (conc.). The reaction mixture was partitioned between aq ammonium chloride and ethyl acetate. The dried extracts were evaporated and the residue purified by prep HPLC giving the title compound as a colourless solid (17mg).
- ¹H NMR (DMSO, δ) 0.69-0.98 (4H, m), 1.71-1.84 (1H, m), 1.89-2.03 (2H, m), 2.24 (3H, s), 2.46-2.62 (4H, m), 3.02-3.39 (6H, m), 3.57 (2H, s), 3.63-3.74 (2H, m), 7.25 (1H, d), 7.35 (2H, d), 7.51 (2H, d), 7.55-7.69 (2H, m), 7.88 (2H, d), 8.09 (2H, d), 9.45 (1H, s), 9.65 (1H, s).



5 **(S)-[1-(4-Nitro-benzyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester**

A mixture of 4-nitro-benzyl bromide (391mg), pyrrolidin-3-yl-carbamic acid tert-butyl ester (337mg) and potassium carbonate (993mg) in DMF (15ml) was stirred at room temperature for 18h. The mixture was then partitioned between water and DCM. The dried organic layer was evaporated giving a yellow oil which crystallised on standing

10 (579mg).

(S)-[1-(4-Amino-benzyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

(S)-[1-(4-Nitro-benzyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester (200mg) and platinum (5% on carbon, 70mg) was stirred vigorously under an atmosphere of

15 hydrogen gas for 3h. The catalyst was removed by filtration and the solvent evaporated. The residue was then purified on silica gel. Elution with DCM:EtOH:ammonia;100:8:1 gave the title compound as a pale yellow oil (67mg)

(S)-[1-(4-{{5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carbonyl}-amino}-benzyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

A mixture of 5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid (68mg), (S)-[1-(4-Amino-benzyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

- 5 (67mg), HBTU (131mg) and N-methylmorpholine (0.1ml) in dry DMF (3ml) was stirred at room temperature for 18h. The mixture was partitioned between water and DCM. The dried extracts were evaporated and the residue purified on silica gel. Elution with DCM:EtOH:ammonia;200 to 50:8:1 gave the title compound as a pale yellow gum (104mg)

10

(S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(3-amino-pyrrolidin-1-ylmethyl)-phenyl]-amide

The above Boc-protected amine was stirred in dioxan (4ml) and conc HCl (2ml) for 3h.

The mixture was carefully basified and then extracted with DCM. The solvent was then

- 15 evaporated giving a pale yellow gum (94mg)

Example 60

(S)-5'-(Cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid {4-[3-(propane-1-sulfonylamino)-pyrrolidin-1-ylmethyl]-phenyl}-amide

- 20 A mixture of (S)-5'-(cyclopropanecarbonyl-amino)-2'-methyl-biphenyl-4-carboxylic acid [4-(3-amino-pyrrolidin-1-ylmethyl)-phenyl]-amide (43mg) and N-methylmorpholine (0.04ml) in dry DMF (2ml) was treated with propane-sulfonyl chloride (0.04ml) and was stirred at room temperature for 18h. The mixture was then partitioned between DCM and water. The dried organic layer was evaporated and the residue
- 25 purified on silica gel. Elution with DCM:EtOH:ammonia;200:8:1 gave the title compound as a pale yellow solid (9mg).

Activity Examples

HCV Replicon activity

Materials

HCV replicon cell line

- 5 ○ 1b replicon (Huh.7) described in Science 285, 110-113.
- Huh-9B: liver cell line with persistent bicistronic HCV genotype 1b coding sequence: [I₃₈₉lucubineo_3-3' _ET] includes firefly luciferase-ubiquitin-neomycin phosphotransferase fusion protein and EMCV-IRES driven non-structural HCV (NS3 to NS5B) coding sequence including cell culture adaptive
- 10 mutations E1202G, T1280I and K1846T (Lohmann *et al*, 2001).

Method

This assay is set up using all 96 wells of flat-bottomed 96-well plates. Plates are set up one day before addition of compounds. The assay then runs for 4 days with ELISA development taking place on the 5th day.

15 **Day 1**

Set up of Assay Plates

Exponentially growing Huh-9B monolayers are washed with sterile PBS to remove serum and treated with trypsin to detach cells from the flask.

Cells are suspended in growth media and counted using a haemocytometer.

- 20 Duplicate 96 well plates are seeded with Huh-9B at a density of 10⁴ cells/well in a total volume of 100 µl/well of growth medium without antibiotics. as depicted below.

One of the plates is an opaque white 96-well plate used for IC₅₀ determination based on the luciferase signal (referred as replicon plate), the other one is a clear 96-well plate used for a parallel determination of drug toxicity by methylene blue staining (referred as tox plate). Wells G12 and H12 of the tox plate are left without cells to use as buffer

25 alone background reading.

Plates are then incubated at 37°C in a 5% CO₂ environment for 24 h to obtain a 90% confluent cell monolayer.

Day 2Addition of Compound and Compound Dilutions

Doubling dilutions of each compound are generated in a separate 96 high volume capacity round bottom plate to twice their initial concentration in the assay using growth medium without antibiotics.

Five compounds (C1 to C5) are tested on each assay plate as illustrated below plus a control compound that is also included in each plate.

Compounds are tested across an 8 point doubling dilution series. The initial dilution of each compound to be tested is 25 μ M and 12.5 μ M for the control compound.

- 10 DMSO only wells (A1 and A2) at 1 % provide the signal corresponding to maximal (100%) luciferase detection. Previous optimization experiments showed negligible luciferase signal from non-replicon containing cells and control wells for background (unspecific) level of detection are not routinely included. The signal from the DMSO wells at 1 % (maximal signal) constitutes the assay window.
- 15 For each compound dilution on the 2x 96-well dilution plate 100 μ l are transferred using a multichannel pipette onto the replicon and tox plates mirror wells which contain 100 μ l of medium to obtain the desired final concentration.

Day 5Luciferase detection stage on the replicon plate

- 20 Media is tapped out from wells into Virkon and plates are washed once in warm PBS and tapped dry gently.

For each well 20 μ l of lysis buffer is added by multichannel pipette. Lysates are stable at this point for several hours.

Luciferase assay buffer is placed in the luminometer (Lmax, Molecular Devices).

- 25 The M injector is primed with 4x 300 μ l of luciferase assay buffer. The plate to be analyzed is placed in the luminometer and 100 μ l of luciferase assay buffer injected automatically into one well followed by 4 seconds integration read out.

After one second delay a second well is injected with 100 μ l of luciferase assay buffer followed by 4 seconds integration read out and so forth until all 96 wells are analyzed.

Once the reading is finished the luminometer injection system is washed with deionised water.

The data is acquired using the SOFTmax for Lmax Pro software package.

Toxicity determination on the tox plate:

- 5 Media is tapped out from wells into Virkon and plates tapped dry gently. To each well 100 μ l of 0.5 % solution of methylene blue in 50 % methanol is added to all wells including blanks (G12 and H12). Plates are left at RT for a minimum of 1 h. Plates are then rinsed gently by immersing in a plastic box with water, tapped dry gently and left open until they are fully dry. Dye is solubilized adding 100 μ l of 1 % lauroylsarcosine
- 10 to each well and shaking for 1 h at 37°C. Plates are read on the SpectraMax spectrophotometer at 620 nm wavelength using the SOFTmax Pro software package.

Results

- SOFTmax data files are exported as Excel or text files. A standard four parameters non-linear regression analysis of the data obtained from each compound is then used to
- 15 calculate the IC50.

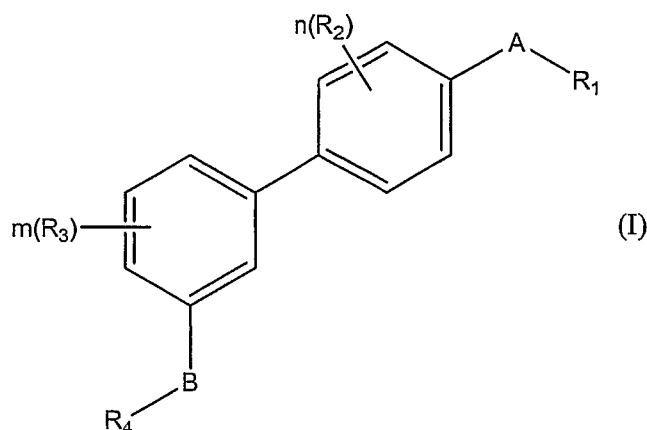
In the above analysis all replicate wells are meaned. The % of control is then calculated for each concentration point as a percentage of the DMSO control wells.

Example	IC50/ μ M *>1 μ M, **<1 μ M	TD50/ μ M, *<25 μ M, **>25 μ M
1	**	*
2	**	*
3	**	*
4	**	*
5	*	**
6	*	**
7	**	*
8	**	**
9	**	*
10	**	**
11	**	*
12	**	**
13	**	*
14	**	**
15	**	*
16	**	*

17		
18	**	
19	**	**
20	**	**
21	**	**
22	**	*
23	*	**
24	**	**
25	**	**
26	**	*
27	**	**
28	**	**
29	**	**
30	**	**
31	**	**
32	**	**
33	**	*
34	**	**
35	*	*
36	**	*
37	**	*
38	*	*
39	**	**
40	*	*
41	*	**
42	*	**
43	**	**
44	*	**
45	**	**
46	**	**
47	**	**
48	**	**
49	**	**
50	**	*
51	**	**
52	**	*
53	*	*
54	**	**
55	*	*
56	**	**
57	*	*
58	**	**
59	**	**

CLAIMS

1. Use of a compound which is a biphenyl derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or alleviating HCV



wherein:

- R_1 is a moiety $-A_1-L_1-A_1'$, $-A_1-L_1-A_1''-A_1'''$ or $-A_1-L_1-A_1'-Y_1-A_1'''$;
- 10 - A and B are the same or different and each represent a direct bond or a $-CO-NR'$, $-NR'-CO-$, $-NR'-CO-NR''-$, $-NR'-S(O)_2-$, $-S(O)_2-NR'-$ or $-NR'-$ moiety, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl;
- R_2 and R_3 are the same or different and each represent C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, halogen, hydroxy, thio,
- 15 $-NR'R''$, $-SO_2-R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1-C_4 alkyl and R''' represents C_1-C_4 alkyl;
- n and m are the same or different and each represent 0, 1 or 2;
- R_4 is a C_1-C_6 alkyl or C_1-C_6 haloalkyl group or a moiety $-A_4$, $-A_4-A_4'$, $-L_4-A_4$, $-A_4-L_4-A_4'$, $-A_4-Het_4-L_4-Het_4'-L_4'$ or $-L_4-Het_4-L_4'$,
- 20 - each A_1 , A_4 , A_1' , A_1'' and A_4' are the same or different and represent a phenyl, 5- to 10- membered heteroaryl, 5- to 10- membered heterocyclyl or C_3-C_6 carbocyclyl moiety;
- each L_1 and L_4 is the same or different and represents a C_1-C_4 alkylene or a C_1-C_4 hydroxyalkylene group;
- 25 - Y_1 represents $-CO-NR'$, $-CO-(C_1-C_4 \text{ alkylene})-$, $-CO-(C_1-C_4 \text{ alkylene})-NR'$, $-NR'-CO-$, $-CO-$, $-O-CO-$ or $-CO-O-$, wherein R' is hydrogen or C_1-C_4 alkyl;

- L_4' represents hydrogen or a C_1 - C_4 alkyl group;
- Het_4 and Het_4' are the same or different and represent -O-, -S- or -NR', wherein R' is hydrogen or a C_1 - C_4 alkyl group;

the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4 being

5 unsubstituted or substituted by (a) a single unsubstituted substituent selected from

-CO₂R', -SO₂NR''R'', -S(O)₂-R', -CONR''R'', -COR''', -CO-CO-OR''', -CO-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-CO-R''', -CO-(C₁-C₄ alkylene)-CO-NR''R'', -CO-(C₁-C₄ alkylene)-SO₂-R''', -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''-(C₁-C₄ alkylene)-NR''R'', -SO₂-(C₁-C₄ alkylene)-OR'', -NR''-SO₂-R''', -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R''', -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO-NR''R'' and -SO₂-(C₁-C₄ alkylene)-SO₂-R' and/or (b) 1, 2 or 3 unsubstituted substituents selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, C_1 - C_4 hydroxyalkyl,

10 hydroxy, cyano, nitro and -NR''R'', wherein each R' is the same or different and represents hydrogen, C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl,

provided that either:

- 20 (a) R_1 is -A₁-L₁-A₁'-A₁'' or -A₁-L₁-A₁'-Y₁-A₁''; or
- (b) R_1 is -A₁-L₁-A₁' and A₁' is substituted by a -CO₂R', -SO₂NR''R'', -SO₂-R', -CONR''R'', -COR''', -CO-CO-OR''', -CO-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-CO-R''', -CO-(C₁-C₄ alkylene)-CO-NR''R'', -CO-(C₁-C₄ alkylene)-SO₂-R''', -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-O-(C₁-C₄ alkylene)-NR''R'', -CO-(C₁-C₄ alkylene)-NR''-(C₁-C₄ alkylene)-OR'', -CO-(C₁-C₄ alkylene)-NR''-(C₁-C₄ alkylene)-NR''R'', -SO₂-(C₁-C₄ alkylene)-OR'', -NR''-SO₂-R''', -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO₂-R''', -(C₁-C₄ alkylene)-CO-(C₁-C₄ alkylene)-CO-NR''R'' or -SO₂-(C₁-C₄ alkylene)-SO₂-R' substituent, wherein each R' is the same or different and represents hydrogen, C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each
- 25 R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl; or
- 30 R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl; or

(c) n is 1 and R_2 is C_1 - C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2R'''$, $-NR'$ - COR''' or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl; or

(e) m is 1 and R_3 is C_1 - C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2R'''$, $-NR'$ - COR''' or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl; or

(e) R_4 is $-A_4$ -Het₄-L₄-Het₄'-L₄'.

2. Use according to claim 1, wherein the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4 are unsubstituted or substituted by (a) a single unsubstituted substituent selected from $-CO_2R'$, $-S(O)_2R'$, $-CONR''R'''$, $-COR'''$, $-CO-CO-OR'''$, $-CO-(C_1-C_4 \text{ alkylene})-OR''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''R'''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-CO-R'''$, $-CO-(C_1-C_4 \text{ alkylene})-SO_2R'''$, $-CO-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkylene})-OR''$, $-SO_2-(C_1-C_4 \text{ alkylene})-OR''$, $-NR''-SO_2R'''$, $-(C_1-C_4 \text{ alkylene})-CO-(C_1-C_4 \text{ alkylene})-CO_2R'''$, and $-SO_2-(C_1-C_4 \text{ alkylene})-SO_2R'$ and/or (b) 1, 2 or 3 unsubstituted substituents selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl and C_1 - C_4 haloalkoxy substituents, wherein each R' is the same or different and represents hydrogen, C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl.

3. Use according to claim 2, wherein the phenyl, heteroaryl, heterocyclyl and carbocyclyl moieties in R_1 and R_4 are unsubstituted or substituted by (a) a single unsubstituted substituent selected from $-S(O)_2(C_1-C_4 \text{ alkyl})$, $-S(O)_2-(C_1-C_4 \text{ haloalkyl})$, $-CO-NHR'''$, $-COR'''$, $-CO-CO-OR'''$, $-CO-(C_1-C_2 \text{ alkylene})-OR''$, $-CO-(C_1-C_2 \text{ alkylene})-NR''R'''$, $-CO-(C_1-C_2 \text{ alkylene})-NH-CO-R'''$, $-CO-(C_1-C_2 \text{ alkylene})-SO_2R'''$, $-CO-(C_1-C_2 \text{ alkylene})-O-(C_1-C_2 \text{ alkylene})-OR''$, $-SO_2-(C_1-C_4 \text{ alkylene})-OH$, $-NH-SO_2R'''$, $-(C_1-C_2 \text{ alkylene})-CO-(C_1-C_2 \text{ alkylene})-CO_2R'''$, and $-SO_2-(C_1-C_2 \text{ alkylene})-SO_2R'''$ and/or (b) 1 or 2 unsubstituted substituents selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 haloalkyl substituents, wherein, each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl.

4. Use according to any one of the preceding claims, wherein A_1 is a phenyl group.

5. Use according to any one of the preceding claims, wherein A_1 is unsubstituted.

6. Use according to any one of the preceding claims, wherein the A_1' moiety
5 represents a 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl group.

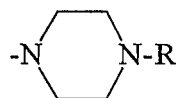
7. Use according to claim 6, wherein A_1' represents an unsubstituted S,S-dioxothiomorpholino group or a moiety



wherein R represents $-\text{CO}-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ haloalkyl})$ or $-\text{SO}_2-(\text{C}_1-\text{C}_2 \text{ alkylene})-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$.

8. Use according to claim 7 wherein R represents $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$.

9. Use according to any one of claims 1 to 7 wherein the compound of formula (I) is not a compound wherein R_1 is $-\text{phenyl}-\text{CH}_2-A_1'$ and A_1' is a moiety



wherein R is $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$.

10. Use according to any one of the preceding claims, wherein A_1'' is a C_3-C_6 cycloalkyl group.

11. Use according to claim 10, wherein A_1'' is unsubstituted.

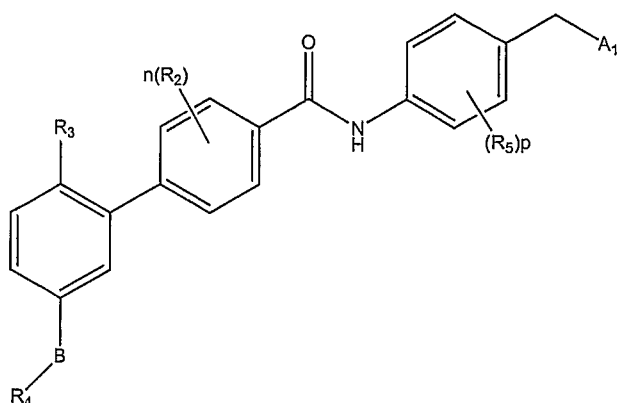
12. Use according to any one of the preceding claims, wherein each A_4 moiety is the same or different and is phenyl, 5- to 6- membered heteroaryl, 5- to 6- membered heterocyclyl or C_3-C_6 cycloalkyl.

13. Use according to any one of the preceding claims, wherein each A_4 moiety is unsubstituted or substituted with a C_1-C_2 alkyl group.

14. Use according to any one of the preceding claims, wherein each A_4' moiety is the same or different and represents a phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl group.
- 5
15. Use according to any one of the preceding claims, wherein each A_4' moiety is unsubstituted or substituted by a C_1 - C_2 alkyl group.
16. Use according to any one of the preceding claims, wherein L_1 and L_4 are the same or different and represent a C_1 - C_4 alkylene group.
- 10
17. Use according to any one of the preceding claims, wherein Y_1 represents $-CO-NR'$ - or $-NR'-CO-$, wherein R' is hydrogen or C_1 - C_4 alkyl.
18. Use according to any one of the preceding claims, wherein each Het_4 and Het_4' are the same or different and represent $-O-$ or $-NR'$ -, wherein R' is hydrogen or C_1 - C_2 alkyl.
- 15
19. Use according to any one of the preceding claims, wherein R_1 is $-A_1-L_1-A_1'$, wherein A_1 , L_1 and A_1' are as defined in any one of the preceding claims.
- 20
20. Use according to claim 19, wherein R_1 is a moiety $-phenyl-CH_2-A_1'$ wherein A_1' is as defined in any one of the preceding claims.
21. Use according to any one of the preceding claims, wherein A and B are the same or different and each represent $-NR'-CO-NR''-$, $-CO-NR'-$ or $-NR'-CO-$, wherein R' and R'' are the same or different and each represent hydrogen or C_1 - C_4 alkyl.
- 25
22. Use according to any one of the preceding claims, wherein n is 0 or 1 and/or m is 1.
- 30

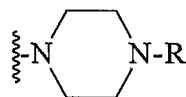
23. Use according to any one of the preceding claims, wherein each R_2 is the same or different and represents $-SO_2R'''$, $-CO_2R'''$, hydroxy or thio, wherein R''' is C_1 - C_4 alkyl.
- 5 24. Use according to any one of the preceding claims, wherein each R_3 is the same or different and represents C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, C_1 - C_2 haloalkyl, C_1 - C_2 haloalkoxy or $-NR'R''$, wherein R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl.
- 10 25. Use according to any one of the preceding claims, wherein R_4 is a moiety $-A_4$, $-A_4-A_4'$, $-A_4-L_4-A_4'$, $-A_4-Het_4-L_4-Het_4'-L_4'$ or $-L_4-Het_4-L_4'$.
27. Use according to any one of the preceding claims, wherein either:
- (a) R_1 is $-A_1-L_1-A_1'-A_1''$ or $-A_1-L_1-A_1'-Y_1-A_1''$; or
- 15 (b) R_1 is $-A_1-L_1-A_1'$ and A_1' is substituted by a $-CO_2-(C_1-C_4 \text{ haloalkyl})$, $-SO_2-(C_1-C_4 \text{ haloalkyl})$, $-COR'''$, $-SO_2-(C_1-C_4 \text{ alkylene})-SO_2-(C_1-C_4 \text{ haloalkyl})$, $-SO_2-(C_1-C_4 \text{ alkylene})-SO_2-R'''$, $CO-CO-OR'''$, $-CO-(C_1-C_4 \text{ alkylene})-OR''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''R''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-CO-R'''$, $-CO-(C_1-C_4 \text{ alkylene})-CO-NR''R''$, $-CO-(C_1-C_4 \text{ alkylene})-SO_2-R'''$, $-CO-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkylene})-OR''$,
20 $-CO-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkylene})-NR''R''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-(C_1-C_4 \text{ alkylene})-OR''$, $-CO-(C_1-C_4 \text{ alkylene})-NR''-(C_1-C_4 \text{ alkylene})-NR''R''$, $-SO_2-(C_1-C_4 \text{ alkylene})-OR''$, $-(C_1-C_4 \text{ alkylene})-CO-(C_1-C_4 \text{ alkylene})-CO_2-R'''$, $-(C_1-C_4 \text{ alkylene})-CO-(C_1-C_4 \text{ alkylene})-CO-NR''R''$ substituent, wherein each R'' is the same or different and represents hydrogen or C_1 - C_4 alkyl and R''' is a C_1 - C_4 alkyl group; or
- 25 (c) n is 1 and R_2 is C_1 - C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2-R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl; or
- (d) m is 1 and R_3 is C_1 - C_4 alkylthio, hydroxy, thio, $-NR'R''$, $-SO_2-R'''$, $-NR'-COR'''$ or $-CO_2R'''$, wherein R' and R'' are the same or different and represent hydrogen
30 or C_1 - C_4 alkyl and R''' represents C_1 - C_4 alkyl; or
- (e) R_4 is $-A_4-Het_4-L_4-Het_4'-L_4'$.
28. Use according to any of the preceding claims, wherein the biphenyl derivative of

formula (I) is a biphenyl derivative of formula (Ia)



wherein:

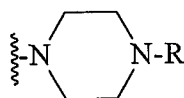
- 5 - A_1' is an unsubstituted S,S-dioxothiomorpholino group, a pyrrolidinyl group substituted with $-NH-SO_2-R'''$ or a moiety



- 10 wherein R represents $-S(O)_2-(C_1-C_4 \text{ alkyl})$, $-S(O)_2-(C_1-C_4 \text{ haloalkyl})$, $-CONHR'''$, $-COR'''$, $-CO-CO-OR'''$, $-CO-(C_1-C_2 \text{ alkylene})-OR''$, $-CO-(C_1-C_2 \text{ alkylene})-NR''R''$, $-CO-(C_1-C_2 \text{ alkylene})-NH-CO-R'''$, $-CO-(C_1-C_2 \text{ alkylene})-SO_2-R'''$, $-CO-(C_1-C_2 \text{ alkylene})-O-(C_1-C_2 \text{ alkylene})-OR''$, $-NH-SO_2-R'''$, $-SO_2-(C_1-C_4 \text{ alkylene})-OH$, $-(C_1-C_2 \text{ alkylene})-CO-(C_1-C_2 \text{ alkylene})-CO_2-R'''$ and $-SO_2(C_1-C_2 \text{ alkylene})-SO_2-R'''$, wherein each R'' is
- 15 the same or different and represents hydrogen or C_1-C_4 alkyl and each R''' is the same or different and represents C_1-C_4 alkyl;
- n is 0 or 1;
 - R_2 represents hydroxy, $-N(R''')_2$, $-NH-CO-R'''$ or $-SO_2-R'''$, wherein R''' represents C_1-C_4 alkyl;
- 20 - R_3 represents C_1-C_2 alkyl, C_1-C_2 alkoxy, halogen, C_1-C_2 haloalkoxy, C_1-C_2 haloalkyl or $-NR'R''$, wherein R' and R'' are the same or different and each represent C_1-C_2 alkyl;
- B represents $-NH-CO-NH-$, $-CO-NH-$ or $-NH-CO-$;
 - R_4 represents $-A_4$, $-A_4-A_4'$, $-L_4-A_4$, $-A_4-L_4-A_4'$, $-A_4-Het_4-L_4-Het_4'-L_4'$ or
- 25 $-L_4-Het_4-L_4'$;

- R_5 is C_1 - C_2 alkoxy, C_1 - C_2 haloalkyl or halogen;
- p is 0 or 1;
- each A_4 is a phenyl, 5- to 6- membered heteroaryl or C_3 - C_6 cycloalkyl group (preferably a phenyl, piperidiny, pyridyl, piperaziny, pyrrolidiny, cyclopropyl or
- 5 cyclohexyl group) which is unsubstituted or substituted by a C_1 - C_2 alkyl group;
- each A_4' moiety is a phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl group (preferably a morpholiny, phenyl, 2,6-dioxopiperidiny or triazolyl group) which is unsubstituted or substituted by a C_1 - C_2 alkyl group;
- L_4 is a C_1 - C_2 alkylene group;
- 10 - each Het_4 and Het_4' are the same or different and represent -O- or -NR', wherein R' represents hydrogen or C_1 - C_2 alkyl; and
- L_4' is a C_1 - C_2 alkyl group.

28. Use according to claim 27, wherein either:
- 15 (a) A_1' is a moiety



- wherein R is - SO_2 -(C_1 - C_4 haloalkyl), - CO - R''' , - CO - CO - OR''' , - CO -(C_1 - C_2 alkylene)- OR'' , - CO -(C_1 - C_2 alkylene)- $NR''R''$, - CO -(C_1 - C_2 alkylene)- NH - CO - R''' , - CO -(C_1 - C_2 alkylene)- SO_2 - R''' , - CO -(C_1 - C_2 alkylene)- O -(C_1 - C_2 alkylene)- OR'' , - SO_2 -(C_1 - C_4 alkylene)- OH , -(C_1 - C_2 alkylene)- CO -(C_1 - C_2 alkylene)- CO_2 - R''' or - SO_2 -(C_1 - C_2 alkylene)- SO_2 - R''' , wherein each R'' is the same or different and represent hydrogen or C_1 - C_4 alkyl and each R''' is the same or different and represents C_1 - C_4 alkyl;
- 25 (b) n is 1; or
- (c) R_3 is - $NR'R''$, wherein R' and R'' are the same or different and each represent C_1 - C_2 alkyl; or
- (d) R_4 represents - A_4 - Het_4 - L_4 - Het_4' - L_4' .

- 30 29. A biphenyl derivative of the formula (I), as defined in any preceding claim, or a pharmaceutically acceptable salt thereof, for the treatment of the human or animal body.

30. A biphenyl derivative of the formula (I), as defined in any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising a biphenyl derivative of formula (I),
5 as defined in any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

32. A pharmaceutical composition according to claim 31, which further comprises interferon and/or ribavirin.

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33. A product containing:

(a) biphenyl derivative of formula (I), as defined in any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof:

(b) interferon and/or ribavirin; and

15 (c) a pharmaceutically acceptable carrier or diluent;

for simultaneous separate or sequential use in the treatment of the human or animal body.

34. A method for ameliorating a hepatitis C infection in a patient, which method
20 comprises administering to said patient an effective amount of a biphenyl derivative of formula (I), as defined in any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof.