Recently, with the introduction of pegylated interferon, both initial and sustained response rates have improved, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy persist. Ribavirin causes significant hemolysis in 10-20% of patients treated at currently recommended doses, and the drug is both teratogenic and embryotoxic. Furthermore, a substantial number of patients do not respond with a sustained reduction in viral load, and there is a clear need for more effective antiviral therapy for HCV infection.

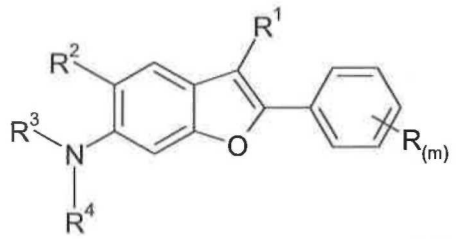
A number of approaches are being pursued to combat the virus. These include, for example, application of antisense oligonucleotides or ribozymes for inhibiting HCV replication. Furthermore, low-molecular weight compounds that directly inhibit HCV proteins and interfere with viral replication are considered attractive strategies to control HCV infection. Among the viral targets, the NS3/4a protease/helicase and the NS5b RNA-dependent RNA polymerase are considered the most promising viral targets for new drugs.

Based on the foregoing, there exists a significant need for new effective drugs for treating infections caused by HCV.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure provides benzofuran compounds substituted at the 6-position with a boron-containing moiety, pharmaceutical compositions comprising said compounds, methods of synthesis and uses of such compounds in treating and/or preventing viral infections, such as flavivirus infections, for example, HCV infections.

In one aspect, there is provided a compound of formula (I):



(I)

wherein:

R is independently selected from the group consisting of halogen, C_{1-6}alkyl, alkoxy, -CN, $-CF_3$, -O- C_{6-10}aryl optionally substituted by halogen, and -O-heteroaryl optionally substituted by halogen;

R^1 is $-C(O)OH$, $-C(O)NHR^5$ or heterocyclyl;

R^2 is C_{1-6}alkyl, C_{3-6}cycloalkyl, $-C(H)F_2$, $-CF_3$, or $-OR^6$;

R^3 is $-S(O)_2R^7$ or $-C(O)R^7$;

R^4 is

(a) heteroaryl substituted with $B(R^8)(R^9)$, $XB(R^8)(R^9)$, $OXB(R^8(R^9)$, $B^-(R^8)(R^9)(R^{12})$, $XB(R^8)R^9)(R^{12})$ or Het optionally substituted with hydroxy or hydroxyalkyl; and wherein heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, $-C(H)F_2$, $-CF_3$, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, $-C(O)NH_2$, $-C(O)OH$, $-C(O)NHR^5$, $-S(O)_2R^6$, $-S(O)_2NH_2$, -CN, $-OCF_3$, $-OR^6$, $-NR^{10}R^{11}$, $-NHC(O)R^{10}$, C_{3-6}cycloalkyl, and heterocyclyl;

(b) C_{6-10}aryl substituted with $B(R^8)(R^9)$, $XB(R^8)(R^9)$, $OXB(R^8(R^9)$, $B^-(R^8)(R^9)(R^{12})$, $XB(R^8)R^9)(R^{12})$ or Het optionally substituted with hydroxy or hydroxyalkyl; and wherein C_{6-10}aryl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, $-C(H)F_2$, $-CF_3$, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, $-C(O)NH_2$, $-C(O)OH$, $-C(O)NHR^5$, $-S(O)_2R^6$, $-S(O)_2NH_2$, -CN, $-OCF_3$, $-OR^6$, $-NR^{10}R^{11}$, $-NHC(O)R^{10}$, C_{3-6}cycloalkyl, and heterocyclyl; or

(c) Het optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, $-C(H)F_2$, $-CF_3$, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, $-C(O)NH_2$, $-C(O)OH$, $-C(O)NHR^5$, $-S(O)_2R^6$, $-S(O)_2NH_2$, -CN, $-OCF_3$, $-OR^6$, $-NR^{10}R^{11}$, $-NHC(O)R^{10}$, C_{3-6}cycloalkyl, and heterocyclyl;

Het is a 5 or 6-membered monocyclic heterocyclic ring or 8- to 11- membered bicyclic heterocyclic ring system any ring of which is either saturated, partially saturated or unsaturated, which may be optionally benzofused if monocyclic or which may be optionally spiro-fused, and wherein each Het consists of one or more carbon atoms and one boron atom and one or more oxygen atoms; one boron atom, one oxygen atom, and one nitrogen atom; or one boron atom and one or more nitrogen atoms;

R^5 is hydrogen, C_{1-6}alkyl ,hydroxy, or $-OR^6$;

R^6 is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^7 is C_{1-6}alkyl, hydroxyalkyl, or aminoalkyl,

R^8, R^9, and R^{12} are each independently hydroxy, alkoxy, or aminoalkyl; or R^8 and R^9 or R^8, R^9, and R^{12} together with the boron atom to which they are attached form a 5 to 14-membered ring, said ring comprising carbon atoms and optionally one or more heteroatoms which can be N or O; said ring may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxyalkyl, aminoalkyl, amino, oxo, C(O)OH, $C(O)OXOR^{13}$, $C(O)N(R^{10})(R^{11})$, $N(R^{10})(R^{11})$, and C_{3-6}cycloalkyl each of which may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, halogen, C(O)OH, $C(O)N(R^{10})(R^{11})$, and $N(R^{10})(R^{11})$;

R^{10} and R^{11} are each independently hydrogen or C_{1-6}alkyl;

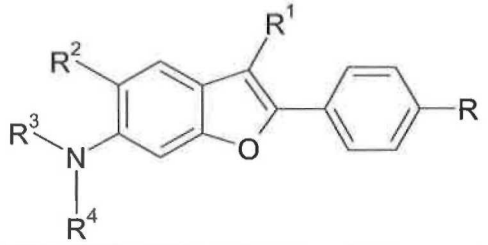
R^{13} is alkoxy;

X is alkylene or –Oalkylene wherein alkylene is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F_2, -CF_3, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2NH_2$, -CN, -OCF_3, -OR^6, -$NR^{10}R^{11}$, -$NHC(O)R^{10}$ and C_{3-6}cycloalkyl;

m is 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound of formula (I)'



(I)'

wherein:

R is F or Cl;

R^1 is -C(O)NHR^5;

R^2 is C_{3-6}cycloalkyl;

R^3 is -S(O)$_2R^7$;

R^4 is

(a) heteroaryl substituted with B(R^8)(R^9) or X B(R^8)(R^9), and optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F_2, -CF_3, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2NH_2$, -CN, -OCF_3, -OR^6, -$NR^{10}R^{11}$, -$NHC(O)R^{10}$, C_{3-6}cycloalkyl, and heterocyclyl;

(b) C_{6-10}aryl substituted with B(R^8)(R^9), or XB(R^8)(R^9), and optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F_2, -CF_3, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2NH_2$, -CN, -OCF_3, -OR^6, -$NR^{10}R^{11}$, -$NHC(O)R^{10}$, C_{3-6}cycloalkyl, and heterocyclyl; or

(c) Het optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F_2, -CF_3, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2NH_2$, -CN, -OCF_3, -OR^6, -$NR^{10}R^{11}$, -$NHC(O)R^{10}$, C_{3-6}cycloalkyl, and heterocyclyl;

Het is a 5 or 6-membered monocyclic heterocyclic ring or 8- to 11- membered bicyclic heterocyclic ring system any ring of which is either saturated, partially saturated or unsaturated, which may be optionally benzofused if monocyclic or which may be optionally

spiro-fused, and wherein each Het consists of one or more carbon atoms and one boron atom and one or more oxygen atoms; one boron atom, one oxygen atom, and one nitrogen atom; or one boron atom and one or more nitrogen atoms;

R^5 is C_{1-6}alkyl;

R^6 is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^7 is C_{1-6}alkyl, hydroxyalkyl or aminoalkyl;

R^8 and R^9 are each independently hydroxy, alkoxy, or aminoalkyl; or R^8 and R^9 together with the boron atom to which they are attached form a 5 to 14-membered ring, said ring comprising carbon atoms and optionally one or more heteroatoms which can be N or O; said ring may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxyalkyl, aminoalkyl, amino, oxo, C(O)OH, C(O)OXOR^{13}, C(O)N(R^{10})(R^{11}), N(R^{10})(R^{11}), and C_{3-6}cycloalkyl each of which may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, halogen, and C(O)OH, C(O)N(R^{10})(R^{11}), and N(R^{10})(R^{11});

R^{10} and R^{11} are each independently hydrogen or C_{1-6}alkyl;

R^{13} is alkoxy;

X is alkylene or –Oalkylene, wherein alkylene is optionally substituted with halogen, C_{1-6}alkoxy, -C(H)F_2, -CF_3, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2NH_2$, -CN, -OCF_3, -OR^6, -$NR^{10}R^{11}$, -NHC(O)R^{10} , C_{3-6}cycloalkyl; or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound selected from the group consisting of:
(2-Chloro-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid;
(2-Chloro-4-(N-(2-(4-chlorophenyl)-5-cyclopropyl-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid;
4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenylboronic acid;
3-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenylboronic acid;
4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-fluorophenylboronic acid;
4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-3-fluorophenylboronic acid;
4-(N-(2-(4-chlorophenyl)-5-cyclopropyl-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-fluorophenylboronic acid;
6-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)pyridin-3-ylboronic acid;

(4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-(difluoromethyl)phenyl)boronic acid;

(4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-(trifluoromethyl)phenyl)boronic acid;

(4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2,6-difluorophenyl)boronic acid;

(2-cyano-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)boronic acid;

6-(N-(4-borono-3-chlorophenyl)methylsulfonamido)-2-(4-chlorophenyl)-5-cyclopropylbenzofuran-3-carboxylic acid;

(4-(N-(3-carbamoyl-2-(4-chlorophenyl)-5-cyclopropylbenzofuran-6-yl)methylsulfonamido)-2-chlorophenyl)boronic acid;

6-(N-(7-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide;

(4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-(methylsulfonyl)phenyl)boronic acid;

1-(2-Chloro-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenyl)-4-methyl-2,6,7-trioxa-1-borabicyclo[2.2.2]octan-1-uide;

((4-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenoxy)methyl)boronic acid;

((2-Chloro-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenoxy)methyl)boronic acid;

5-Cyclopropyl-2-(4-fluorophenyl)-6-(N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide;

(4-(N-(2-(4-Chlorophenyl)-5-cyclopropyl-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)-2-cyanophenyl)boronic acid;

5-Cyclopropyl-2-(4-fluorophenyl)-N-methyl-6-(N-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)benzofuran-3-carboxamide;

(2-Chloro-4-(N-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenethyl)boronic acid;

5-Cyclopropyl-6-(N-(7-fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)methylsulfonamido)-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide;

6-(N-(3-Chloro-4-(2-hydroxy-1,2-oxaborolan-4-yl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide;

(3-(N-(5-Cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)phenethyl)boronic acid;

6-(N-(3-Chloro-4-(2-hydroxy-1,2-oxaborolan-5-yl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide;

6-(N-(3-Chloro-4-(2-hydroxy-1,2-oxaborolan-5-yl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, enantiomer 1;

6-(N-(3-Chloro-4-(2-hydroxy-1,2-oxaborolan-5-yl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide, enantiomer 2;

5-Cyclopropyl-2-(4-fluorophenyl)-6-(N-(1-hydroxy-3,4-dihydro-1H-benzo[c][1,2]oxaborinin-6-yl)methylsulfonamido)-N-methylbenzofuran-3-carboxamide;

and pharmaceutically acceptable salts thereof.

In another aspect, there is provided a pharmaceutically acceptable salt of a compound as disclosed herein.

In another aspect, there is provided a pharmaceutical composition comprising a compound as disclosed herein together with at least one pharmaceutically acceptable excipient.

In another aspect, there is provided a compound as disclosed herein for use in medical therapy.

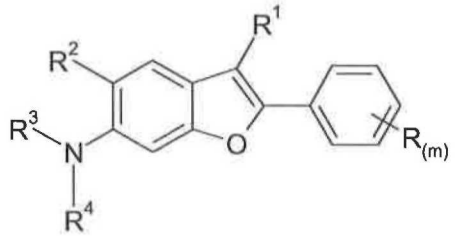
In another aspect, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating or preventing a viral infection or disease associated with such infection.

In another aspect, there is provided a compound as disclosed herein for use in treating or preventing a viral infection or disease associated with such infection.

In another aspect, there is provided a compound of formula (I) or (I)' as disclosed herein in combination with one or more active anti-viral agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound of formula (I):



(I)

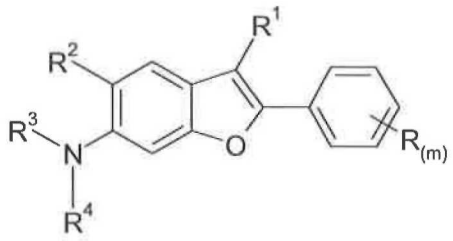
wherein:

R is independently selected from the group consisting of halogen, C_{1-6}alkyl, alkoxy, -CN, $-CF_3$, -O- C_{6-10}aryl optionally substituted by halogen, and -O-heteroaryl optionally substituted by halogen;

R^1 is $-C(O)OH$, $-C(O)NHR^5$ or heterocyclyl;

Claims

1. A compound of formula (I):



(I)

~~W~~wherein:

R is independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkyl, alkoxy, -CN, $-CF_3$, -O- C_{6-10}aryl optionally substituted by halogen, and -O-heteroaryl optionally substituted by halogen;

R^1 is –C(O)OH, -C(O)NHR^5 or heterocyclyl;

R^2 is $C_{1\text{-}6}$alkyl, $C_{3\text{-}6}$cycloalkyl, -C(H)F_2, -CF_3, or -OR^6;

R^3 is -S(O)$_2$R^7 or -C(O)R^7;

R^4 is

(a) heteroaryl substituted with B(R^8)(R^9), X B(R^8)(R^9), OXB(R^8(R^9), B$^-$(R^8)(R^9)(R^{12}), XB(R^8)R^9)(R^{12}) or Het optionally substituted with hydroxy or hydroxyalkyl; and wherein heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkoxy, -C(H)F_2, -CF_3, $C_{1\text{-}6}$alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2$$NH_2$, -CN, -$OCF_3$, -OR^6,' -NR^{10}R^{11}, -NHC(O)R^{10} , $C_{3\text{-}6}$cycloalkyl, and heterocyclyl;

(b) C_{6-10}aryl substituted with B(R^8)(R^9), X B(R^8)(R^9), OXB(R^8(R^9), B$^-$(R^8)(R^9)(R^{12}), XB(R^8)R^9)(R^{12}) or Het optionally substituted with hydroxy or hydroxyalkyl; and wherein C_{6-10}aryl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkoxy, -C(H)F_2, -CF_3, $C_{1\text{-}6}$alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2$$NH_2$, -CN, -$OCF_3$, -OR^6, -NR^{10}R^{11}, -NHC(O)R^{10} , $C_{3\text{-}6}$cycloalkyl, and heterocyclyl; or

(c) Het optionally substituted with one or more substituents independently selected from the group consisting of halogen, $C_{1\text{-}6}$alkoxy, -C(H)F_2, -CF_3, $C_{1\text{-}6}$alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2$$NH_2$, -CN, -$OCF_3$, -OR^6, -NR^{10}R^{11}, -NHC(O)R^{10} , $C_{3\text{-}6}$cycloalkyl, and heterocyclyl;

Het is a 5 or 6-membered monocyclic heterocyclic ring or 8- to 11- membered bicyclic heterocyclic ring system any ring of which is either saturated, partially saturated or

unsaturated, which may be optionally benzofused if monocyclic or which may be optionally spiro-fused, and wherein each Het consists of one or more carbon atoms and one boron atom and one or more oxygen atoms; one boron atom, one oxygen atom, and one nitrogen atom; or one boron atom and one or more nitrogen atoms;

R^5 is hydrogen, C_{1-6}alkyl ,hydroxy, or -OR^6;

R^6 is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^7 is C_{1-6}alkyl, hydroxyalkyl, or aminoalkyl,

R^8 , R^9 , and R^{12} are each independently hydroxy, alkoxy, or aminoalkyl; or R^8 and R^9 or R^8 , R^9 , and R^{12} together with the boron atom to which they are attached form a 5 to 14-membered ring, said ring comprising carbon atoms and optionally one or more heteroatoms which can be N or O; said ring may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxyalkyl, aminoalkyl, amino, oxo, C(O)OH, C(O)OXOR^{13}, C(O)N(R^{10})(R^{11}), N(R^{10})(R^{11}), and C_{3-6}cycloalkyl each of which may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, halogen, C(O)OH, C(O)N(R^{10})(R^{11}), and N(R^{10})(R^{11});

R^{10} and R^{11} are each independently hydrogen or C_{1-6}alkyl;

R^{13} is alkoxy;

X is alkylene or –Oalkylene, wherein alkylene is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F_2, -CF_3, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH_2, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2NH_2$, -CN, -OCF_3, -OR^6, -$NR^{10}R^{11}$, -NHC(O)R^{10} and C_{3-6}cycloalkyl;

m is 1, 2, or 3;

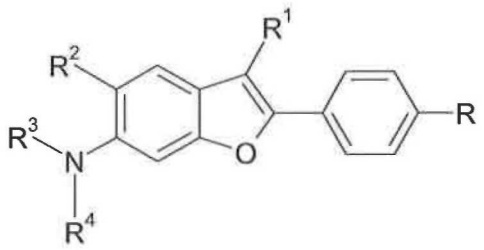
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1 wherein R is halogen; m is 1; R^1 is -C(O)NHR^5 wherein R^5 is C_{1-6}alkyl; R^2 is C_{3-6}cycloalkyl; R^3 is -S(O)$_2R^7$ wherein R^7 is C_{1-6}alkyl and R^4 is C_{6-10}aryl substituted ~~with~~ with B(R^8)(R^9) or X(R^8)(R^9), wherein R^8 and R^9 are both hydroxy, and wherein C_{6-10}aryl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -CN, -C(H)F_2 and -CF_3.

3. A compound of formula (I) according to claim 1 wherein R is halogen; m is 1; R^1 is -C(O)NHR^5 wherein R^5 is C_{1-6}alkyl; R^2 is C_{3-6}cycloalkyl; R^3 is -S(O)$_2R^7$ wherein R^7 is C_{1-6}alkyl and R^4 is heteroaryl substituted with B(R^8)(R^9) or X(R^8)(R^9), wherein R^8 and R^9 are both hydroxy, and wherein heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -CN, -C(H)F_2 and -CF_3.

4. A compound of formula (I) according to claim 1 wherein R is halogen; m is 1;R^1 is -C(O)NHR^5 wherein R^5 is C_{1-6}alkyl; R^2 is C_{3-6}cycloalkyl; R^3 is -S(O)$_2$R^7 wherein R^7 is C_{1-6}alkyl, and R^4 is Het substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, and -CN.

5. A compound of formula (I)'



(I)'

wherein:

R is F or Cl;

R^1 is -C(O)NHR^5;

R^2 is C_{3-6}cycloalkyl;

R^3 is -S(O)$_2$R^7 ;

R^4 is

(a) heteroaryl substituted with B(R^8)(R^9) or X B(R^8)(R^9), and optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F$_2$, -CF$_3$, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH$_2$, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2$NH$_2$, -CN, -OCF$_3$, -OR^6, -NR^{10}R^{11}, -NHC(O)R^{10} , C_{3-6}cycloalkyl, and heterocyclyl;

(b) C_{6-10}aryl substituted with B(R^8)(R^9), or XB(R^8)(R^9), and optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F$_2$, -CF$_3$, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH$_2$, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2$NH$_2$, -CN, -OCF$_3$, -OR^6, -NR^{10}R^{11}, -NHC(O)R^{10} , C_{3-6}cycloalkyl, and heterocyclyl; or

(c) Het optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6}alkoxy, -C(H)F$_2$, -CF$_3$, C_{1-6}alkyl, hydroxy, hydroxyalkyl, aminoalkyl, -C(O)NH$_2$, –C(O)OH, -C(O)NHR^5, -S(O)$_2$ R^6, -S(O)$_2$NH$_2$, -CN, -OCF$_3$, -OR^6, -NR^{10}R^{11}, -NHC(O)R^{10} , C_{3-6}cycloalkyl, and heterocyclyl;

Het is a 5 or 6-membered monocyclic heterocyclic ring or 8- to 11- membered bicyclic heterocyclic ring system any ring of which is either saturated, partially saturated or unsaturated, which may be optionally benzofused if monocyclic or which may be optionally spiro-fused, and wherein each Het consists of one or more carbon atoms and one boron