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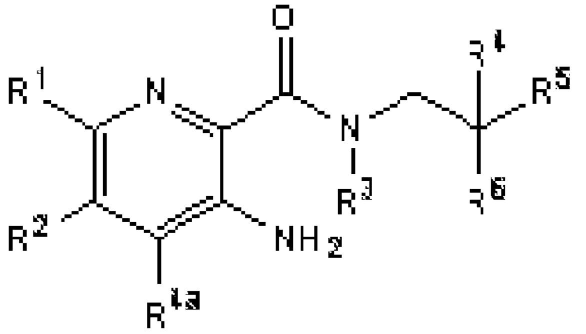

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(57) Abstract: The present invention provides pyridine derivatives which restore or enhance the function of mutant and/or wild type CFTR to treat cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sire, or constipation (IBS, IBD, opioid induced). Pharmaceutical compositions comprising such derivatives are also encompassed.

Title

PYRIDINE AMIDE DERIVATIVES USEFUL IN THE TREATMENT OF CYSTIC FIBROSIS

Field of the invention

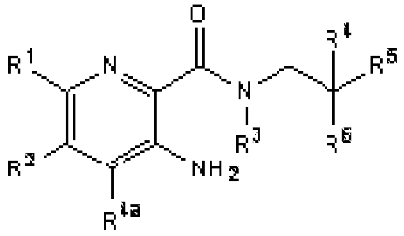
This invention relates to pyridine amide derivatives, their preparation and use as pharmaceuticals.

Background

Cystic fibrosis (CF) is a fatal genetic disease caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR), a protein kinase A (PKA)-activated epithelial anion channel involved in salt and fluid transport in multiple organs, including the lung. Most CF mutations either reduce the number of CFTR channels at the cell surface (e.g., synthesis or processing mutations) or impair channel function (e.g., gating or conductance mutations) or both. There are currently no approved therapies that target CFTR directly. The present invention discloses compounds which restore or enhance the function of mutant and/or wild type CFTR to treat cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sire, or constipation (IBS, IBD, opioid induced).

Description of the invention

In a first aspect, the invention provides compounds according to Formula I:



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wherein:

R^1 is H; C-i-Ce alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -$C_{1\text{-}C4}$ alkyl-C_3-C_8 cycloalkyl; C_1-C_8

alkoxy optionally substituted by one or more halogen atoms; halogen; $SO_2NR^8R^9$; SO_2R^{10}; S-C_1-C_8alkyl optionally substituted by one or more halogen atoms; S-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; CN; $NR^{11}R^{12}$; $CONR^{13}R^{14}$; $NR^{13}SO_2R^{15}$; $NR^{13}C(0)R^{15}$ and CO_2R^{15}, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is $C_{1\text{-}C4}$ haloalkyl;

R^3 and R^4 are each independently H or C_1-C_8 alkyl optionally substituted by one or more halogen atoms;

R^{4a} is selected from halogen; C_2-C_8 alkenyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl; and C_1-C_8 hydroxyalkyl; wherein the -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^5 and R^6 are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -C_1-C_4 alkyl-C_3-C_8 cycloalkyl; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -(C_0-C_4 alkyl)-CO_2R^{15}, wherein the cycloalkyl, cycloalkenyl, -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or

R^5 and R^6 are each independently a group of the formula:
-$(CH_2)_m$-$NR^{17}R^{18}$; or

R^5 and R^6 are each independently a group of the formula:
-$(CH_2)_m$-OR^4; or

R^4 and R^5 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered carbocyclic ring system or a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R^4, R^5 and R^6 cannot all be the same;

m is 0, 1, 2 or 3;

R^8, R^{11}, R^{13} and R^{17} are each independently H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms, C_3-C_{10} cycloalkyl or -(C_{1}-C_4 alkyl)-C_3-C_8 cycloalkyl;

R^9, R^{10}, R^{12}, R^{14}, R^{15}, R^{16} and R^{18} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -C_1-C_4 alkyl-C_3-C_8 cycloalkyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^8 and R^9, R^{11} and R^{12}, R^{13} and R^{14}, and R^{17} and R^{18} together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{18}(S0_2)R^{21}$, $(S0_2)NR^{19}R^{21}$, $(S0_2)R^{21}$, $NR^{18}C(0)R^{21}$, $C(0)NR^{19}R^{21}$, $NR^{18}C(0)NR^{19}R^{21}$, $NR^{18}C(0)OR^{19}$, $NR^{19}R^{21}$, $C(0)OR^{19}$, $C(0)R^{19}$, SR^{19}, OR^{19}, oxo, CN,

$N0_2$, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C1-C4 alkoxy-CrC$_4$ alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and C(0)Ci-C$_6$ alkyl; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- 0-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(0)CrC$_6$ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH_2, C(0)NHC"|-C$_6$ alkyl or C(0)N(Ci-C$_6$ alkyl)2; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0)$_2$-aryl; S(0)$_2$-Ci-C$_6$ alkyl; Ci-C$_6$ alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC$_6$ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by Ci-C$_6$ alkyl, Ci-C$_6$ haloalkyl or Ci-C$_6$ alkoxy;
or a pharmaceutically acceptable salt thereof.

Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In an embodiment of the invention as described anywhere herein, R^1 is selected from H; C-i-Ce alkoxy optionally substituted by one or more halogen atoms; or halogen.

In an embodiment of the invention as described anywhere herein, R^1 is C_1-C_4 alkyl optional substituted by one or more halogen atoms. For example, $-CH_3$ or CF_3.

In an embodiment of the invention as described anywhere herein, R^1 is C_1-C_4 alkoxy optional substituted by one or more halogen atoms. For example, $-OCH_3$ or $-OCF_3$.

In an embodiment of the invention as described anywhere herein, R^1 is aryl, wherein aryl is phenyl optionally substituted by one or more Z substituents, specific example are 4-fluorophenyl, 4-chloro-2-methylphenyl, or 2,4-dichlorophenyl.

In an embodiment of the invention as described anywhere herein, R^1 is 6 membered heterocyclyl group, wherein 6 membered heterocyclyl group is pyridyl optionally substituted by one or more Z substituents, specific example is 1-methyl-4-pyridyl.

In an embodiment of the invention as described anywhere herein, R^1 is Br, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, 4-fluorophenyl, 4-chloro-2-methylphenyl, or 2,4-dichlorophenyl.

In an embodiment of the invention as described anywhere herein, R^2 is CF_3CF_2-, $(CF_3)_2CH$-, CH_3-CF_2-, CF_3CF_2-, CF_3, CF_2H-, CH_3-CCl_2-, $CF_3CFCClH$-, CBr_3, CBr_2H-$CF_3CF_2CHCF_3$ or $CF_3CF_2CF_2CF_2$-.

In an embodiment of the invention as described anywhere herein, R^2 is CF_3.

In an embodiment of the invention as described anywhere herein, R^3 is H or methyl.

An embodiment of the invention, as defined above provides a compound, where R^5 provides a heteroatom two carbons from the amide nitrogen, wherein the heteroatom is oxygen or nitrogen.

An embodiment of the invention as defined above provides a compound according to Formula I, wherein
R^4 is H, C_1-C_4 alkyl optionally substituted by one or more halogen atoms or not present;

R^5 is C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; -$(CH_2)_m$-$NR^{17}R^{18}$; -$(CH_2)_m$-OR',or OH;
m is 0, or 1;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or
R^4 and R^5 together form an oxo group (C=0); or
R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein
R^1 is halogen, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, or C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;
R^2 is C1-C4 haloalkyl;
R^3 is H;
R^4 is H or Me;
R^5 is -$(CH_2)_m$-$NR^{17}R^{18}$; -$(CH_2)_m$-OR'; or OH;
m is 0, or 1;
R^6 is C-i-C_4 alkyl optionally substituted by one or more halogen atoms; or
R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R^1 is halogen, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, or C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;

R^2 is C1-C4 haloalkyl;

R^3 is H;

R^4 and R^5 together form an oxo group (C =0); and

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents..

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R^1 is C-i-C_4 alkyl optionally substituted by one or more halogen atoms;

R^2 is C1-C4 haloalkyl;

R^3 is H;

R^4 is H or Me;

R^5 is -$(CH_2)_m$-$NR^{17}R^{18}$; -$(CH_2)_m$-OR'; or OH;

m is 0, or 1;

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and

R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R^1 is C-i-C_4 alkoxy optionally substituted by one or more halogen atoms;

R^2 is C_{1}-C_4 haloalkyl;

R^3 is H;

R^4 is H or Me;

R^5 is $-(CH_2)_m-NR^{17}R^{18}$; $-(CH_2)_m-OR$; or OH;

m is 0, or 1;

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and

R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R^1 is C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;;

R^2 is C_{1}-C_4 haloalkyl;

R^3 is H;

R^4 is H or Me;

R^5 is $-NR^{17}R^{18}$; or OH;

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and

R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein

R^1 is C-i-C_4 alkyl optionally substituted by one or more halogen atoms;

R^2 is C_{1}-C_4 haloalkyl;

R^3 is H;

R^4 is H or Me;
R^5 is $-NR^{17}R^{18}$; or OH;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; and
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

An embodiment of the invention as defined above provides compounds according to Formula I, wherein
R^1 is C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;
R^2 is C_1-C_4 haloalkyl;
R^3 is H;
R^4 is H or Me;
R^5 is $-NR^{17}R^{18}$; or OH;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; and
R^{17} and R^{18} are each independently H; or d-C $_4$ alkyl optionally substituted by one or more halogen atoms.

In an embodiment of the invention as described anywhere herein, wherein
Z is independently OH, d-C $_4$ alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or d-C $_4$ alkoxy, $NR^{19}R^{21}$, C(0)OR ^{19}, C(0)R ^{19}, SR^{19}, OR^{19}, CN, $N0_2$, or halogen;
R^{19} and R^{21} are each independently H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; or C_1-C_4 alkoxy-Cr C_4 alkyl, wherein all alkyls are optionally substituted with halogens.

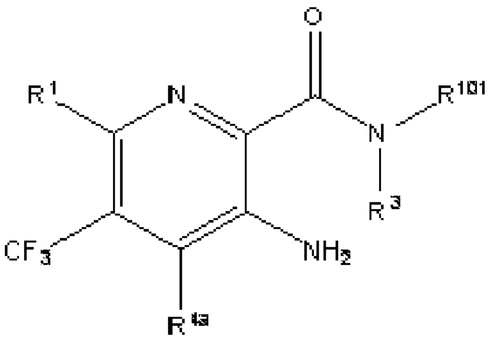
In an embodiment of the invention as described anywhere herein, wherein
Z is independently OH, d-C $_4$ alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or d-C $_4$ alkoxy, C(0)OR ^{19}, C(0)R ^{19}, OR^{19}, CN, or halogen;
R^{19} is H; d-C $_4$ alkyl; C_3-C_6 cycloalkyl; or d-C $_4$ alkoxy-C_1-C_4 alkyl, wherein all alkyl are optionally substituted with halogens.

In an embodiment of the invention as described anywhere herein, wherein Z is independently, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy or halogen.

Another embodiment of the invention as defined above provides compounds with substantially pure enantiomers with the R configuration.

Another embodiment of the invention as defined above provides compounds with substantially pure enantiomers with the S configuration.

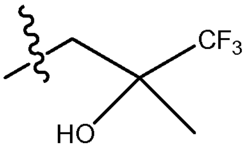
Certain compounds of Formula I include compounds of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein A, R^1, R^2 and R^3 have the definitions of Formula I and

R^{101} is



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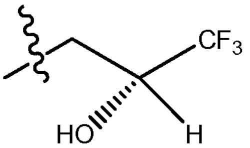

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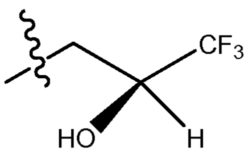

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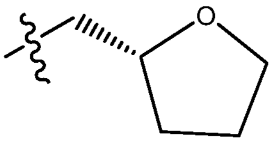

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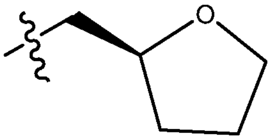

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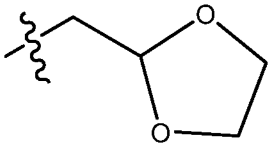

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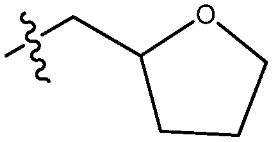

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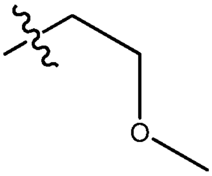
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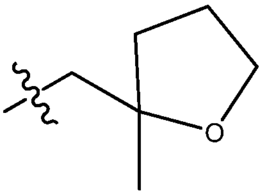
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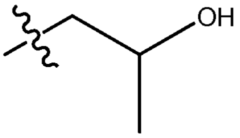
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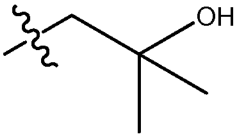
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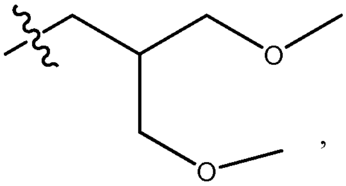
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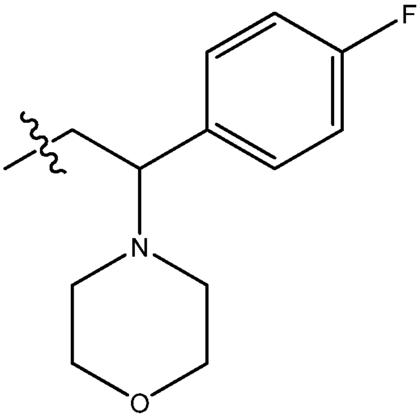
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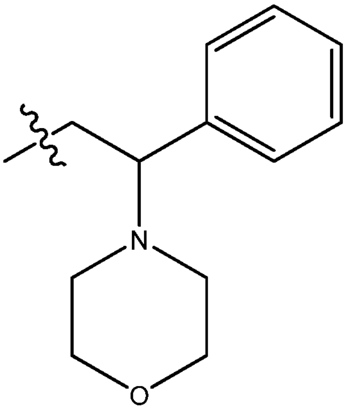
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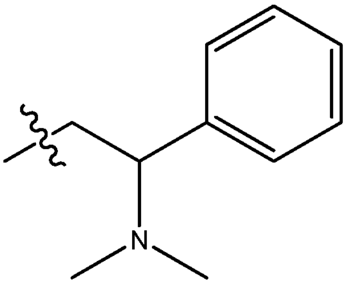
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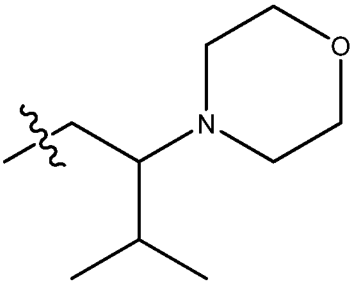
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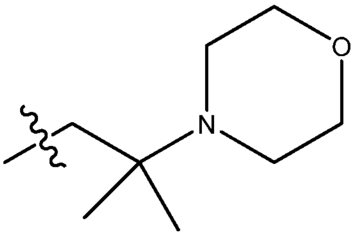
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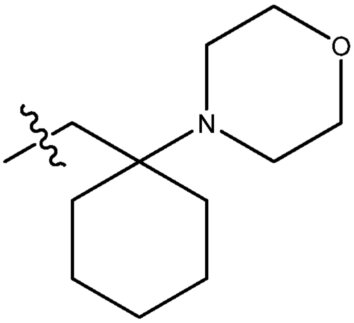
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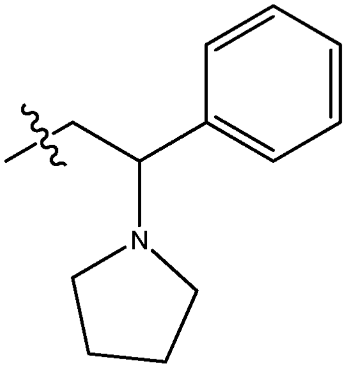

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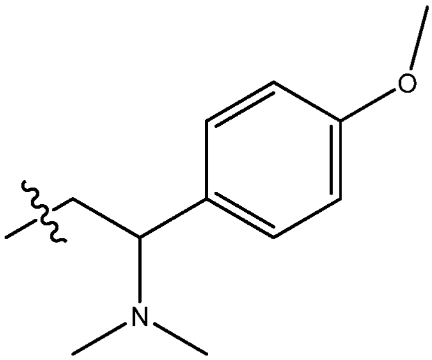

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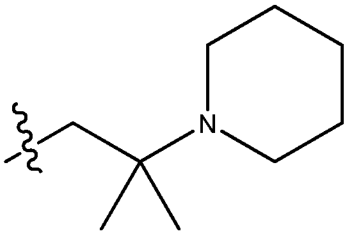

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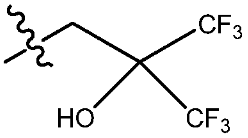

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In a further embodiment of Formula II of the invention herein, R^1 is selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; halogen; C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; and $NR^{11}R^{12}$, wherein the aryl and heterocyclic groups are each optionally substituted by one or more Z substituents.

In a further embodiment of Formula II of the invention wherein, R^1 is C_1-C_4 alkyl optional substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; halogen; C_6 aryl; or 6 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclic groups are each optionally substituted by one or more Z substituents.

In a further embodiment of Formula II of the invention wherein, R^1 is C_1-C_4 alkyl optional substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; or halogen.

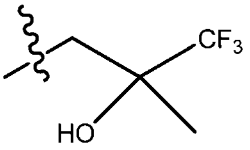
In a further embodiment of Formula II of the invention herein, R^3 is H or methyl.

An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is halogen;

R^3 is H;

R^{101} is



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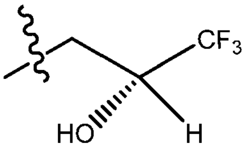

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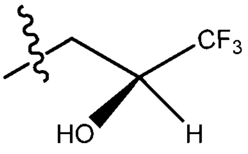

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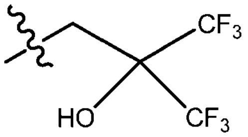

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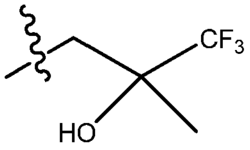
An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is C_1-C4 alkyl optionally substituted by one or more halogen atoms;

R^3 is H;

R^{101} is



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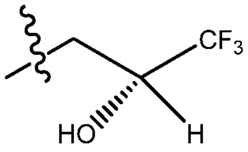

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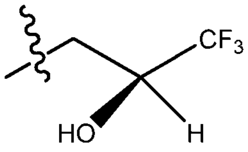

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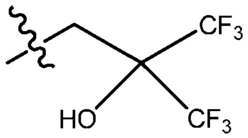

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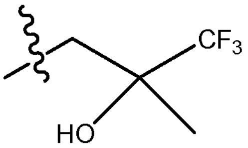
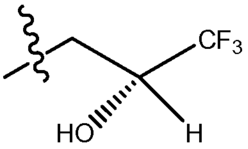
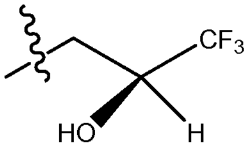
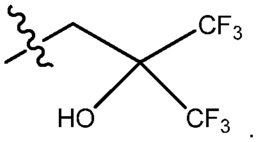
An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is C_1-C4 alkoxy optionally substituted by one or more halogen atoms;

R^3 is H;

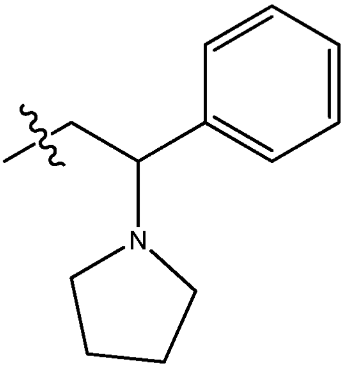
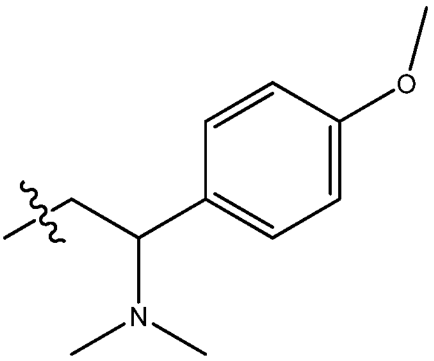
R^{101} is , , , or

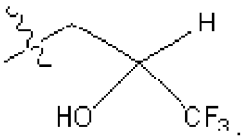
.

An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is halogen, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, or C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;

R^3 is H;

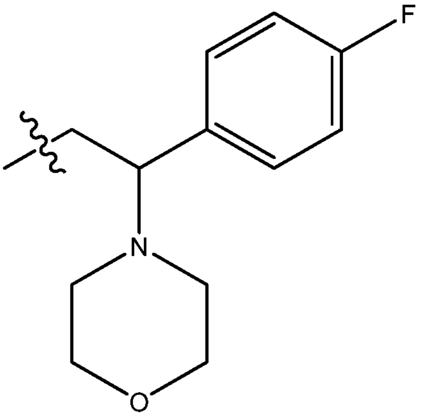
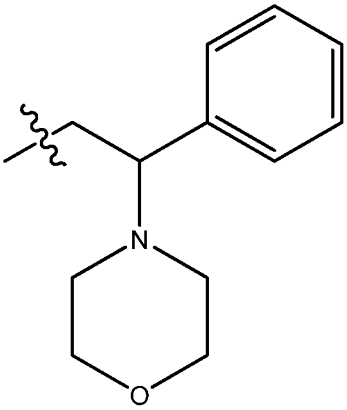
R^{101} is , , or

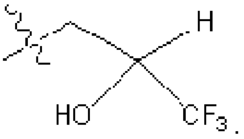
.

An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is halogen, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, or C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;

R^3 is H;

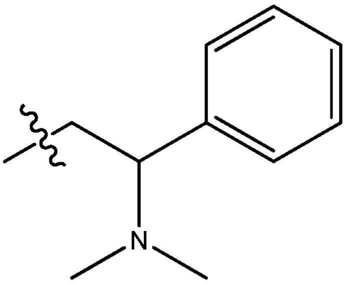
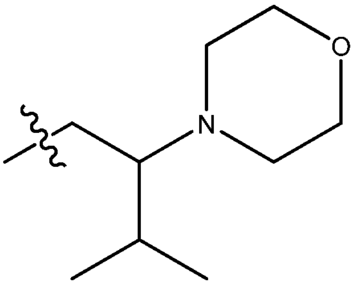
R^{101} is , , or

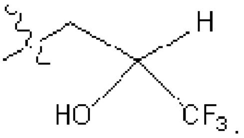
.

An embodiment of the invention as defined above provides compounds according to Formula II, wherein

R^1 is halogen, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, or C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;

R^3 is H;

R^{101} is , , or

.

Another embodiment of the invention as defined above provides compounds according to Formula I and Formula II, represented by

(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide;
(S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-4-vinylpicolinamide; and
3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide;
or a pharmaceutically acceptable salt thereof.

It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments. It is understood by those skilled in the art that combinations of substituents where not possible are not an aspect of the present invention.

Especially preferred specific compounds of formula (I) or formula II are those described hereinafter in the Examples.

Definitions

Terms used in the specification have the following meanings:

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

Optionally substituted by one or more Z groups" denotes that the relevant group may include one or more substituents, each independently selected from the groups included within the definition of Z. Thus, where there are two or more Z group substituents, these may be the same or different.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

"C-i-Ce-Alkyl", as used herein, denotes straight chain or branched alkyl having 1-8 carbon atoms. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "Ci-C $_4$-Alkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

"C-i-Ce -Alkoxy", as used herein, denotes straight chain or branched alkoxy having 1-8 carbon atoms. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "C-i-C_4-Alkoxy" will represent methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

"C_1-C_4-Haloalkyl", as used herein, denotes straight chain or branched alkyl having 1-4 carbon atoms with at least one hydrogen substituted with a halogen. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "d-Q-Haloalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with halogen, such as where the halogen is fluorine: CF_3CF_2-, $(CF_3)_2CH$-, CH_3-CF_2-, CF_3CF_2-, CF_3, CF_2H-, $CF_3CF_2CHCF_3$ or $CF_3CF_2CF_2CF_2$-.

"C-i-Ce -hydroxyalkyl", as used herein, denotes straight chain or branched alkyl having 1-8 carbon atoms with at least one hydrogen substituted with a hydroxy group. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "d-Q-hydroxyalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with a hydroxy group.

The term '$C_{2\text{-}8}$ alkenyl' as used herein refers to a linear or branched saturated hydrocarbon group containing from 2 to 8 carbon atoms that contains at least one carbon to carbon double bond. Examples of such groups include ethenyl, propenyl, butenyl and pentenyl. Unless a particular structure is specified, the terms butenyl and pentenyl etc. include all possible Eand Z isomers.

The term "$C_{2\text{-}8}$ alkynyl" as used herein refers to a linear or branched saturated hydrocarbon group containing from 2 to 8 carbon atoms that contains at least one carbon to carbon triple bond. Examples of such groups include ethynyl, propynyl, butynyl and pentynyl.

The term 'C_{3-8} cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 6 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkylene" denotes a straight chain or branched saturated hydrocarbon chain containing between 1 and 8 carbon atoms. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.
"Amino-C-i-Ce-alkyl" and "amino-C-i-Cs-alkoxy" denote amino attached by a nitrogen atom to C_1-C_8-alkyl, e.g., NH_2-(Ci-C_8)-, or to Ci-C_8-alkoxy, e.g., NH_2-(Ci-C_8)-0-. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.
"CrC_8-Alkylamino" and "di(CrC_8-alkyl)amino" denote Ci-C_8-alkyl, as hereinbefore defined, attached by a carbon atom to an amino group. The C-i-C_8-alkyl groups in di(CrC_8-alkyl)amino may be the same or different. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.

"Amino-(hydroxy)-C_1-C_8-alkyl" denotes amino attached by a nitrogen atom to C_1-C_8-alkyl and hydroxy attached by an oxygen atom to the same CrC_8-alkyl. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.

"CrCs-Alkylcarbonyl" and "CrC_8-alkoxycarbonyl", as used herein, denote CrCe-alkyl or C_1-C_8-alkoxy, respectively, as hereinbefore defined, attached by a carbon atom to a carbonyl group. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.

"C_3-C_8-Cycloalkylcarbonyl", as used herein, denotes C_3-C_8-cycloalkyl, as hereinbefore defined, attached by a carbon atom to a carbonyl group. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.

"C_7-C_{14}-Aralkyl", as used herein, denotes alkyl, e.g., Ci-C_4-alkyl, as hereinbefore defined, substituted by a C_6-C_{10}-aromatic carbocyclic group, as herein defined. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly.

"C_3-C_{15}-Cycloalkyl", as used herein, denotes a cycloalkyl having 3- to 15-ring carbon atoms that is saturated or partially saturated, such as a C_3-C_8-cycloalkyl. Examples of C_3-C_{15}-cycloalkyls include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl or a bicyclic group, such as bicyclooctyl, bicyclononyl including indanyl and indenyl and bicyclodecyl. If a different number of carbon atoms is specified, such as C_6, then the definition is to be amended accordingly.

"aryl" or "C_6-C_{15}-Aromatic carbocyclic group", as used herein, denotes an aromatic group having 6- to 15-ring carbon atoms. Examples of C_6-C_{15}-aromatic carbocyclic groups include, but are not limited to, phenyl, phenylene, benzenetriyl, naphthyl, naphthylene, naphthalenetriyl or anthrylene. If a different number of carbon atoms is specified, such as C-io, then the definition is to be amended accordingly.

"4- to 8-Membered heterocyclyl", "5- to 6- membered heterocyclyl", "3- to 10-membered heterocyclyl", "3- to 14-membered heterocyclyl", "4- to 14-membered heterocyclyl" and "5- to 14-membered heterocyclyl", refers, respectively, to 4- to 8-membered, 5- to 6-membered, 3- to 10-membered, 3- to 14-membered, 4- to 14-membered and 5- to 14-membered heterocyclic rings containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, which may be saturated, partially saturated or unsaturated (aromatic). The heterocyclyl includes single ring groups, fused ring groups and bridged groups. Examples of such heterocyclyls include, but are not limited to, furan, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, isotriazole, tetrazole, thiadiazole, isothiazole, oxadiazole, pyridine, piperidine, pyrazine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, pyrrolidine, pyrrolidinone, morpholine, triazine, oxazine, tetrahyrofuran, tetrahydrothiophene, tetrahydrothiopyran, tetrahydropyran, 1,4-dioxane, 1,4-oxathiane, indazole, quinoline, indazole, indole, 8-aza-bicyclo[3.2.1]octane or thiazole.

A second aspect of the invention provides a compound of Formula I or II as defined anywhere herein for use as a pharmaceutical.

A further aspect of the invention provides a compound of Formula I or II for use in the treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease or mucosal hydration. Such conditions include, for example, cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sire, or constipation (IBS, IBD, opioid induced).

A still further aspect of the present invention provides for the use of a compound of formula (I) or (II), as defined in any of the aforementioned embodiments, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease or mucosal hydration.

An embodiment of the present invention provides for the use of a compound of formula (I) or (II), as defined in any of the aforementioned embodiments, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition selected from cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sire, or constipation (IBS, IBD, opioid induced).

An embodiment of the present invention provides for the use of a compound of formula (I) or (II), as defined in any of the aforementioned embodiments, in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition which is cystic fibrosis.

An embodiment of the present invention provides method for the prevention or treatment of a CFTR mediated condition or disease comprising administering an effective amount of at least one compound as described herein to a subject in need of such treatment. Such CFTR mediated condition or disease are selected from cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sire, or constipation (IBS, IBD, opioid induced).

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", should be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfornate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, and sulfosalicylic acid.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/0781 63. Hence the invention further provides co-crystals comprising a compound of formula (I).

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as *(R)-* or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active *(R)-* and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the *(R)-*, (S)- or *(R,S)-* configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the *(R)-* or (S)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis-* (Z)- or *trans-* (E)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric *(cis* or *trans)* isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-0, 0'-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-1 0-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1 %, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

Compounds of the present invention are either obtained in the free form, or as a salt thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}g, ^{36}Cl, 125, respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labeled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I) or (II). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-labeled compounds of formula (I) or (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_20 , de-acetone, de-DMSO.

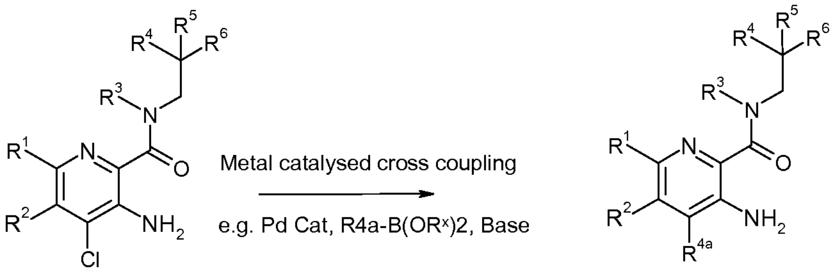
Compounds of the invention, i.e. compounds of formula (I) or formula (II) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) or formula (II) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) or formula (II) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I) or formula (II).

Synthesis

Generally, compounds according to Formula I or (II) can be synthesized by the routes described in Scheme 1, 2 and 3 and the Examples.

When R^{4a} is alkenyl, aryl or heteroaryl, compounds may be synthesized according to general scheme 1

Scheme 1

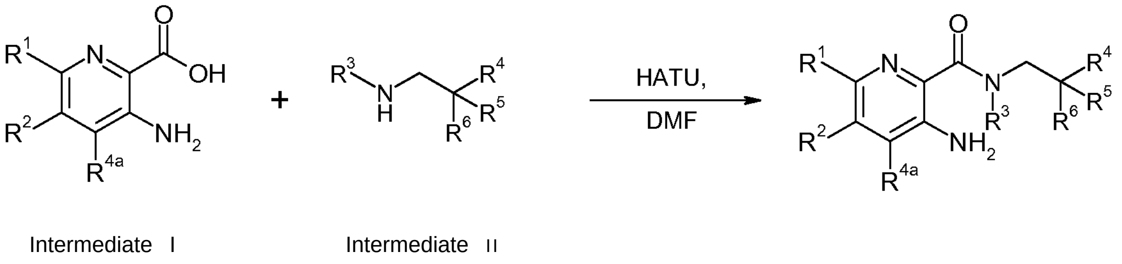


wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as previously defined for compounds of formula I and II, and $B(OR^x)_2$ refers to a boronic acid or boronate ester coupling agent.

A suitable palladium catalyst to use is [1,1'-bis(di-tertbutylphospino)ferrocene] dichloropalladium(II). A skilled person would understand that other palladium catalysts may also be suitable.

The right hand side of the moiety is typically added via an amide formation reaction as shown below in general scheme 2.

Scheme 2

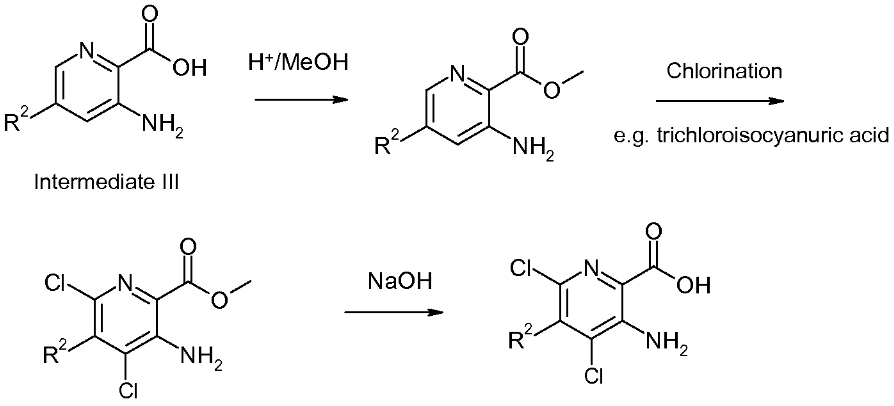


HATU (2-(1 H-7-Azabenzotriazol-1-yl)-1 ,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium) is a peptide coupling agent. A skilled person would understand that other coupling agents could possibly work.

The amine intermediate II, is either available commercially, or has a published synthesis.

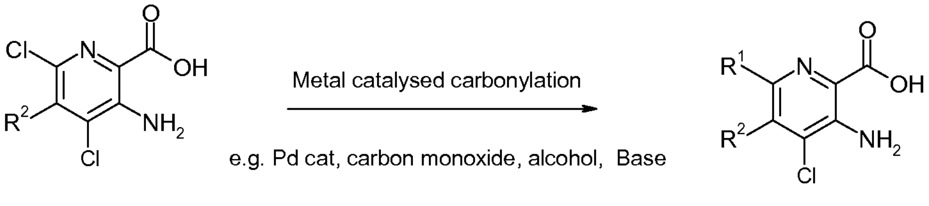
When R^1 is halogen and R^{4a} is halogen, intermediate I may be synthesized according to scheme 3.

Scheme 3



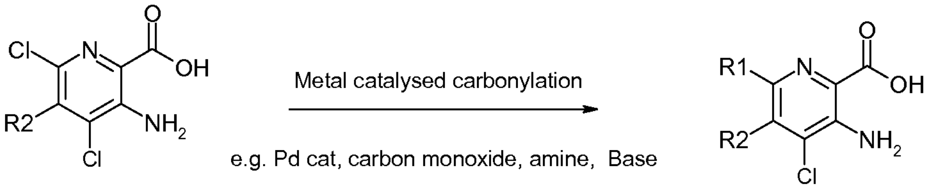
When R^1 is carboxylate, and R^{4a} is halogen, intermediate I may be synthesized according to the method in scheme 4

Scheme 4



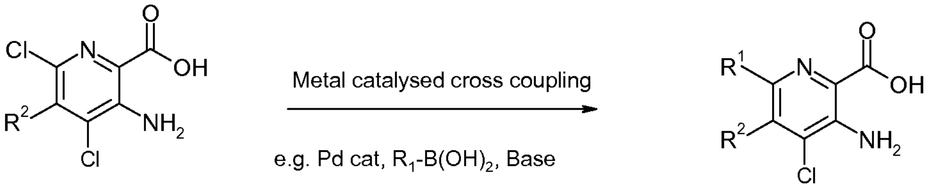
When R1 is carboxamide, and R4a is halogen, intermediate I may be synthesized according to the method in scheme 5

Scheme 5



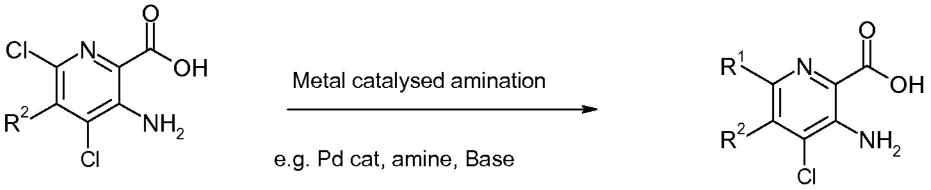
When R^1 is alkyl, aryl, or heteroaryl, and R^{4a} is halogen intermediate I may be synthesized according to scheme 6.

Scheme 6



When R^1 is alkyl amino and R^4 is halogen, intermediate I may be synthesized according to the general scheme 7

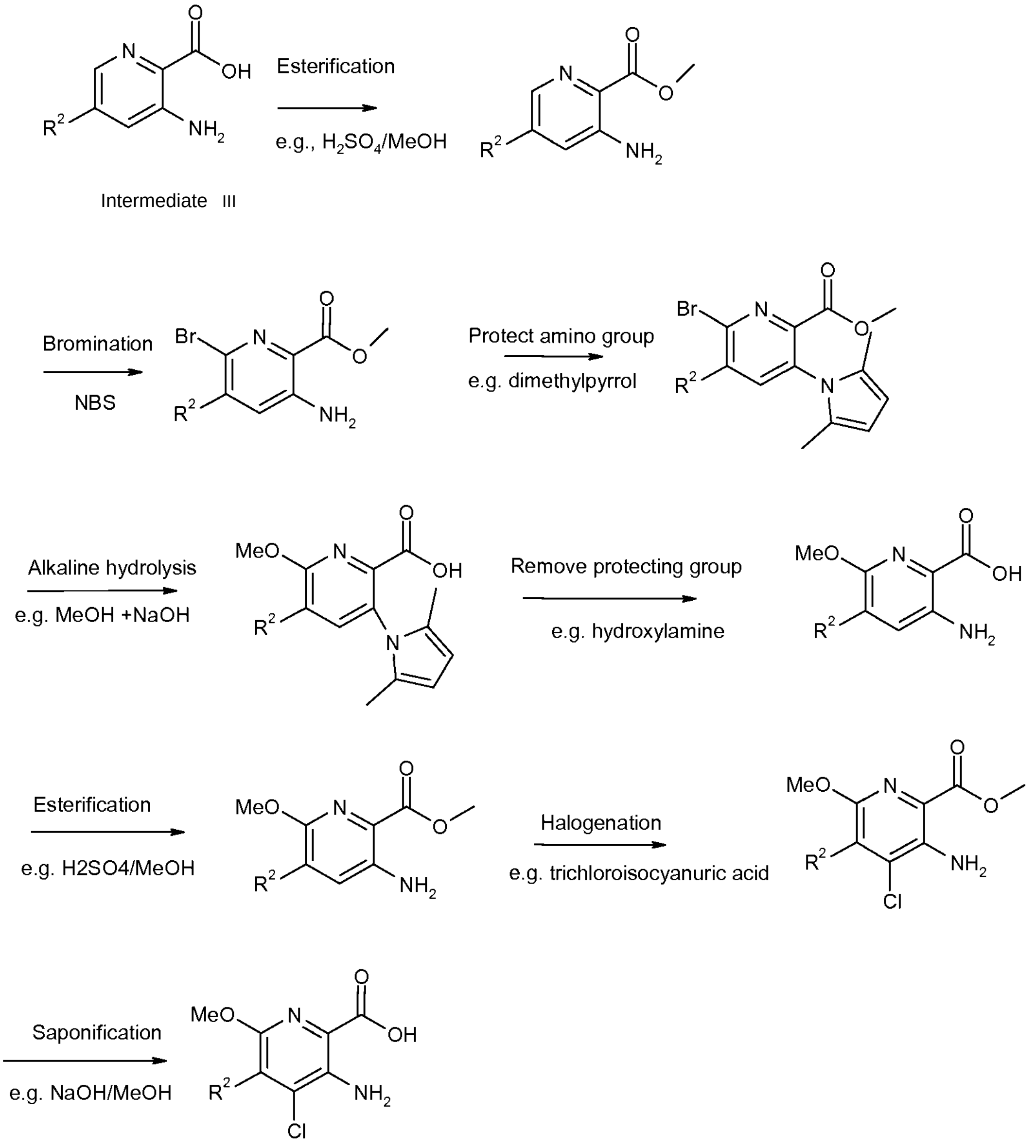
Scheme 7



For schemes 4 to 7, a suitable palladium catalyst to use is [1,1'-bis(di-tertbutylphospino)ferrocene] dichloropalladium(II). A skilled person would understand that other palladium catalysts may also be suitable.

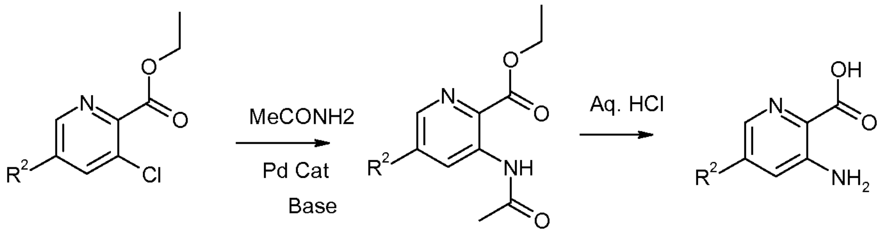
When R^1 is methoxy, R^{4a} is halogen, Intermedate I may be synthesized according to the general scheme 8

Scheme 8



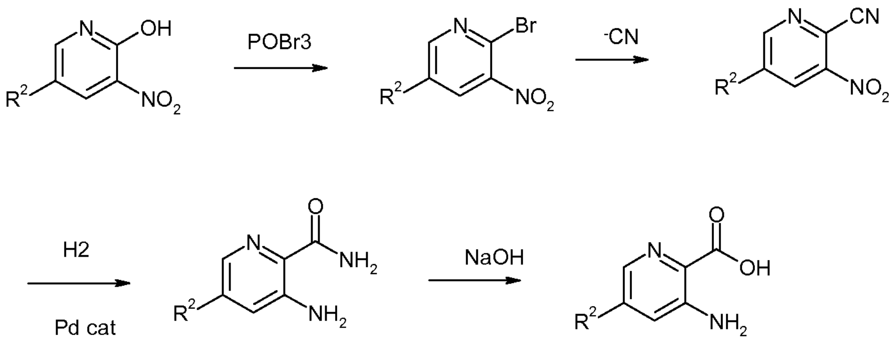
Intermediate III may be synthesized according to the general scheme 9 or scheme 10

Scheme 9.



Or alternatively

Scheme 10



The skilled person will appreciate that the general synthetic routes detailed above show common reactions to transform the starting materials as required. The specific reaction conditions are not provided, but these are well known to those skilled in the art and appropriate conditions considered to be within the skilled person's common general knowledge.

The starting materials are either commercially available compounds or are known compounds and can be prepared from procedures described in the organic chemistry art.

Compounds of formula (I) or (II), in free form, may be converted into salt form, and vice versa, in a conventional manner understood by those skilled in the art. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula (I) or (II) can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as stereoisomers, may be obtained in a conventional manner, e.g., by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g., optically active, starting materials.

The compounds of formula (I) or (II) can be prepared, e.g., using the reactions and techniques described below and in the Examples. The reactions may be performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The various substituents on the synthetic intermediates and final products shown in the following reaction schemes can be present in their fully elaborated forms, with suitable protecting groups where required as understood by one skilled in the art, or in precursor forms which can later be elaborated into their final forms by methods familiar to one skilled in the art. The substituents can also be added at various stages throughout the synthetic sequence or after completion of the synthetic sequence. In many cases, commonly used functional group manipulations can be used to transform one intermediate into another intermediate, or one compound of formula (I) or (II) into another compound of formula (I) or (II). Examples of such manipulations are conversion of an ester or a ketone to an alcohol; conversion of an ester to a ketone; interconversions of esters, acids and amides; alkylation, acylation and sulfonylation of alcohols and amines; and many others. Substituents can also be added using common reactions, such as alkylation, acylation, halogenation or oxidation. Such manipulations are well-known in the art, and many reference works summarize procedures and methods for such manipulations. Some reference works which gives examples and references to the primary literature of organic synthesis for many functional group manipulations, as well as other transformations commonly used in the art of organic synthesis are *March's Organic Chemistry,* 5th Edition, Wiley and Chichester, Eds. (2001); *Comprehensive Organic Transformations,* Larock, Ed., VCH (1989); *Comprehensive Organic Functional Group Transformations,* Katritzky et al. (series editors), Pergamon (1995); and *Comprehensive Organic Synthesis,* Trost and Fleming (series editors), Pergamon (1991). It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. Multiple protecting groups within the same molecule can be chosen such that each of these protecting groups can either be removed without removal of other protecting groups in the same molecule, or several protecting groups can be removed using the same reaction step, depending upon the outcome desired. An authoritative account describing many alternatives to the trained practitioner is Greene and Wuts, *Protective Groups in Organic Synthesis,* Wiley and Sons (1999).

Pharmacological activity

Having regard to their modulation of CFTR activity, compounds of formula (I), in free or pharmaceutically acceptable salt form, hereinafter alternately referred to as "agents of the invention", are useful in the treatment of conditions which respond to the modulation of CFTR activity, particularly conditions benefiting from mucosal hydration such as cystic fibrosis.

Diseases mediated by modulation of CFTR activity, include diseases associated with the regulation of fluid volumes across epithelial membranes. For example, the volume of airway surface liquid is a key regulator of mucociliary clearance and the maintenance of lung health. The modulation of CFTR activity will promote fluid accumulation on the mucosal side of the airway epithelium thereby promoting mucus clearance and preventing the accumulation of mucus and sputum in respiratory tissues (including lung airways). Such diseases include respiratory diseases, such as cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, respiratory tract infections (acute and chronic; viral and bacterial) and lung carcinoma. Diseases mediated by modulation of CFTR activity also include diseases other than respiratory diseases that are associated with abnormal fluid regulation across an epithelium, perhaps involving abnormal physiology of the protective surface liquids on their surface, e.g., Sjogren's Syndrome, xerostomia (dry mouth) or keratoconjunctivitis sire (dry eye). Furthermore, modulation of CFTR activity in the kidney could be used to promote diuresis and thereby induce a hypotensive effect.

Treatment in accordance with the invention may be symptomatic or prophylactic.

Asthma includes intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g., of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g., of acute asthmatic or bronchoconstrictor attack, improvements in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e., therapy for or intended to restrict or abort symptomatic attack when it occurs, e.g., anti-inflammatory (e.g., cortico-steroid) or bronchodilatory. Prophylactic benefit in asthma may, in particular, be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g., between the hours of about 4-6 am, i.e., at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Chronic obstructive pulmonary disease includes chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular, other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis.

Dry eye disease is characterized by a decrease in tear aqueous production and abnormal tear film lipid, protein and mucin profiles. There are many causes of dry eye, some of which include age, laser eye surgery, arthritis, medications, chemical/thermal burns, allergies and diseases, such as cystic fibrosis and Sjogren's Syndrome.

Increasing anion secretion via CFTR would enhance fluid transport from the corneal endothelial cells and secretory glands surrounding the eye to increase corneal hydration. This would help to alleviate the symptoms associated with dry eye disease.

Sjogren's Syndrome is an autoimmune disease in which the immune system attacks moisture-producing glands throughout the body, including eye, mouth, skin, respiratory tissue, liver, vagina and gut. Symptoms include dry eye, dry mouth and dry vagina, as well as lung disease. The disease is also associated rheumatoid arthritis, systemic lupus, systemic sclerosis and polymypositis/dermatomyositis. Defective protein trafficking is believed to cause the disease, for which treatment options are limited. Modulators of CFTR activity may hydrate the various organs affected by the disease and help to alleviate the associated symptoms.

The suitability of CFTR activity modulators as a treatment of a disease benefiting from mucosal hydration may be tested by determining the movement of chloride ions in a suitable cell-based assay. For example single cells or confluent epithelia, endogenously expressing or engineered to overexpress CFTR can be used to assess channel function using electrophysiological techniques or ion flux studies. See methods described in: Hirsh et al., *J Pharm Exp Ther* (2004); Moody et al., *Am J Physiol Cell Physiol* (2005).

CFTR activity modulators, including the compounds of formula (I), are also useful as co-therapeutic agents for use in combination with other drug substances, such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of cystic fibrosis or obstructive or inflammatory airways diseases such as those mentioned hereinbefore, e.g., as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs.

The compounds of Formula (I) or (II) may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Accordingly, the invention includes as a further aspect a combination of a CFTR activity modulator with osmotic agents (hypertonic saline, dextran, mannitol, Xylitol), ENaC blockers, an anti-inflammatory, bronchodilatory, antihistamine, anti-tussive, antibiotic and/or DNase drug substance, wherein the CFTR activity modulator and the further drug substance may be in the same or different pharmaceutical composition.

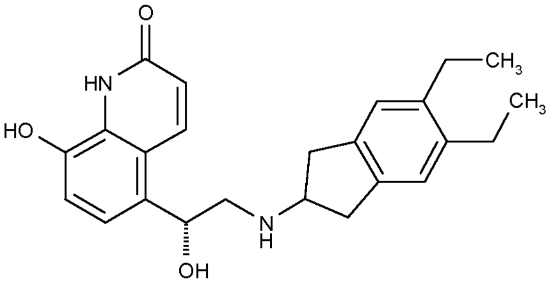
Suitable antibiotics include macrolide antibiotics, e.g., tobramycin (TOBI™).

Suitable DNase drug substances include dornase alfa (Pulmozyme™), a highly-purified solution of recombinant human deoxyribonuclease I (rhDNase), which selectively cleaves DNA. Dornase alfa is used to treat cystic fibrosis.

Other useful combinations of CFTR activity modulators with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1 , CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists, such as Schering-Plough antagonists SC-351 125, SCH-55700 and SCH-D; Takeda antagonists, such as A/-[[4-[[[6,7-dihydro-2-(4-methyl-phenyl)-5/-/-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-A/,A/-dimethyl-2H-pyran-4-amin-ium chloride (TAK-770); and CCR-5 antagonists described in USP 6,166,037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

Suitable anti-inflammatory drugs include steroids, in particular, glucocorticosteroids, such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/35668, WO 03/48181 , WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 and WO 04/66920; non-steroidal glucocorticoid receptor agonists, such as those described in DE 10261874, WO 00/00531 , WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935 and WO 04/26248; LTD4 antagonists, such as montelukast and zafirlukast; PDE4 inhibitors, such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-1 1294A (Napp), BAY19-8004

(Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659/PD1 68787 (Parke-Davis), **AWD - 12-281** (Asia Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751 , WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451 , WO 04/018457, WO 04/018465, WO 04/018431 , WO 04/018449, WO 04/018450, WO 04/018451 , WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; adenosine A2B receptor antagonists such as those described in WO 02/42298; and beta-2 adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol, carmoterol or pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula (I) of WO 00751 14, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula:



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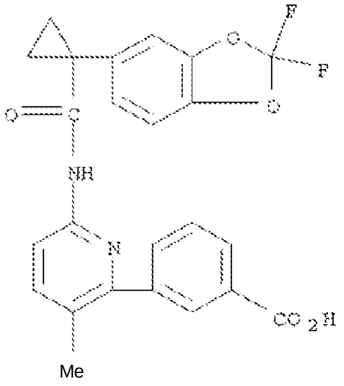
corresponding to indacaterol or pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula (I) of WO 04/16601, and also compounds of EP 1440966, JP 05025045, WO 93/18007, WO 99/64035, USP 2002/0055651 , WO 01/42193, WO 01/83462, WO 02/66422, WO 02/70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618, WO 04/46083, WO 04/80964, WO 04/108765 and WO 04/108676.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular, ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in EP 424021 , USP 3,714,357, USP 5,171,744, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/018422 and WO 04/05285.

Suitable dual anti-inflammatory and bronchodilatory drugs include dual beta-2 adrenoceptor agonist/muscarinic antagonists such as those disclosed in USP 2004/0167167, WO 04/74246 and WO 04/74812.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine, as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841.

The invention includes as a further aspect a combination of a CFTR activity modulator with a CFTR corrector, wherein the CFTR activity modulator and the CFTR corrector may be in the same or different pharmaceutical composition. Suitable CFTR correctors include VX-809



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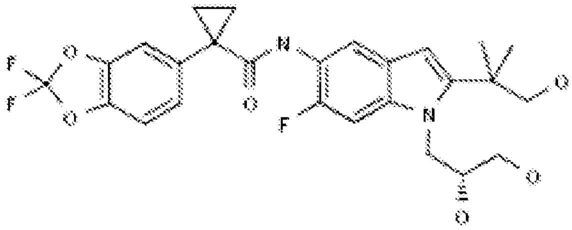
and

VX-661



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In accordance with the foregoing, the invention also provides as a further aspect a method for the treatment of a condition responsive to modulation of CFTR activity, e.g., diseases associated with the regulation of fluid volumes across epithelial membranes, particularly an obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula (I) or (II), in free form or in the form of a pharmaceutically acceptable salt.

In another aspect the invention provides a compound of formula (I) or (II), in free form or in the form of a pharmaceutically acceptable salt, for use in the manufacture of a medicament for the treatment of a condition responsive to modulation of CFTR activity, particularly an obstructive airways disease, e.g., cystic fibrosis and COPD.

The agents of the invention may be administered by any appropriate route, e.g. orally, e.g., in the form of a tablet or capsule; parenterally, e.g., intravenously; by inhalation, e.g., in the treatment of an obstructive airways disease; intranasally, e.g., in the treatment of allergic rhinitis; topically to the skin; or rectally. In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula (I), in free form or in the form of a pharmaceutically acceptable salt, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent, such as an anti-inflammatory, broncho-dilatory, antihistamine or anti-tussive drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g., patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, e.g., a hydro-fluoro-alkane (HFA) propellant, such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art, such as ethanol (up to 20% by weight), and/or one or more surfactants, such as oleic acid or sorbitan trioleate, and/or one or more bulking agents, such as lactose. When the composition comprises a dry powder formulation, it preferably contains, e.g., the compound of formula (I) or (II) having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture, e.g., magnesium stearate. When the composition comprises a nebulised formulation, it preferably contains, e.g., the compound of formula (I) or (II) either dissolved, or suspended, in a vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a stabilizer, which may be a surfactant.

Further aspects of the invention include:

(a) a compound of formula (I) or (II) in inhalable form, e.g., in an aerosol or other atomisable composition or in inhalable particulate, e.g., micronised form;

(b) an inhalable medicament comprising a compound of formula (I) or (II) in inhalable form;

(c) a pharmaceutical product comprising a compound of formula (I) in inhalable form in association with an inhalation device; and

(d) an inhalation device containing a compound of formula I or II in inhalable form.

Dosages of compounds of formula (I) or (II) employed in practicing the present invention will of course vary depending, e.g., on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.005-10 mg, while for oral administration suitable daily doses are of the order of 0.05-100 mg.

Pharmaceutical Use and Assay

Compounds of formula (I) or (II) and their pharmaceutically acceptable salts, hereinafter referred to alternatively as "agents of the invention", are useful as pharmaceuticals. In particular, the compounds are suitable CFTR activity modulators and may be tested in the following assays.

Membrane potential assay

CFTR activity can be quantified by measuring the transmembrane potential. The means for measuring the transmembrane potential in a biological system can employ a number of methods including electrophysiological and optical fluorescence-based membrane potential assays.

The optical membrane potential assay utilises a negatively charged potentiometric dye, such as the FLIPR membrane potential dye (FMP) (see Baxter DF, Kirk M, Garcia AF, Raimondi A, Holmqvist MH, Flint KK, Bojanic D, Distefano PS, Curtis R, Xie Y. 'A novel membrane potential-sensitive fluorescent dye improves cell-based assays for ion channels.' J Biomol Screen. 2002 Feb;7(1):79-85) which when extracellular is bound to a quenching agent . Upon cellular depolarisation the negatively charged dye redistributes to the intracellular compartment, unbinding from the membrane impermeant quench agent, yielding an increase in fluorescence. This change in fluorescence is proportional to the change in transmembrane potential which can result from the activity of CFTR. The changes in fluorescence can be monitored in real time by an appropriately equipped fluorescence detector such as the FLIPR (fluorometric imaging plate reader) in 96 or 384-well microtitre plates.

Cell culture:

Chinese hamster ovary (CHO) cells stably expressing the F508-CFTR channel were used for membrane potential experiments. Cells were maintained at 37 °C in 5% v/v $C0_2$ at 100% humidity in Modified Eagles medium (MEM) supplemenetd with 8% v/v foetal calf serum, 100µg/ml methotrexate and 100U/ml penicillin/streptomycin. Cells were grown in 225 cm^2 tissue culture flasks. For membrane potential assays cells were seeded into 96 well plates at 40,000 cells per well, allowed to adhere and then maintained at 26 °C for 48h to facilitate channel insertion.

Potentiator assay:

The membrane potential screening assay utilised a low chloride ion containing extracellular solution (~5mM) combined with a double addition protocol. The first addition was of buffer with or without test compound followed 5 minutes later by an addition of forskolin (1-20 μM) - this protocol favours maximum chloride efflux in response to F508-CFTR activation. The F508-CFTR mediated chloride ion efflux leads to a membrane depolarisation which is optically monitored by the FMP dye.

Solutions:

Low chloride extracellular (mM): 120 Na-gluconate, 1.2 $CaCl_2$, 3.3 KH_2P0_4, 0.8 K_2HP0_4, 1.2 $MgCl_2$, 10.0 D-glucose, 20.0 HEPES, pH 7.4 with NaOH

FMP dye: made up as per manufacturers' instructions in low chloride extracellular solution detailed above, at 10x final concentration, and stored as 1 mL aliquots at -20°C.

IonWorks Quattro assay:

CFTR activity can also be quantified electrophysiologically using the whole-cell configuration of the patch clamp technique (Hamill et al Pflugers Acrhive 1981). This assay directly measures the currents associated with chloride flow through CFTR channels whilst either maintaining or adjusting the transmembrane voltage. This assay can use either single glass micropipettes or parallel planar arrays to measure CFTR activity from native or recombinant cell systems. Currents measured using parallel planar arrays can be quantified using an appropriately equipped instrument such as the IonWorks Quattro (Molecular Devices) or the Qpatch (Sophion). The Quattro system can measure CFTR currents from either a single cell per recording well (HT configuration) or alternatively from a population of 64 cells per well (Population Patch Clamp PPC) (Finkel A, Wittel A, Yang N, Handran S, Hughes J, Costantin J. 'Population patch clamp improves data consistency and success rates in the measurement of ionic currents.' J Biomol Screen. 2006 Aug;1 1(5):488-96).

Cell culture:

Chinese hamster ovary (CHO) cells stably expressing the F508-CFTR channel were used for IonWorks Quattro experiments. Cells were maintained at 37 °C in 5% v/v $C0_2$

at 100% humidity in D-MEM supplemented with 10 % (v/v) FCS, 100 U/mL Penicillin/Streptomycin, 1 % (v/v) NEAA, 1 mg/ml Zeocin and 500 ug/ml Hygromycin B. For experiments cells were grown in 225 cm^2 tissue culture flasks until near confluence and then cultured at 26 °C for 48-72h to facilitate channel insertion. Cells were removed from the flask and resuspended in either extracellular recording solution for immediate experimentation or alternatively in growth medium supplemented with 10% v/v DMSO and frozen to -80°C as 1-2 mL aliquots for use at a later date.

Potentiator assay:
Cells, at a density of 1.5-3 million per ml_, were placed on the Quattro system, added to the planar patch array and seals allowed to establish for 5-10 mins. After assessing seal resistances (commonly >50 M), whole-cell access was obtained by perforation with 100 µg/mL amphotericin B. Baseline currents were measured by a pre-compound scan obtained by application of a voltage ramp from -100 to +100 mV. This was followed by addition of either buffer or test compound diluted in the extracellular solution supplemented with 20 µM forskolin, to each of the 384 wells of the planar parch array. After incubation step (5-20 minutes) the post-compound currents were measured again by application of a voltage ramp from -100 to +100 mV. The difference in currents between the pre- and post-compound scans defined the efficacy of CFTR potentiation.

Solutions:
Extracellular solution (ECS) : 145 mM NaCl, 4 mM CsCl, 5 mM D-glucose, 10 mM TES, 1 mM CaCl$_2$, 1 mM MgCl$_2$, pH 7.4 NaOH
Intracellular buffer (ICS): 113 mM L-Aspartic acid, 113 mM CsOH, 27 mM CsCl, 1 mM NaCl, 1 mM MgCl$_2$, 1 mM EGTA, 10 mM TES. pH 7.2 with CsOH. Filter sterilized before use.

Ion transport assay:
Another method to measure CFTR function is Ussings chamber short circuit current measurement. Engineered or native epithelial cells are grown to confluent monolayer on a semi-permeable filter and sandwiched between two perspex blocks. The flow of chloride ions via CFTR from one side of the epithelia to the other can be quantified by measuring the flow of current whilst maintaining the transepithelial potential at OmV. This

is achieved using KCl filled agar-based electrodes to both clamp the cellular monolayer and measure the flow of currents.

Cell culture:

FRT cells stably expressing AF508-CFTR were cultured on plastic in Coon's modified F-12 medium supplemented with 32mM $NaHC0_3$, 10% v/v fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin and 30 µg/mL hygromycin B as the growth medium. For Ussing chamber experiments, the cells were grown as polarized epithelia on Snapwell permeable support inserts (500000 cells/insert in growth medium) and cultured for 7 to 9 days. The inserts were fed with fresh Coon's modified F-12 growth medium every 48 hours, and 24 hours prior to Ussing chamber experiment. To increase the AF508 CFTR protein expression at the cell surface, plates were incubated at 27°C for 48h before performing an Ussing chamber experiment.

Potentiator assay:

Fischer Rat Thyroid (FRT) epithelial cells, stably expressing human AF508-CFTR were used as monolayer cultures on permeable supports. Cl^- current was measured using the short circuit current technique, under an imposed basolateral to apical Cl^- gradient in Ussing chambers. To measure stable Cl^- currents, FRT cells were cultured for 48h at 27°C to facilitate the insertion of AF508 CFTR into the plasma membrane. Ussing chamber studies were likewise conducted at 27°C . Under these conditions, the effects of cumulative additions of test compounds on AF508 CFTR currents could be quantitated with both potency and efficacy endpoints. Compounds were added to both the apical and basloalteral sides subsequent to addition of 10µM forskolin. Efficacy of compounds was compared to a known potentiator such as gensitein.

Solutions:

Basolateral Ringer solution (mM): 126 NaCl, 24 $NaHC0_3$, 0.38 KH_2P0_4, 2.13 K_2HP0_4, 1 $MgS0_4$, 1 $CaCl_2$ and 10 glucose.

Apical Ringer solution (mM): 140 Na-gluconate, 1 $MgS0_4$, 2 $CaCl_2$, 1 HCl, 10 glucose and 24 $NaHC0_3$.

Compounds can also be tested for their ability to stimulate insertion of AF508 CFTR into the cell membrane using the above assays. For these assays the protocols were identical other than cells were not cultured at low temperature (26 or 27°C) but instead incubated with test compounds for 12-24 h prior to assay.

Compounds of the Examples, herein below, generally have EC_{50} values in the data measurements described above below 10 µM. Table 1 provides a list of representative compounds with their EC_{50} value.

Table 1.

Example No	EC_{50} µM
1.0	0.0035

The invention is illustrated by the following Examples.

Examples

General Conditions:

Mass spectra were run on LCMS systems using electrospray ionization. These were either Agilent 1100 HPLC/Micromass Platform Mass Spectrometer combinations or Waters Acquity UPLC with SQD Mass Spectrometer. $[M+H]^+$ refers to mono-isotopic molecular weights.

NMR spectra were run on open access Bruker AVANCE 400 NMR spectrometers using ICON-NMR. Spectra were measured at 298K and were referenced using the solvent peak.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.,* microanalysis and spectroscopic characteristics, *e.g.,* MS, IR, NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

Abbreviations:

app	apparent
br	broad

d	doublet
dd	doublet of doublets
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
h	hour(s)
HATU	2-(7-Aza-1 H-benzotriazole-1-yl)-1 ,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high pressure liquid chromatography
Int.	intermediate
LC-MS	liquid chromatography and mass spectrometry
MeOH	methanol
MS	mass spectrometry
m	multiplet
min	minutes
ml	milliliter(s)
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
ppm	parts per million
PS	polymer supported
RT	room temperature
Rt	retention time
s	singlet
SCX-2	strong cation exchange (e.g. Isolute® SCX-2 columns from Biotage)
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified, where appropriate, using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Unless otherwise stated, all starting materials are obtained from commercial suppliers and used without further purification. Salts may be prepared from compounds by known salt-forming procedures.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

If not indicated otherwise, the analytical LC-MS conditions are as follows:

Method 2minl_owpH:

Column:	Waters Acquity CSH 1.7µm, 2.1 x 50mm
Temperature:	50 °C
Mobile Phase:	A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate:	1.0mL/min
Gradient:	O.Omin 5%B, 0.2-1.3min 5-98%B, 1.3-1.55min 98%B, 1.55-1.6min 98-5%B

Method 10minLowpH:

Column:	Waters Acquity CSH 1.7µm, 2.1 x 100mm
Temperature:	50 °C
Mobile Phase:	A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate:	0.7mL/min
Gradient:	O.Omin 2%B, 0.5-8.0min 2-98%B, 8.0-9.0min 98%B, 9.0-9.1min 98-2%B

Method 10minl_C_v002

Column	Waters BEH C18 50x2.1 mm, 1.7 μηη
Column Temperature	50 °C
Eluents	A: H_20 , B: methanol, both containing 0.1% TFA
Flow Rate	0.8 mL/min
Gradient	0.20 min 5% B; 5% to 95% B in 7.80 min, 1.00 min 95% B

Method 10minl_C_v003

Column	Waters BEH C18 50x2.1 mm, 1.7 μηη
Column Temperature	50 °C
Eluents	A: H_20 , B: acetonitrile, both containing 0.1% TFA
Flow Rate	0.8 mL/min
Gradient	0.20 min 5% B; 5% to 95% B in 7.80 min, 1.00 min 95% B

Method 2minl_C_v002

Column	Waters BEH C18 50x2.1 mm, 1.7 μηη
Column Temperature	50 °C
Eluents	A: H_20 , B: methanol, both containing 0.1% TFA
Flow Rate	0.8 mL/min
Gradient	0.20 min 5% B; 5% to 95% B in 1.30 min, 0.25 min 95% B

Method 2minLC_v003

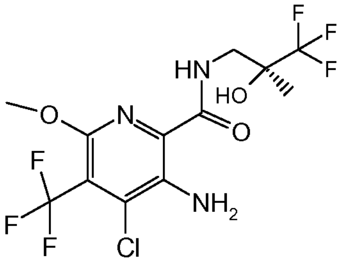
Column	Waters BEH C18 50x2.1 mm, 1.7 μηη
Column Temperature	50 °C
Eluents	A: H_20 , B: acetonitrile, both containing 0.1% TFA
Flow Rate	0.8 mL/min
Gradient	0.20 min 5% B; 5% to 95% B in 1.30 min, 0.25 min 95% B

Example compounds of the present invention include:

Preparation of Final Compounds

Example 1.0

(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide



Step 1: Methyl 3-amino-6-methoxy-5-(trifluoronnethyl)picolinate

3-Amino-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid (Intermediate B)(43 g, 182 mmol) was dissolved in MeOH (650 ml). H_2S0_4 (48.5 ml, 910 mmol) was added dropwise and the solution was heated at reflux overnight. The solvent was removed under reduced pressure and the mixture was diluted with EtOAc, washed with sat. sodium bicarbonate solution and brine. The organic portion was separated, dried ($MgS0_4$) and concentrated under reduced pressure. Purification by chromatography on silica eluting with 0-20% EtOAc in iso-hexane afforded the title compound;

LC-MS Rt = 1.07 min [M+H]+ 251 .2 ; Method 2minl_C_v003

Step 2: Methyl 3-amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinate

Methyl 3-amino-6-methoxy-5-(trifluoromethyl)picolinate (step 1)(1 g, 4.00 mmol) in acetonitrile (15 ml) was treated with trichloroisocyanuric acid (0.307 g, 1.319 mmol). The resulting mixture was heated using microwave radiation at 130°C for 30 minutes and then partitioned between EtOAc and water. The organic portion was separated and washed with sat.$NaHC0_3$, brine and dried using a phase separating column. The solvent was removed under reduced pressure and purification of the crude product by chromatography on silica eluting with 0-30% EtOAc in iso-hexane afforded the title compound;

LC-MS Rt = 1.10 mins; [M+H]+ 285.3, Method 2minl_C_v003.

Step 3: 3-Amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinic acid

To a solution of methyl 3-amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinate (step 2) (819 mg, 2.88 mmol) in MeOH (20 ml) was added 2M NaOH (8.63 ml, 17.27 mmol) and the mixture was stirred for at RT for 2 hours. The solvent was removed under reduced pressure and the crude was diluted with water. The pH of the mixture was adjusted using to pH 1 using 2M HCl. The resulting suspension was collected by filtration to afford the title compound;

LC-MS Rt = 1.01 mins; [M+H]+ 285.3, Method 2minl_C_v003.

Step 4: (S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide

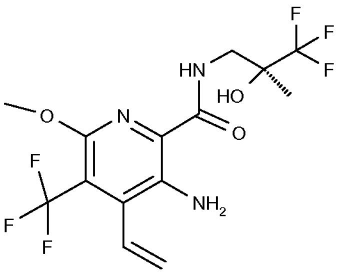
A mixture comprising 3-amino-4-chloro-6-methoxy-5-(trifluoromethyl)picolinic acid (step 3)(1.002 g, 3.70 mmol) and (S)-3-amino-1,1,1-trifluoro-2-methylpropan-2-ol (Intermediate C, free base) (0.530 g, 3.70 mmol) in NMP (15 ml) was treated with HATU (1.690 g, 4.44 mmol) followed by DIPEA (1.617 ml, 9.26 mmol) added dropwise over 5 mins. The mixture was stirred for 2 h at RT and poured into water. The product was extracted with EtOAc and the combined organic extracts were washed with sat $NaHC0_3$, water, brine dried over $MgS0_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica eluting in a 0-50% iso-hexane:EtOAc to afford the title compound;

LC-MS Rt = 1.13 mins; [M+H]+ 396.3, Method 2minl_owpH

1H NMR (400 MHz, DMSO-d6) δ 8.45 (1H, t), 6.93 (2H, s), 6.30 (1H, s), 3.95 (3H, s), 3.66 (1H, mult), 3.49 (1H, mult), 1.27 (3H, s).

Example 2.0

(S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-4-vinylpicolinamide



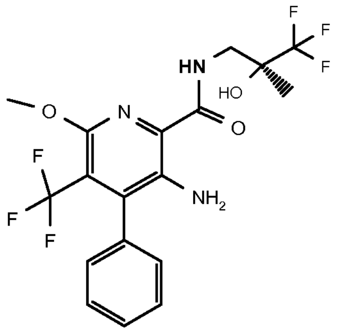
To a solution of (S)-3-amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide (Ex. 1.0) (500 mg, 1.264 mmol) in 1,4-dioxane (4 ml) was added potassium phosphate (536 mg, 2.53 mmol) followed by [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (41.2 mg, 0.063 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.214 ml, 1.264 mmol) and water(1.0 ml). The mixture was heated using microwave radition at 100°C for 10 minutes and then filtered through Celite® (filter material). The filtrate was diluted further with EtOAc and washed with sat.$NaHCO_3$, water, brine and dried over $MgSO_4$. Isolute Si-TMT (2,4,6-trimercaptotriazine silica, palladium scavenger) was added and after stirring for 30 mins, the mixture was filtered. The solvent was removed under reduced pressure and purification of the crude product by chromatography on silica eluting with 0-40% EtOAc in iso-hexane afforded the title compound;

LC-MS Rt = 5.24 min [M+H]+ 388.4; Method 10minl_owpH.

1H NMR (400 MHz, DMSO-d6) δ 8.40 (1H, t), 6.66 (1H, m), 6.46 (2H, s), 6.30 (1H, s), 5.72 (1H, m), 5.41 (1H, m), 3.92 (3H, s), 3.66 (1H, mult), 3.48 (1H, mult), 1.27 (3H, s)

Example 2.1

3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide



The title compound was prepared analogously to Example 2.0 by replacing 4,4,5,5-tetramethyl-2-vinyl-1 ,3,2-dioxaborolane with 4,4,5,5-tetramethyl-2-phenyl-1 ,3,2-dioxaborolane;

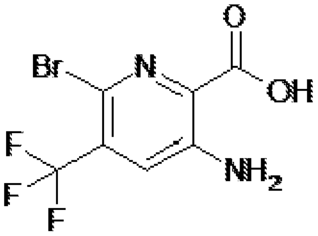
LC-MS Rt = 1.20mins; [M+H]+ 438.4, Method 2minl_owpH

1H NMR (400 MHz, DMSO-d6) δ 8.46 (1H, t), 7.52 (3H, m), 7.23 (2H, m), 6.31 (1H, s), 5.84 (2H, s), 3.95 (3H, s), 3.66 (1H, m), 3.52 (1H, m), 1.28 (3H, s).

Preparation of Intermediates

Intermediate A

3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid



Step 1: 2-Bronno-3-nitro-5-trifluoronnethyl-pyridine

3-Nitro-5-(trifluoromethyl)pyridin-2-ol (31 .00 g, 149 mmol) was dissolved in acetonitrile (250 ml) to give a dark brown solution. Phosphorus(V) oxybromide (85 g, 298 mmol) was added and the mixture was heated at reflux for 4 hours and then stirred at RT overnight. The reaction mixture was quenched by pouring into vigorously stirring water (600 ml) containing sodium hydrogencarbonate (110 g). The dark brown mixture was extracted with DCM (3 x 200 ml) and the organic phase was washed with water (200 ml) and brine (100ml), dried ($MgS0_4$) and concentrated under reduced pressure to afford the title product as a brown oil.

^{1}H-NMR: [400MHz, $CDCI_3$, δ 8.87 (1H, d, J = 1.4Hz, ArH), 8.39 (1H, d, J = 1.9Hz, ArH).

Step 2: 3-Nitro-5-trifluoromethyl-pyridine-2-carbonitrile

2-Bromo-3-nitro-5-trifluoromethyl-pyridine (10.00 g, 36.87 mmol) was dissolved in toluene (250 ml) with stirring to give a pale yellow solution. Tetrabutylammonium bromide (11.90 g, 36.9 mmol) was added followed by copper(l) cyanide (9.92 g, 111 mmol) and the mixture was heated at reflux for 9 h. After cooling to RT, the reaction mixture was partitioned between water (750 ml) and EtOAc (750 ml). The organic fractions were combined, washed with water (2 x 250 ml), brine (100 ml), dried ($MgS0_4$) and concentrated under reduced pressure to afford the title product.

^{1}H-NMR: [400MHz, DMSO-d_6] δ 9.55 (1H, m, ArH), 9.24 (1H, m, ArH)

Step 3: 3-Amino-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester

3-Nitro-5-trifluoromethyl-pyridine-2-carbonitrile (6.5 g, 29.9 mmol) was dissolved in EtOAc (150 ml) to give a pale yellow solution. 10 % Palladium on activated carbon (3.19 g, 2.99 mmol) was added and the reaction mixture stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was dissolved in HCI cone. (45 ml) and heated to reflux for 24 hours. The reaction mixture was allowed to cool to RT and concentrated under reduced pressure. The solid was dissolved in MeOH (200 ml) and sulfuric acid (8 ml) was added. The resulting solution was heated at reflux for 84 hours. The reaction was allowed to cool to RT, then neutralised by addition of 10% $NaHC0_3$(aq) (600 ml). The product was extracted into DCM (3 x 200 ml) and the combined organic phases were washed with water (200 ml), brine (50 ml), dried ($MgS0_4$) and concentrated under reduced pressure. The resulting solid was purified by chromatography on silica : Eluant gradient: iso-hexane (500ml), 10% EtOAc in isohexane (1000 ml), 20% EtOAc in iso-hexane (1500 ml) to afford the titled compound as a pale yellow solid

^{1}H-NMR: [400MHz, DMSO-d_6] δ 8.13 (1H, d, J = 1.7Hz, ArH), 7.60 (1H, d, J = 1.3Hz, ArH), 7.01 (2H, br, NH_2), 3.85 (3H, s, $ArOCH_3$), m/z 221.1 $[M+H]^+$

Step 4 3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester

3-Amino-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (9.49 g, 43.16 mmol) was dissolved in water (300 ml). Sulfuric acid (4.60 ml, 86 mmol) was added followed by dropwise addition over 30 minutes of a solution of bromine (2.222 ml, 43.1 mmol) in acetic acid (29.6 ml, 517 mmol). The reaction mixture was stirred at RT for 18 hours. A further 100 ml of water was added, followed by a further 0.25 equivalents of the bromine/AcOH mixture (550 µl bromine in 7.4 ml AcOH) and the reaction mixture stirred at RT for an additional 90 minutes. The reaction mixture was diluted with water (500 ml) and neutralised by addition of solid $NaHC0_3$ (-85 g). The suspension was extracted with DCM (3 x 300 ml) and the combined organic phases washed with sat.$NaHC0_{3(aq)}$ (250 ml), water (250 ml) and brine (100 ml), dried ($MgS0_4$) and concentrated under reduced pressure. The crude material was recrystallised from boiling MeOH (-300 ml) to give the title product as a pale orange solid:

LC-MS m/z 301.0 $[M+H]^+$

^{1}H-NMR (400MHz, DMSO-d_6)δ 7.77 (1H, s, ArH), 7.17 (2H, s, NH_2), 3.86 (3H, s, $ArC0_2CH_3$).

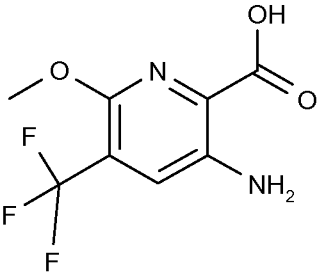
Step 5: 3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid

3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (1.40 g, 4.68 mmol) was suspended in MeOH (15 ml); Sodium hydroxide (2.0 M aqueous solution) (14.04 ml, 28.1 mmol) was added and the suspension was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (100 ml) and then acidifed by the addition of 5.0M HCl(aq). The product was extracted into ethyl acetate (2 x 75 ml) and the combined organic extracts were washed with water (50 ml), brine (25 ml), dried ($MgS0_4$) and concentrated under reduced pressure to afford the title product as a yellow solid.

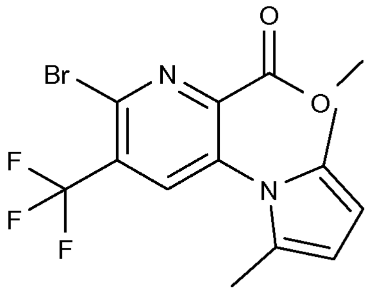
^{1}H-NMR: 9400MHz, DMSO-d$_6$) δ 13.24 (1H, br s, C0$_2$H), 7.74 (1H, s, ArH), 7.17 92H, br s ArNH$_2$). m/z 285.1 , 287.1 [M+H]$^+$

Intermediate B

3-Amino-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid



Step 1: 6-Bromo-3-(2,5-dimethyl-pyrrol-1-yl)-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester



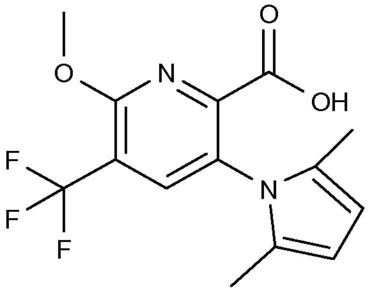
3-Amino-6-bromo-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester(Intermediate A step 4) (2 g, 6.69 mmol) was suspended in toluene (8 ml), then p-toluenesulfonic acid (TsOH) (0.1 15 g, 0.669 mmol) and acetonylacetone (0.941 ml, 8.03 mmol) was added. The reaction mixture was heated at reflux for 2 h and allowed to cool to RT overnight. The resulting dark red/ black solution was concentrated under reduced pressure to remove toluene and the crude residue was diluted with EtOAc (200 ml), washed with NaHC0$_3$ (50 ml), dried (MgS0$_4$) and concentrated under reduced pressure to give a brown solid;

LC-MS Rt = 5.58 min [M+H]+ 377/379 (Method 10minl_C_v002).

1H NMR (400 MHz, DMSO-d6) δ 8.50 (1H, s), 7.77 (2H, s), 5.83 (3H, s), 1.90 (6H, s);

19F NMR (400 MHz, DMSO-d6) δ -62.26 (CF3, s)

Step 2: 3-(2,5-Dimethvl-pvrrol-1-vl)-6-methoxv-5-trifluoromethvl-pyridine-2-carboxvlic acid



6-Bromo-3-(2,5-dimethyl-pyrrol-1-yl)-5-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (2 g, 5.30 mmol) was dissolved in MeOH (40 ml) and treated with 2M NaOH (20 ml) to give a suspension which was stirred at RT for 1h to afford a clear solution. The solvent was removed under reduced pressure and the residue was acidified to pH1 with 5M HCl. The mixture was extracted with EtOAc (200 ml) and the organic extract was dried ($MgS0_4$) and concentrated under reduced pressure to afford the title compound as a dark brown solid which was used in the next step without further purification;

LC-MS Rt=1 .50 min [M+H]+ 315.2.1/316.2; Method 2minl_C_v002

1H NMR (400 MHz, DMSO-d6) 514.42-12.61 (COOH, b hump), 8.25 (1H, s), 5.84 (2H, s), 4.13 (3H, s), 1.97 (6H, s);

19F NMR (400 MHz, DMSO-d6) δ -62.43 (CF3, s).

Step 3: 3-Amino-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid

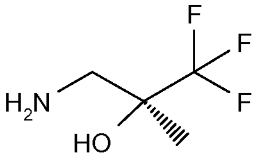
3-(2,5-Dimethyl-pyrrol-1-yl)-6-methoxy-5-trifluoromethyl-pyridine-2-carboxylic acid(833 mg, 2.65 mmol) was dissolved in EtOH (45 ml) and water (23 ml). To this mixture was added TEA (1.102 ml, 7.95 mmol) followed by hydroxylamine hydrochloride (1842 mg, 26.5 mmol). The resulting mixture was heated at reflux overnight. After cooling to RT, the mixture was stirred with 20g Isolute® PE-AX (silica-based sorbent with a chemically bonded quaternary amine functional group used for isolation of acidic compounds) for 30 mins, washed with MeOH (100 ml), 1M HCl: MeCN 2:8 (200 ml). The organic portion was removed and the mixture was filtered. The filtrate was acidified with 2M HCl (50 ml) and the EtOH was removed under reduced pressure. The aqueous portion was extracted with DCM (200 ml) and the organic extract was dried ($MgS0_4$) and concentrated under reduced pressure to give a brown oil. Purification by chromatography on silica eluting with DCM: MeOH afforded the title product as a yellow solid;

LC-MS Rt = 2.90 min [M+H]+ 237 ; Method 10minl_C_v002

1H NMR (400 MHz, DMSO-d6) δ 9.62-7.79 (NH2, b hump), 7.70 (1H, s), 3.89 (3H, s); 19F NMR (400 MHz, DMSO-d6) δ -62.92 (CF3, s).

Intermediate C

(S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol hydrochloride



Route 1:

Step 1: Benzyl 3,3,3-trifluoro-2-hydroxy-2-methylpropylcarbamate

To a stirring suspension of amino-1,1,1-trifluoro-2-methylpropan-2-ol hydrochloride (Intermediate E) (1.5 g, 8.35 mmol) in DCM (50 ml) was added TEA 93.54 g, 35.0 mmol) followed by benzyl 2,5-dioxopyrrolidin-1-yl carbonate (1.983 g, 7.96 mmol). The mixture was stirred at RT for 6 hours and then diluted with water. The organic portion was separated using a phase separator and concentrated under reduced pressure. Purification by chromatography on silica eluting with 0-70% EtOAc in iso-hexane afforded the title product;

LC-MS: Rt 1.05 min; MS m/z 278.1 [M+H]+; Method 2minl_C_v003.

1H NMR (400 MHz, DMSO-d6) δ 7.34 (6H, m), 5.98 (1H, s), 5.05 (2H, s), 3.31 (1H, m), 3.18 (1H, m), 1.21 (3H. s)

Step 2: Separation of Enantiomers of benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate

Benzyl 3,3,3-trifluoro-2-hydroxy-2-methylpropylcarbamate (1.7 g) was dissolved in 2-propanol (10 ml) and purified using the following chromatographic conditions:

Mobile Phase:	10% 2-propanol / 90% CO_2
Column:	2 x Chiralcel OJ-H, 250 x 10 mm id, 5 μm (columns coupled in series)
Detection:	UV @ 220nm
Flow rate:	10 ml/min

Sample concentration: 1.7 g in 10 ml 2-propanol

Injection volume: 75μl

First eluted peak: Rt = 6.94 minutes (R)-benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate

Second eluted peak: Rt = 8.04 minutes (S)-benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate

Step 3: (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol hydrochloride

A mixture comprising (S)-benzyl 3,3,3-trifluoro-2-hydroxy-2-methyl propylcarbamate in EtOH(165 ml) was pumped through a H-Cube (hydrogenation reactor, 1-2 ml/min, 1 bar pressure, RT) for 8 hours using a 10% palladium on carbon catalyst cartridge. 1.25 M HCl in methanol (130 ml) was added to the mixture was stirred for 30mins. The solvent was removed under reduced pressure azeotroping with MeCN to afford the title product as a white powder; 1H NMR (400 MHz, DMSO-d6) δ 8.3 (3H, broad), 6.8 (1H, s), 3.0 (2H, s), 1.5 (3H, s).

Alternatively, racemic 3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol can be resolved into separate enantiomers by recrystallistion with either (S)-Mandelic acid or L-tartaric acid in isopropanol or ethanol to afford (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol:

Route 2:

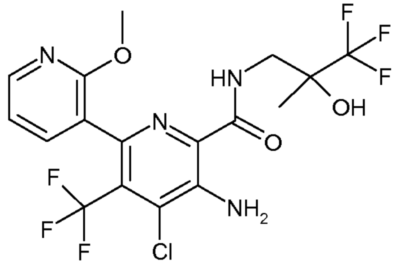
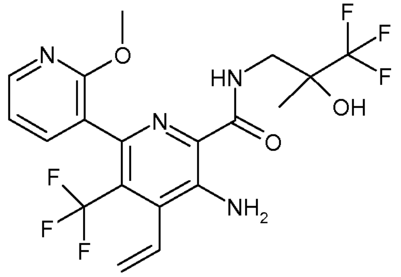
Step 1: (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt

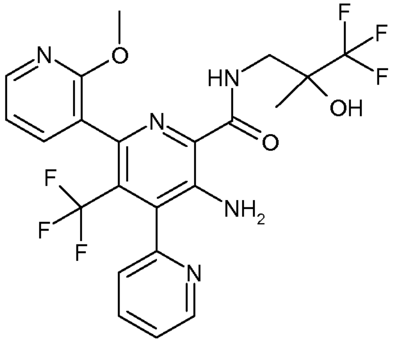
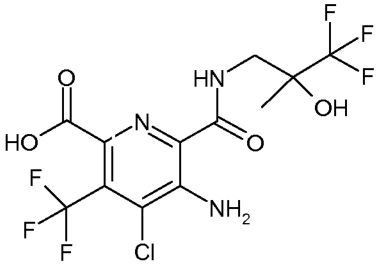
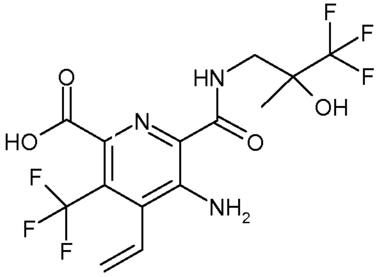
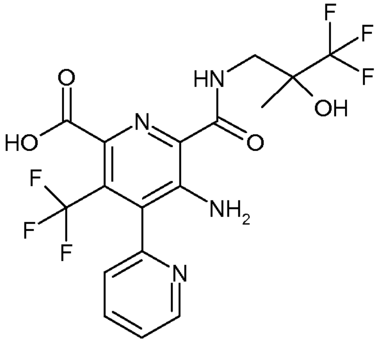
3-Amino-1,1,1-trifluoro-2-methyl-propan-2-ol (40 g, 280 mmol) and L-(+)-tartaric acid (42.0 g, 280 mmol) were dissolved in EtOH + 4 % H_20 (1398 ml) and warmed to 65 °C in an oil bath at 80 °C over 30 minutes. The resultant solution was left to cool and crystallise overnight at room temperature. The white precipitate was collected by filtration and dried in a vacuum oven at 40 °C for 2 hours to afford the title compound (22.5 g, 27.5 %, enantiomeric excess (e.e) = 76.6 %). A second crystallization was carried out as follows to enrich the e.e. (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt (22.5 g, 76.7 mmol) was dissolved in EtOH + 4 % H_20 (384 ml, 0.2 M) at 80 °C and left to crystallise overnight. The white precipitate was collected by filtration and allowed to dry at RT overnight (18.4 g, e.e. = 94.4 %). A third crystallisation was carried out; (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt (18.4 g, 62.8 mmol) was heated in EtOH + 4 % H_20 (314 ml, 0.2 M) at 80 °C for 2 h and allowed to cool and crystallize overnight. The white precipitate was collected by filtration and dried in a vacuum oven at 50 °C for 5 hours to afford the title compound; e.e. = 97.4 %.

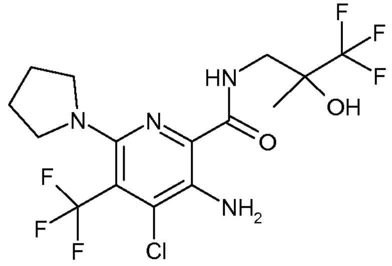
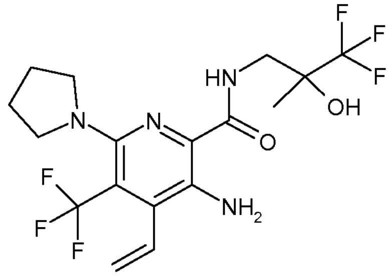
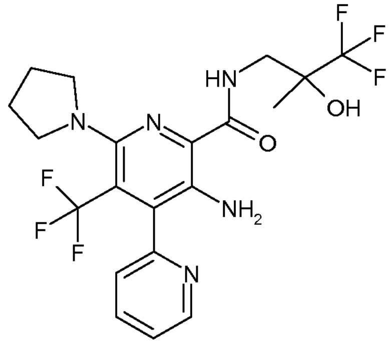
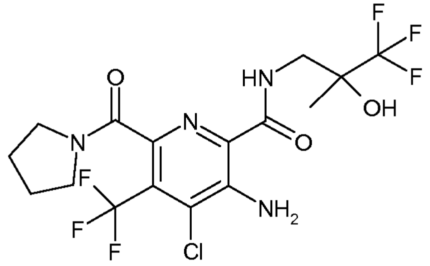
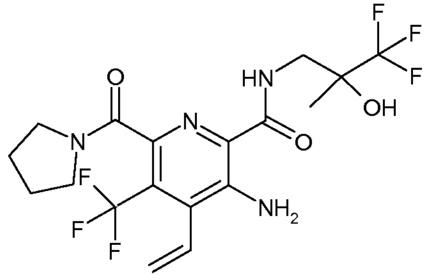
Step 2: (S)-3-Amino-1,1,1-trifluoro-2-methylpropan-2-ol

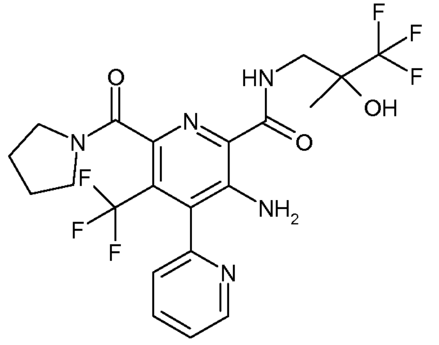
To a suspension of Isolute® SCX-2 (Si-propylsulfonic acid) (537 g, 222 mmol) in DCM (1.5 L) was added (S)-3-amino-1,1,1-trifluoro-2-methylpropan-2-ol L-tartrate salt (step 1)(65 g, 222 mmol) pre-dissolved in warm MeOH (500 ml). The silica suspension was stirred at RT for 30 min and the slurry was poured onto a large silica frit. The frit was washed with 10 % MeOH in DCM (3.5 litres) and the washings were discarded. The plug was eluted with 7M NHa/MeOH (300 ml) in DCM (2 litres) followed by 2M NH_3/MeOH (300 ml) in DCM (1 litre). The combined washings were concentrated under reduced pressure to afford the title compound.

The following compounds may be prepared by the processes described in the general schemes above, or by processes analogous to those of Examples 1.0, 2.0 and 3.0, or by processes analogous to those described in international patent application W0201 1/1 13894 (PCT/EP201 1/054038). .

Structure	Name
	5-Amino-4-chloro-2'-methoxy-3-trifluoromethyl-[2,3']bipyridinyl-6-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	5-Amino-4-vinyl-2'-methoxy-3-trifluoromethyl-[2,3']bipyridinyl-6-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide

	5'-Amino-2''-methoxy-3'-trifluoromethyl-[2,4';2',3'']terpyridine-6'-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	5-Amino-4-chloro-6-(3,3,3-trifluoro-2-hydroxy-2-methyl-propylcarbamoyl)-3-trifluoromethyl-pyridine-2-carboxylic acid
	5-Amino-4-vinyl-6-(3,3,3-trifluoro-2-hydroxy-2-methyl-propylcarbamoyl)-3-trifluoromethyl-pyridine-2-carboxylic acid
	5'-Amino-6'-(3,3,3-trifluoro-2-hydroxy-2-methyl-propylcarbamoyl)-3'-trifluoromethyl-[2,4']bipyridinyl-2'-carboxylic acid

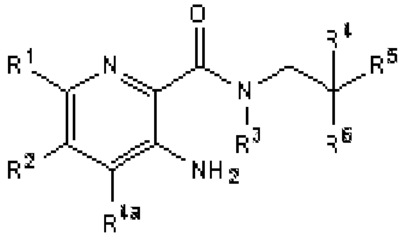
	3-Amino-4-chloro-6-pyrrolidin-1-yl-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	3-Amino-4-vinyl-6-pyrrolidin-1-yl-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	3'-Amino-6'-pyrrolidin-1-yl-5'-trifluoromethyl-[2,4']bipyridinyl-2'-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	3-Amino-4-chloro-6-(pyrrolidine-1-carbonyl)-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide
	3-Amino-4-vinyl-6-(pyrrolidine-1-carbonyl)-5-trifluoromethyl-pyridine-2-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide

	3'-Amino-6'-(pyrrolidine-1-carbonyl)-5'-trifluoromethyl-[2,4']bipyridinyl-2'-carboxylic acid (3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

Embodiments:

Embodiment 1. A compound of Formula I



I

wherein:

R^1 is H; C-i-Ce alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -Ci-C_4 alkyl-C_3-C_8 cycloalkyl; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; halogen; $S0_2NR^8R^9$; $S0_2R^{10}$; S-Ci-C_8alkyl optionally substituted by one or more halogen atoms; S-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; CN; $NR^{11}R^{12}$; $CONR^{13}R^{14}$; $NR^{13}S0_2R^{15}$; $NR^{13}C(0)R^{15}$ and $C0_2R^{15}$, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is C_1-C_4 haloalkyl;

R^3 and R^4 are each independently H or C_1-C_8 alkyl optionally substituted by one or more halogen atoms;

R^{4a} is selected from halogen; C_2-C_8 alkenyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl; and C_1-C_8 hydroxyalkyl; wherein the -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^5 and R^6 are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -C_1-C_4 alkyl-C_3-C_8 cycloalkyl; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -(C_0-C_4 alkyl)-CO_2R^{15}, wherein the cycloalkyl, cycloalkenyl, -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or

R^5 and R^6 are each independently a group of the formula:
$-(CH_2)_m-NR^{17}R^{18}$; or

R^5 and R^6 are each independently a group of the formula:
$-(CH_2)_m-OR^4$; or

R^4 and R^5 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered carbocyclic ring system or a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R^4, R^5 and R^6 cannot all be the same;

m is 0, 1, 2 or 3;

R^8, R^{11}, R^{13} and R^{17} are each independently H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms, C_3-C_{10} cycloalkyl or -(C1-C4 alkyl)-C_3-C_8 cycloalkyl;

R^9, R^{10}, R^{12}, R^{14}, R^{15}, R^{16} and R^{18} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -Ci-C 4 alkyl-C_3-C_8 cycloalkyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^8 and R^9, R^{11} and R^{12}, R^{13} and R^{14}, and R^{17} and R^{18} together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or C1-C4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, oxo, CN, NO_2, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C1-C4 alkoxy-CrC 4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and

C(0)Ci-C $_6$ alkyl; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- 0-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(0)CrC $_6$ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH $_2$, C(0)NHC_1-C_6 alkyl or C(0)N(Ci-C $_6$ alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0) $_2$-aryl; S(0) $_2$-Ci-C $_6$ alkyl; Ci-C $_6$ alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC $_6$ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by Ci-C $_6$ alkyl, Ci-C $_6$ haloalkyl or Ci-C $_6$ alkoxy;
or a pharmaceutically acceptable salt thereof.

Embodiment 2: The compound according to embodiment 1, wherein R^{4a} is selected from halogen; C_2-C_8 alkenyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl; C_1-C_8 hydroxyalkyl; -$(CH_2)_m$-$NR^{17}R^{18}$; -(C_0-C_4 alkyl)-C0 $_2R^{15}$ and -(C_0-C_4 alkyl)-C(0)NR $^{17}R^{18}$.

Embodiment 3: The compound according to embodiment 1 or 2, wherein R^{4a} is selected from halogen; C_2-C_8 alkenyl, -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)- 3 to 14 membered heterocyclyl.

Embodiment 4: The compound according to any one of embodiments 1 to 3, wherein R^{4a} is selected from chlorine; ethenyl, -(C_0-C_4 alkyl)-phenyl and -(C_0-C_4 alkyl)-pyridyl.

Embodiment 5: The compound according to any one of embodiments 1 to 4,
or pharmaceutically acceptable salts thereof, wherein:

R^1 is H; C-i-Ce alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyi; C_5-C_{10} cycloalkenyl; -C1-C4 alkyl-C_3-C_8 cycloalkyi; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; halogen; $S0_2NR^8R^9$; $S0_2R^{10}$; S-Ci-C_8alkyl optionally substituted by one or more halogen atoms; S-C_6-C_{14} aryl; CN; $NR^{11}R^{12}$; C(0)NR $^{13}R^{14}$; $NR^{13}S0_2R^{15}$; $NR^{13}C(0)R^{15}$, $C0_2R^{15}$, -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyi, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is C1-C4 haloalkyl;

R^3 is H or C-i-Ce alkyl optionally substituted by one or more halogen atoms;

R^4 is H, or C-i-Ce alkyl optional substituted with one or more halogen;

R^5 is $-(CH_2)_m-NR^{17}R^{18}$, $-(CH_2)_m-OR'$; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; -(C_0-C_4 alkyl)-$C0_2R^{15}$; -(C_0-C_4 alkyl)-C_6-C_{14} aryl or -3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^6 is Ci-C_8 alkyl optionally substituted by one or more halogen atoms; C3-C10 cycloalkyi; -C1-C4 alkyl-C_3-C_8 cycloalkyi; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyi, cycloalkenyl, -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C0-C4 alkyl)-3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents; or

R^6 is H, and R^5 is $-(CH_2)_m-NR^{17}R^{18}$, $-(CH_2)_m-OR'$, C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -(C_0-C_4 alkyl)-$C0_2R^{15}$, wherein -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^4 and R^5 together form an oxo group (C=0) and R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^5 and R^6 together with the carbon atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; or

R^4 and R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R' is H, or C-i-Ce alkyl optional substituted with one or more halogen;

m is 0, 1, 2 or 3;

R^8, R^{11}, R^{13} and R^{17} are each independently H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms, C_3-C_{10} cycloalkyl or -(C_1-C_4 alkyl)-C_3-C_8 cycloalkyl;

R^9, R^{10}, R^{12}, R^{14}, R^{15}, R^{16} and R^{18} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -C_1-C_4 alkyl-C_3-C_8 cycloalkyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^8 and R^9, R^{11} and R^{12}, R^{13} and R^{14}, and R^{17} and R^{18} together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or $C_{1\text{-}C4}$ alkoxy, $NR^{18}(S0_2)R^{21}$, $(S0_2)NR^{19}R^{21}$, $(S0_2)R^{21}$, $NR^{18}C(0)R^{21}$, $C(0)NR^{19}R^{21}$, $NR^{18}C(0)NR^{19}R^{21}$, $NR^{18}C(0)OR^{19}$, $NR^{19}R^{21}$, $C(0)OR^{19}$, $C(0)R^{19}$, SR^{19}, OR^{19}, oxo, CN,

NO_2, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;
R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and C(0)Ci-C $_6$ alkyl; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- 0-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(0)CrC $_6$ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH_2, C(0)NHC_1-C_6 alkyl or C(0)N(Ci-C $_6$ alkyl)$_2$; or
R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0) $_2$-aryl; S(0) $_2$-Ci-C $_6$ alkyl; Ci-C $_6$ alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC $_6$ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

Embodiment 6: The compound according to any one of embodiments 1 to 5, wherein R^1 is H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; halogen; C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -$NR^{11}R^{12}$, wherein the aryl and heterocyclic groups are each optionally substituted by one or more Z substituents.

Embodiment 7: The compound according to any one of embodiments 1 to 6, wherein R^1 is C-i-C_4 alkyl optional substituted by one or more halogen atoms.

Embodiment 8: The compound according to any one of embodiments 1 to 7, wherein R^1 is $-CH_3$ or CF_3.

Embodiment 9: The compound according to any one of embodiments 1 to 6, wherein R^1 is C_1-C_4 alkoxy optional substituted by one or more halogen atoms.

Embodiment 10: The compound according to any one of embodiments 1 to 6, wherein R^1 is -OCH3, $-OCH_2CH3$ or -OCF3.

Embodiment 11: The compound according to any one of embodiments 1 to 6, wherein R^1 is aryl, wherein aryl is phenyl optionally substituted by one or more Z substituents,

Embodiment 12: The compound according to any one of embodiments 1 to 6 or 11, wherein R^1 is 4-fluorophenyl, 4-chloro-2-methylphenyl, or 2,4-dichlorophenyl.

Embodiment 13: The compound according to any one of embodiments 1 to 6, wherein R^1 is pyridyl, oxazole, pyrrolidine or pyrazole and is optionally substituted by one or more Z substituents.

Embodiment 14: The compound according to any one of embodiment 1 to 6 or 13, wherein R^1 is 1-methyl-4-pyridyl, oxzaoyl-2-yl, 1-methyl- 1H-pyrazole-4-yl or pyrrolidin-1yl.

Embodiment 15: The compound according to any one of embodiments 1 to 14, wherein R^1 is Br, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, 4-fluorophenyl, 4-chloro-2-methylphenyl, 2,4-dichlorophenyl, 1-methyl-4-pyridyl, 1-methyl-1 H-pyrazole-4-yl, oxzaoyl-2-yl, or pyrrolidin-1 yl.

Embodiment 16: The compound according to any one of embodiments 1 to 15, wherein R^5 provides a heteroatom two carbons from the amide nitrogen, wherein the heteroatom is oxygen or nitrogen.

Embodiment 17: The compound according to any one of embodiments 1 to 16, wherein
R^4 is H or C_1-C_4 alkyl optionally substituted by one or more halogen atoms;
R^5 is C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; -$(CH_2)_m$-$NR^{17}R^{18}$; -$(CH_2)_m$-OR',,or OH;
R' is H, or C_1-C_4 alkyl optional substituted with one or more halogen;
m is 0, 1 or 2;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6 aryl; or -(C_0-C_4 alkyl)-5 to 6 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or
R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or
R^5 and R^6 together with the carbon atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

Embodiment 18: The compound according to any one of embodiments 1 to 17, wherein
R^3 is H;
R^4 is H or Me;
R^5 is -$(CH_2)_m$-$NR^{17}R^{18}$; -$(CH_2)_m$-OR'; or OH;
m is 0, or 1;
R" is H;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; or
R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

Embodiment 19: The compound according to any one of embodiments 1 to 18, wherein
R^3 is H;
R^4 is H or Me;
R^5 is $-NR^{17}R^{18}$; or OH;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; or
R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 6 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; and
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

Embodiment 20: The compound according to any one of embodiments 1 to 19, wherein
R^3 is H;
R^4 is H or Me;
R^5 is $-NR^{17}R^{18}$; or OH;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; and
R^{17} and R^{18} are each independently H; or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

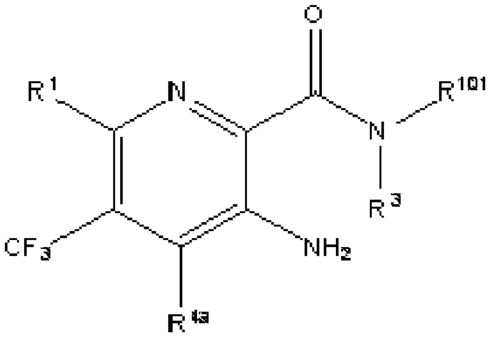
Embodiment 21: The compound according to one of embodiments 1 to 20, wherein
R^3 is H;
R^4 and R^5 form an oxo group;
R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; phenyl; or 5 to 6 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the phenyl and heterocyclyl groups are each optionally substituted by one or more Z substituents.

Embodiment 22: The compound according to any one of embodiments 1 to 16 or 21, wherein
R^3 is H;
R^4 and R^5 form an oxo group;

R^6 is C$_1$-C$_4$ alkyl optionally substituted by one or more halogen atoms; or phenyl, wherein the phenyl is optionally substituted by one or more Z substituents;
Z is independently OH, C$_1$-C$_4$ alkyl optionally substituted by one or more OH groups or NH$_2$ groups, C$_1$-C$_4$ alkyl optionally substituted by one or more halogen atoms, C$_1$-C$_4$ alkoxy optionally substituted by one or more OH groups or d-C$_4$ alkoxy, C(0)OR ^{19}, C(0)R ^{19}, OR^{19}, CN, or halogen;
R^{19} is H; C$_1$-C$_4$ alkyl; C$_3$-C$_6$ cycloalkyl; or d-C$_4$ alkoxy-C$_1$-C$_4$ alkyl, wherein all alkyl are optionally substituted with halogens.

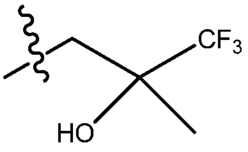
Embodiment 23: The compound according to embodiment 1 to 16 or 2 1 to 22, wherein
R^3 is H;
R^4 and R^5 form an oxo group;
R^6 is C$_1$-C$_4$ alkyl optionally substituted by one or more halogen atoms; or phenyl, wherein the phenyl is optionally substituted by one or more Z substituents;
Z is independently, d-C$_4$ alkyl optionally substituted by one or more halogen atoms, C$_1$-C$_4$ alkoxy or halogen.

Embodiment 24: The compound according to any one of embodiments 1 to 16, wherein the compound is represented by formula II,



II

or a pharmaceutically acceptable salt thereof,
wherein,
R^{1o1} is selected from the following: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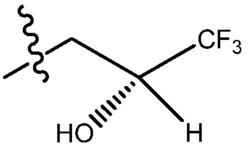
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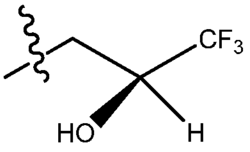
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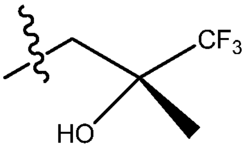
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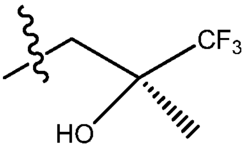
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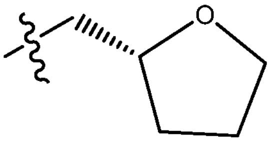
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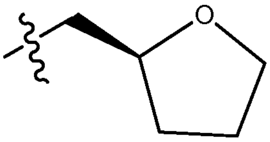
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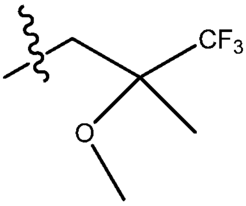
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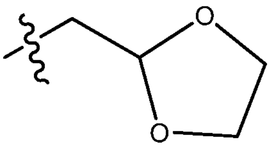
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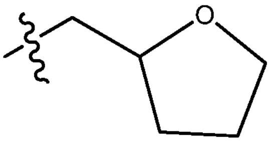
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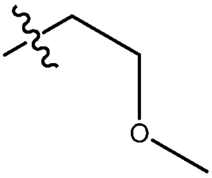
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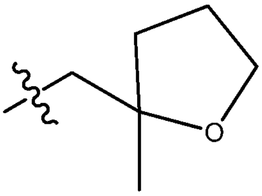
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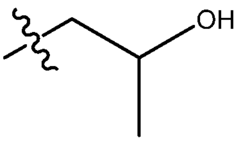
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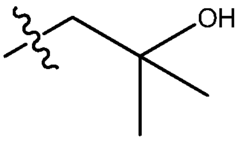
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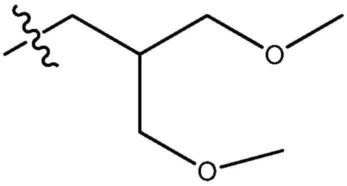
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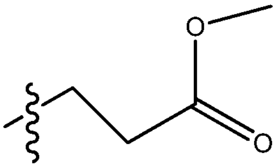
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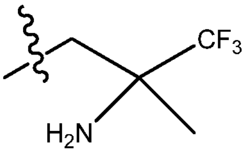
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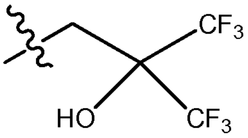
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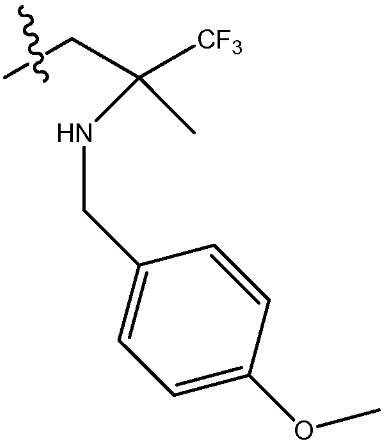
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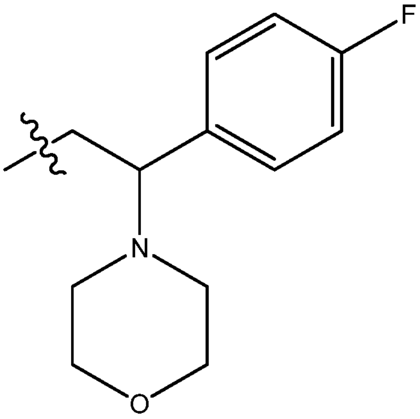
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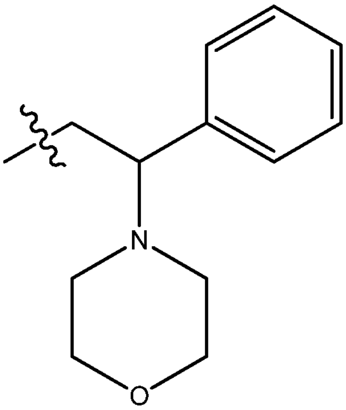
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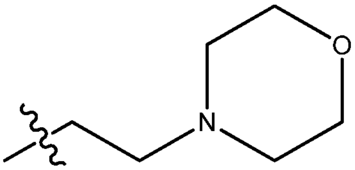
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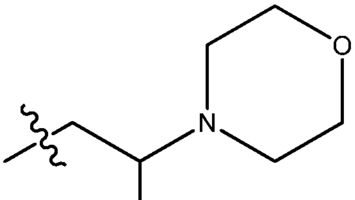
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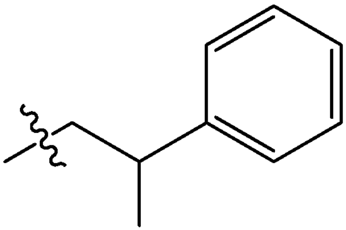
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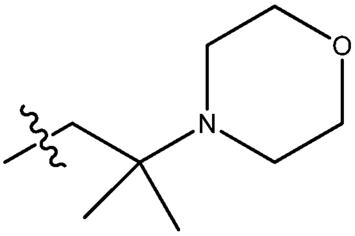

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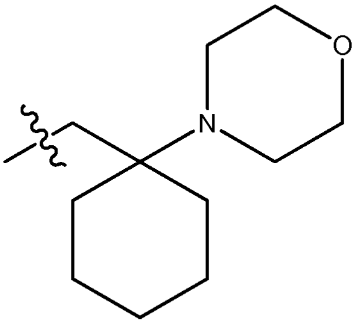

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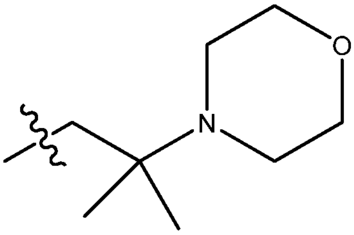

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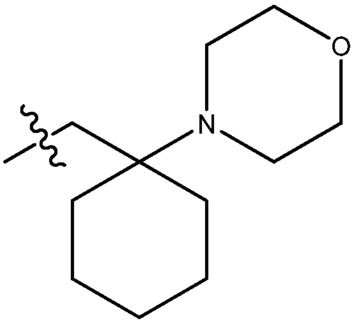

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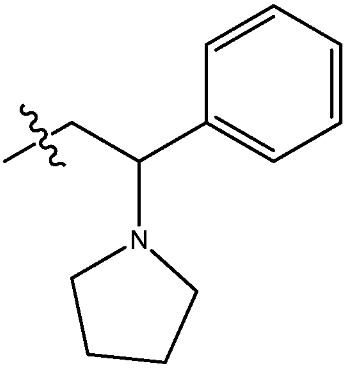

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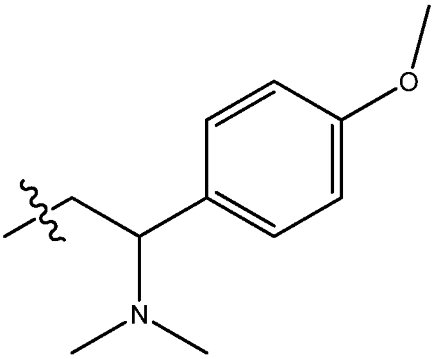

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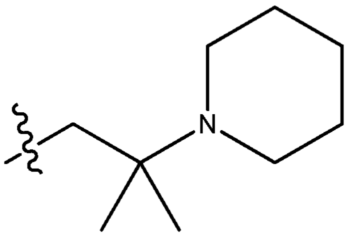
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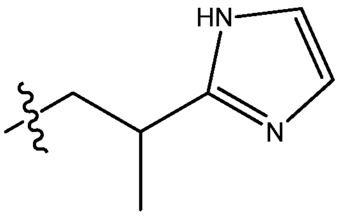
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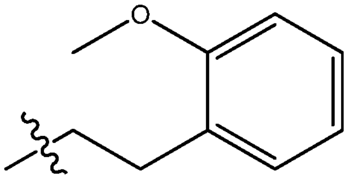
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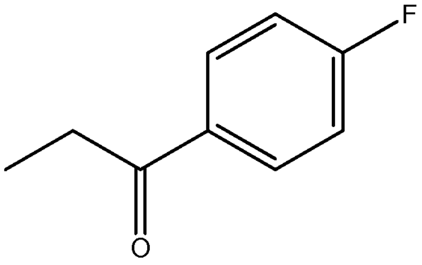
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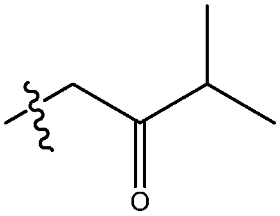
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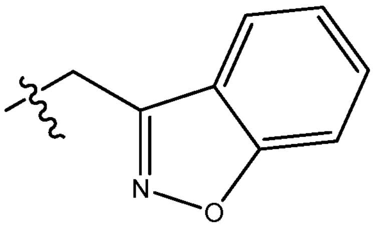
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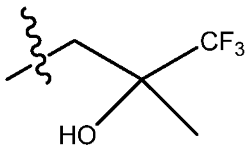
Embodiment 25: The compound according to embodiment 24, wherein
R^3 is H;

R^{101} is

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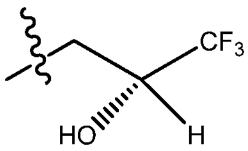
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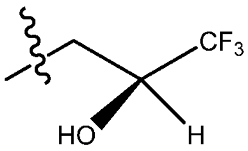
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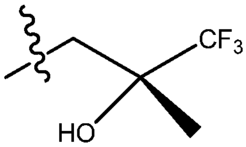
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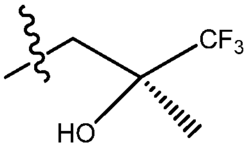
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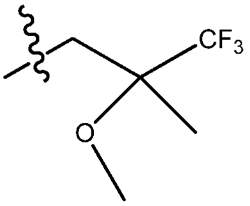
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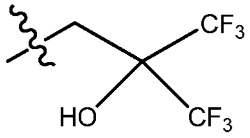
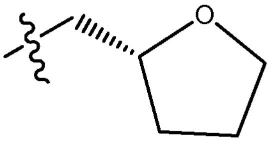
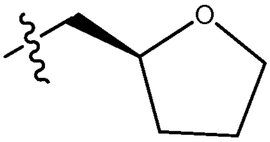
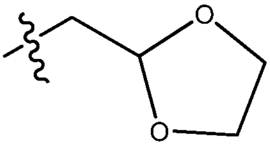
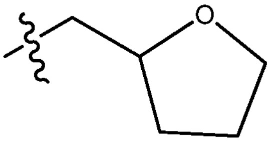
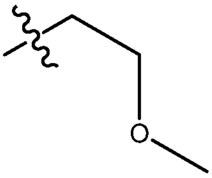
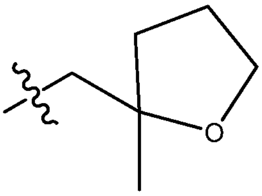
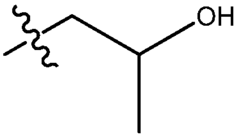
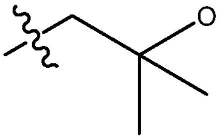
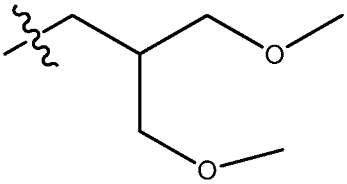
or  .

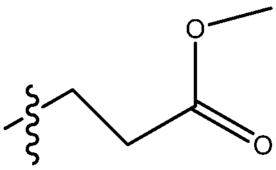
Embodiment 26: The compound according to embodiment 24, wherein

R^3 is H;

R^{101} is  ,  ,  ,

 ,  ,  ,

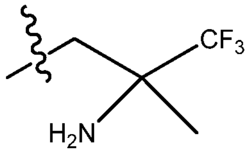
 ,  ,  , or

 .

Embodiment 27: The compound according to embodiment 24, wherein

R^3 is H;

R^{101} is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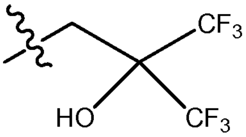
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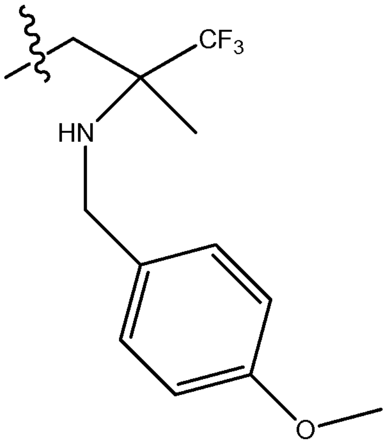
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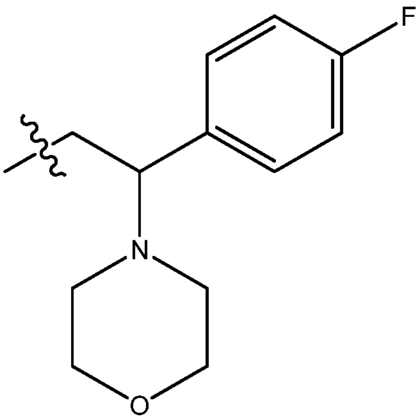
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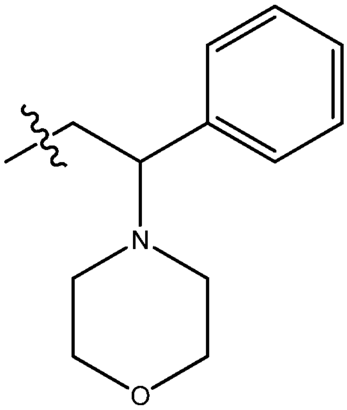
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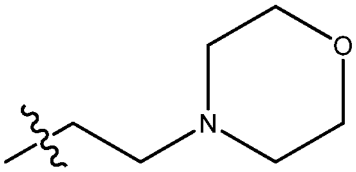
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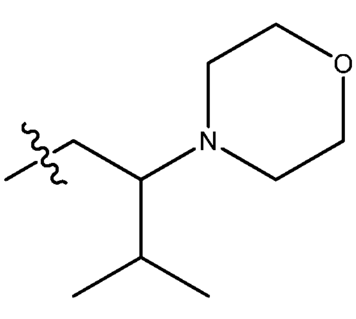
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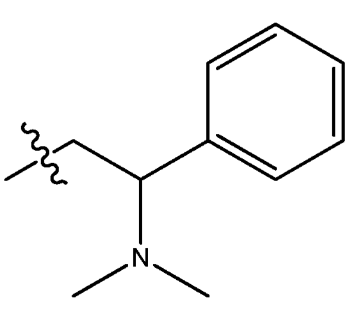
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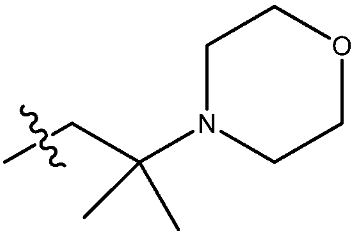

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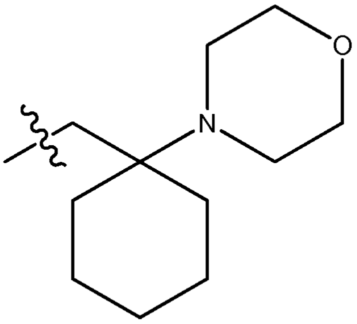

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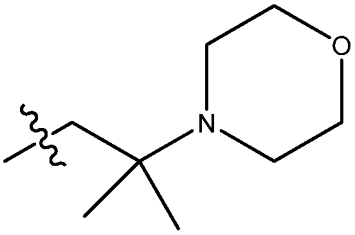

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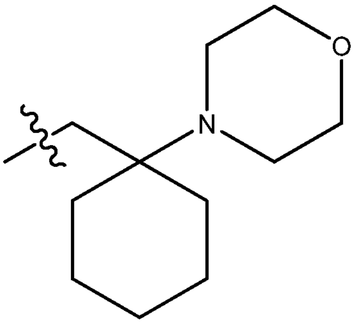

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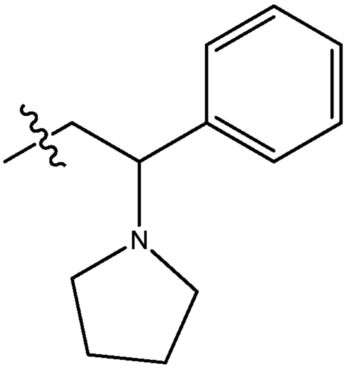

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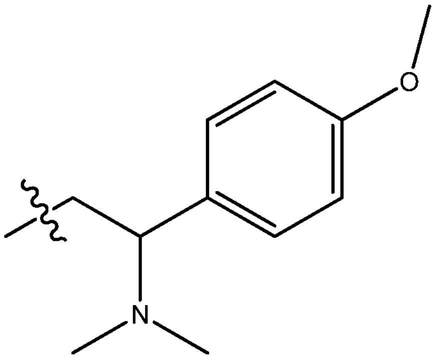

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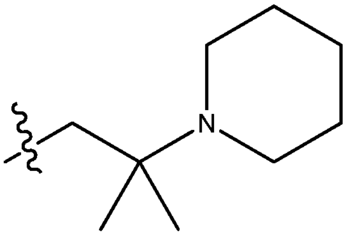

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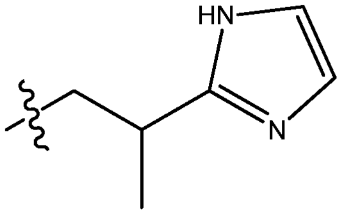

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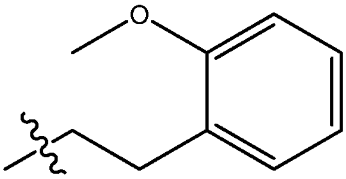
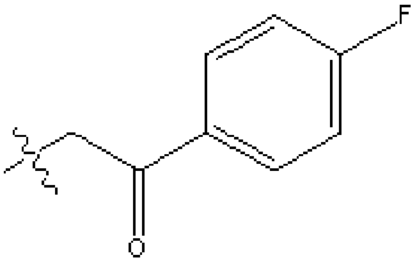
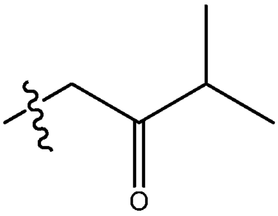
Embodiment 28: The compound according to embodiment 24, wherein

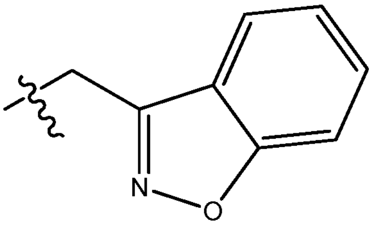
R^3 is H;

R^{101} is , , or

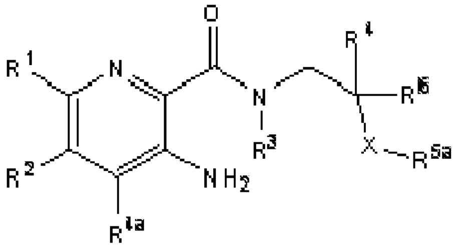
.

Embodiment 29: The compound according to embodiment 1 to 16, wherein
R^3 is H;
R^{101} is -(C_1-C_2 alkyl)-5 to 10 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents.

Embodiment 30: The compound according to embodiment 24 or 29, wherein
R^3 is H;

R^{101} is .

Embodiment 31: The compound of formula III



III

or pharmaceutically acceptable salts thereof, wherein:

X is NR^y or O;

R^1 is C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_3-C_{10} cycloalkyl; -C1-C4 alkyl-C_3-C_8 cycloalkyl; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; halogen; CN; $NR^{11}R^{12}$; C(0)NR $^{13}R^{14}$; $NR^{13}C(0)R$ ^{15}, $C0_2R^{15}$, -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is C1-C4 haloalkyl;

R^3 is H or C-i-Ce alkyl optionally substituted by one or more halogen atoms;

R^{4a} is selected from halogen; C_2-C_8 alkenyl and -(C_0-C_4 alkyl)-C_6-C_{14} aryl;

R^4 is H, or C-i-Ce alkyl optional substituted with one or more halogen;

R^{5a} is H, C-i-Ce alkyl optional substituted with one or more halogen, -(C_0-C_4 alkyl)-C_6-C_{14} aryl or -3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^y is H, C-i-Ce alkyl optional substituted with one or more halogen, -(C_0-C_4 alkyl)-C_6-C_{14} aryl or -3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^6 is C-i-Ce alkyl optionally substituted by one or more halogen atoms; C_3-C_{10} cycloalkyl; -C1-C4 alkyl-C_3-C_8 cycloalkyl; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, cycloalkenyl, -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group are each optionally substituted by one or more Z substituents; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^{5a} and R^6 together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents; or

R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R^{11} and R^{13} are each independently H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms, C3-C10 cycloalkyl or -(C1-C4 alkyl)-C_3-C_8 cycloalkyl;

R^{12}, R^{14}, and R^{15} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C3-C10 cycloalkyl; C5-C10 cycloalkenyl; -C1-C4 alkyl-C_3-Cs cycloalkyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^{11} and R^{12}, and R^{13} and R^{14}together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or C1-C4 alkoxy, $NR^{18}(S0_2)R^{21}$, $(S0_2)NR^{19}R^{21}$, $(S0_2)R^{21}$, $NR^{18}C(0)R^{21}$, $C(0)NR^{19}R^{21}$, $NR^{18}C(0)NR^{19}R^{21}$, $NR^{18}C(0)OR^{19}$, $NR^{19}R^{21}$, $C(0)OR^{19}$, $C(0)R^{19}$, SR^{19}, OR^{19}, oxo, CN, $N0_2$, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C1-C4 alkoxy-CrC 4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from Ci-C 6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and C(0)CrC $_6$ alkyl; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- 0-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(0)CrC $_6$ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH $_2$, C(0)NHC_1-C_6 alkyl or C(0)N(Ci-C $_6$ alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0) $_2$-aryl; S(0) $_2$-Ci-C $_6$ alkyl; Ci-C $_6$ alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC $_6$ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by Ci-C $_6$ alkyl, Ci-C $_6$ haloalkyl or Ci-C $_6$ alkoxy.

Embodiment 32: The compound according to embodiment 31, wherein

X is NR^y or O;

R^1 is C-i-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; halogen; -(C_0-C_4 alkyl)-C_6 aryl; or -(C_0-C_4 alkyl)-5 to 6 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the cycloalkyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is C_1-C4 haloalkyl;

R^3 is H;

R^4 is H, or C_1-C_4 alkyl optional substituted with one or more halogen;

R^{5a} is H, C_1-C_4 alkyl optional substituted with one or more halogen, -(C_0-C_4 alkyl)-C_6 aryl or -5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C_0-C_4 alkyl)-C_6 aryl and -5 to 8 membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^y is H, C_1-C_4 alkyl optional substituted with one or more halogen, -(C_0-C_4 alkyl)-C_6 aryl or -5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -(C_0-C_4 alkyl)-C_6 aryl and -5 to 8 membered heterocyclic group are each optionally substituted by one or more Z substituents;

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; -(C_0-C_4 alkyl)-C_6 aryl; or -5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the -C_6 aryl and -5 to 8 membered heterocyclic group are each optionally substituted by one or more Z substituents; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^{5a} and R^6 together with the atoms to which they are bound a 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from N, O and S, wherein the heterocyclic group is optionally substituted by one or more Z substituents; or

R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{18}C(0)R^{21}$, $C(0)NR^{19}R^{21}$, $NR^{19}R^{21}$, $C(0)OR^{19}$, $C(0)R^{19}$, SR^{19}, OR^{19}, oxo, CN, $N0_2$, halogen or a 5 to 8 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; wherein the heterocyclic group is option substituted by halogen, C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or -CN;

R^{18} is H or C_1-C_4 alkyl;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from Ci-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and C(0)Ci-C $_6$ alkyl; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- 0-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(0)CrC $_6$ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH $_2$, C(0)NHC_1-C_6 alkyl or C(0)N(Ci-C $_6$ alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0) $_2$-aryl; S(0) $_2$-Ci-C $_6$ alkyl; Ci-C $_6$ alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC $_6$ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by Ci-C $_6$ alkyl, Ci-C $_6$ haloalkyl or Ci-C $_6$ alkoxy.

Embodiment 33: The compound according to embodiment 31 or 32, wherein

X is NR^y or O;

R^1 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; or halogen;

R^2 is CF_3;

R^3 is H;

R^4 is H, or C_1-C_4 alkyl optional substituted with one or more halogen;

R^{5a} is H, C_1-C_4 alkyl optional substituted with one or more halogen,

R^y is H, C_1-C_4 alkyl optional substituted with one or more halogen,

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 6 membered carbocyclic ring system; or

R^{5a} and R^6 together with the atoms to which they are bound a 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from N, O and S, wherein the heterocyclic group is optionally substituted by one or more Z substituents; or R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

Z is independently OH, C_1-C_6 alkyi optionally substituted by one or more OH groups or NH_2 groups, Ci-C_6 alkyi optionally substituted by one or more halogen atoms, Ci-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{19}R^{21}$, C(0)OR^{19}, C(0)R^{19}, SR^{19}, OR^{19}, oxo, CN, N0$_2$, or halogen;

R^{19} is H; Ci-C_8 alkyi; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyi, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyi)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, Ci-C_6 alkyi and C(0)Ci-C_6 alkyi; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from Ci-C_6 alkyi, Ci-C_6 alkoxy and halogen; and (C_0-C_4 alkyi)- O-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyi or C(0)CrC$_6$ alkyi; wherein the alkyi groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH$_2$, C(0)NHCi-C$_6$ alkyi or C(0)N(Ci-C$_6$ alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 6-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0)$_2$-aryl; S(0)$_2$-Ci-C$_6$ alkyi; Ci-C$_6$ alkyi optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC$_6$ alkyi, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by C_1-C_6 alkyi, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

Embodiment 34: The compound according to embodiment 31 to 33, wherein
X is NR^y or O;

R^1 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; or halogen;

R^2 is CF_3;

R^3 is H;

R^4 is H, or C_1-C_4 alkyl optional substituted with one or more halogen;

R^{5a} is H, C_1-C_4 alkyl optional substituted with one or more halogen,

R^y is H, C_1-C_4 alkyl optional substituted with one or more halogen,

R^6 is C-i-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; OH; CN; or

R^{5a} and R^6 together with the atoms to which they are bound a 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from N, O and S, wherein the heterocyclic group is optionally substituted by one or more Z substituents; or

R^{5a} and R^y together with the atoms to which they are bound a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

Z is independently OH, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, Ci-C_6 alkyl optionally substituted by one or more halogen atoms, Ci-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, oxo, CN, $N0_2$, or halogen;

Embodiment 35: The compound according to any proceeding embodiment, wherein R^2 is CF3CF $_2$-, $(CF_3)_2CH$-, CH3-CF $_2$-, CF3CF $_2$-, CF_3, CF_2H-, CH_3-CCl_2-, CF3CFCClH-, CBr_3, CBr_2H-$CF_3CF_2CHCF_3$ or $CF_3CF_2CF_2CF_2$-.

Embodiment 36: The compound according to any one of embodiments 1 to 35, wherein R^2 is CF_3.

Embodiment 37: The compound according to any one of embodiments 1 to 36, wherein the compound is a substantially pure enantiomer with the S configuration.

Embodiment 38: The compound according to any one of embodiments 1 to 36, wherein the compound is a substantially pure enantiomer with the R configuration.

Embodiment 39: The compound according to embodiment 5, 24 or 31, wherein the compound is represented by:
(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide;
(S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-4-vinylpicolinamide; and
3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide.

Embodiment 40: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of an inflammatory or obstructive airways disease or mucosal hydration.

Embodiment 41: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of a disease mediated by CFTR.

Embodiment 42: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of a disease mediated by CFTR, wherein the disease is CF or COPD.

Embodiment 43: Use of a compound according to any one of embodiments 1 to 39 in the manufacture of a medicament for use in the treatment of cystic fibrosis.

Embodiment 44: A pharmaceutical composition for treating a disease or disorder mediated by CFTR, comprising:
the compound according to embodiment 1 to 39 and
one or more pharmaceutically acceptable excipients.

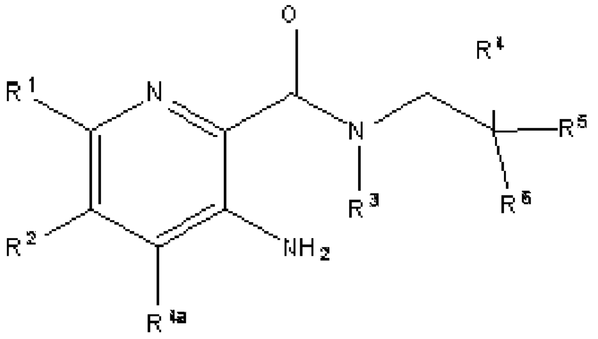
Embodiment 45: A pharmaceutical composition, according to embodiment 44, wherein the disease or disorder is cystic fibrosis or COPD.

Embodiment 46: A pharmaceutical composition, according to embodiment 45, wherein the disease or disorder is cystic fibrosis.

Embodiment 47: A pharmaceutical combination, comprising: a first active comprising the compound according to any one of embodiments 1 to 39 and a second active selected from osmotic agents, ENaC blockers, anti-inflammatory agents, bronchodilatory agents, antihistamine agents, anti-tussive agents, antibiotic agents and DNase drug substances, wherein the first and second actives may be in the same or different pharmaceutical composition.

Embodiment 48: A pharmaceutical combination according to embodiment 47, wherein the second active agent is an EnaC blocker.

Embodiment 49: A process for the preparation of compounds of formula (I), comprising:



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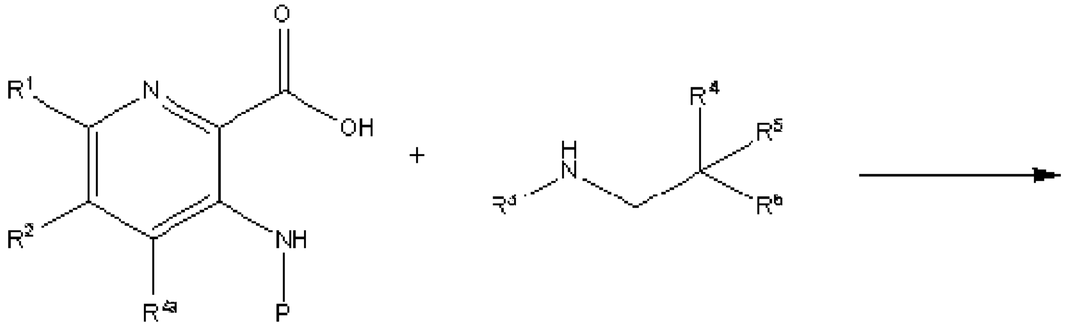
reacting a compound 1 with compound 2 in a peptide coupling reaction,



1 2

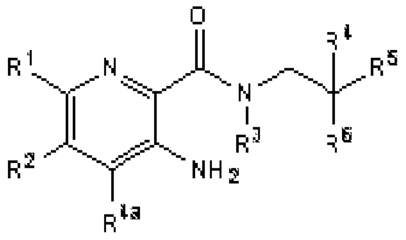
wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined herein and P is a suitable amino protecting group;

removing protecting groups and isolating the compound of formula I.

Embodiment 50: The process according to embodiment 49, wherein the peptide coupling condition is HATU in an aprotic solvent.

Claims

1. A compound of Formula I



I

wherein:

R^1 is H; C-i-Ce alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyl; C_5-C_{10} cycloalkenyl; -Ci-C_4 alkyl-C_3-C_8 cycloalkyl; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; halogen; $S0_2NR^8R^9$; $S0_2R^{10}$; S-Ci-C_8alkyl optionally substituted by one or more halogen atoms; S-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; CN; $NR^{11}R^{12}$; CONR $^{13}R^{14}$; $NR^{13}S0_2R^{15}$; $NR^{13}C(0)R$ ^{15} and $C0_2R^{15}$, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^2 is Ci-C_4 haloalkyl;

R^3 and R^4 are each independently H or C_1-C_8 alkyl optionally substituted by one or more halogen atoms;

R^{4a} is selected from halogen; C_2-C_8 alkenyl; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl; and C_1-C_8 hydroxyalkyl; wherein the -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl groups are each optionally substituted by one or more Z substituents;

R^5 and R^6 are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyi; C_5-C_{10} cycloalkenyl; -C_1-C_4 alkyl-C_3-C_8 cycloalkyi; C_1-C_8 alkoxy optionally substituted by one or more halogen atoms; OH; CN; halogen; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S; or -(C_0-C_4 alkyl)-C0 $_2R^{15}$, wherein the cycloalkyi, cycloalkenyl, -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group groups are each optionally substituted by one or more Z substituents; or

R^5 and R^6 are each independently a group of the formula:
-$(CH_2)_m$-$NR^{17}R^{18}$; or

R^5 and R^6 are each independently a group of the formula:
-$(CH_2)_m$-OR^4; or

R^4 and R^5 together with the carbon atoms to which they are bound form a 3 to 8 membered carbocyclic ring system; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered carbocyclic ring system or a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

R^4, R^5 and R^6 cannot all be the same;

m is 0, 1, 2 or 3;

R^8, R^{11}, R^{13} and R^{17} are each independently H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms, C_3-C_{10} cycloalkyi or -(C_1-C_4 alkyl)-C_3-C_8 cycloalkyi;

R^9, R^{10}, R^{12}, R^{14}, R^{15}, R^{16} and R^{18} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_3-C_{10} cycloalkyi; C_5-C_{10} cycloalkenyl; -C_1-C_4 alkyl-C_3-C_8 cycloalkyi; -(C_0-C_4 alkyl)-C_6-C_{14} aryl; or

-(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are each optionally substituted by one or more Z substituents; or

R^8 and R^9, R^{11} and R^{12}, R^{13} and R^{14}, and R^{17} and R^{18} together with the nitrogen atom to which they are attached may form a 4 to 14 membered heterocyclic group optionally substituted by one or more Z substituents;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups or **C_1-C4** alkoxy, $NR^{18}(S0\ _2)R^{21}$, $(S0\ _2)NR^{19}R^{21}$, $(S0\ _2)R^{21}$, $NR^{18}C(0)R\ ^{21}$, $C(0)NR\ ^{19}R^{21}$, $NR^{18}C(0)NR\ ^{19}R^{21}$, $NR^{18}C(0)OR\ ^{19}$, $NR^{19}R^{21}$, $C(0)OR\ ^{19}$, $C(0)R\ ^{19}$, SR^{19}, OR^{19}, oxo, CN, $N0\ _2$, halogen or a 3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; **C_1-C4** alkoxy-CrC $_4$ alkyl; **(C_0-C_4** alkyl)-aryl optionally substituted by one or more groups selected from **Ci-C_6** alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and C(0)CrC $_6$ alkyl; (C_0-C_4 alkyl)-0-aryl optionally substituted by one or more groups selected from **Ci-C_6** alkyl, **Ci-C_6** alkoxy and halogen; and **(C_0-**C_4 alkyl)- 0-3- to 14-membered heterocyclic group, the heterocyclic group including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(0)CrC $_6$ alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(0)NH $_2$, C(0)NHCrC $_6$ alkyl or C(0)N **(**C_1-C_6 alkyl$)_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclic group, the heterocyclic group including one or more further heteroatoms selected from N, O and S, the heterocyclic group being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclic group including one or more heteroatoms selected from N, O and S; S(0)$_2$-aryl; S(0)2-CrC $_6$ alkyl; C_1-C_6 alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(0)OCrC $_6$ alkyl, wherein the aryl and heterocyclic substituent groups are themselves optionally substituted by Ci-C $_6$ alkyl, Ci-C $_6$ haloalkyl or Ci-C $_6$ alkoxy; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 or 2, wherein R^{4a} is selected from halogen; C_2-C_8 alkenyl; -(C_0-C_4 alkyl)-C $_6$-C_{14} aryl; -(C_0-C_4 alkyl)-3 to 14 membered heterocyclyl; C_1-C_8 hydroxyalkyl.

3. The compound according to claim 1 or 2, wherein
R^1 is C-i-Ce alkoxy optionally substituted by one or more halogen atoms; or halogen.

4. The compound according to any one of claims 1 to 3, wherein
R^1 is C-i-C_4 alkoxy optionally substituted by one or more halogen atoms; or halogen.

5. The compound according to any one of claims 1 to 3, wherein
R^1 is aryl, wherein aryl is phenyl optionally substituted by one or more Z substituents.

6. The compound according to any one of claims 1 to 5, wherein
R^2 is CF_3.

7. The compound according to any one of claims 1 to 6, wherein
R^4 is H or C_1-C_4 alkyl optionally substituted by one or more halogen atoms;
R^5 is C-i-C_4 alkoxy optionally substituted by one or more halogen atoms; -(CH $_2$)$_m$-$NR^{17}R^{18}$, -(CH $_2$)m-OR$'$; or -(C_0-C_4 alkyl)-3 to 14 membered heterocyclic group, wherein the heterocyclic group contains at least one heteroatom selected from N, O and S, wherein the aryl heterocyclyl groups is optionally substituted by one or more Z substituents;

R^6 is C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more halogen atoms; or -(C_0-C_4 alkyl)-C_6-C_{14} aryl wherein the aryl is optionally substituted by one or more Z substituents; or

R^4 and R^6 together with the carbon atoms to which they are bound form a 3 to 6 membered carbocyclic ring system; or

R^5 and R^6 together with the carbon atoms to which they are bound form a 5 to 8 membered heterocyclic ring system containing one or more heteroatoms selected from N, O and S, wherein the ring system is optionally substituted by one or more Z substituents;

m is Oor 1;

R^{17} and R^{18} are each independently H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms.

8. The compound according to any one of claims 1 to 7, wherein

R^1 is or C_1-C_4 alkoxy optionally substituted by one or more halogen atoms;

R^2 is $CF_{3;}$

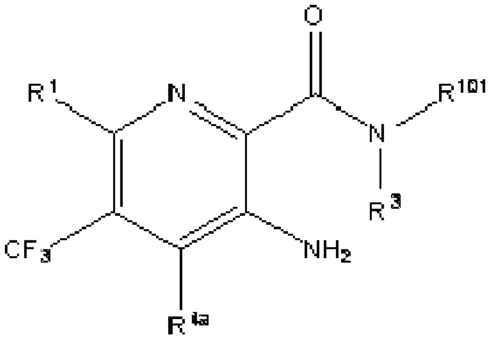
R^3 is H, CH_3 or CF_3;

R^4 is H or Me;

R^5 is $-NR^{17}R^{18}$ or OH, and

R^6 is C-i-C_4 alkyl optionally substituted by one or more halogen atoms.

9. The compound according to claim 1, represented by formula II,

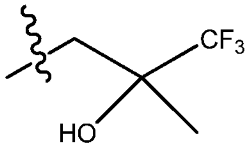
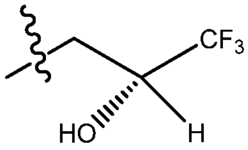
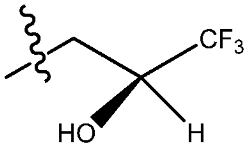


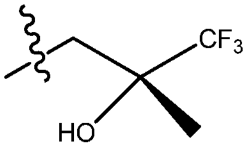
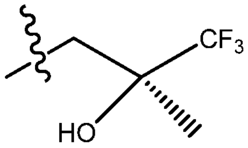
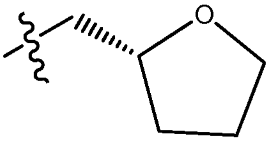
II

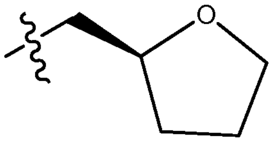
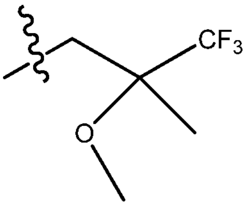
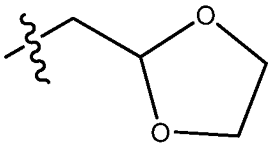
or a pharmaceutically acceptable salt thereof, wherein

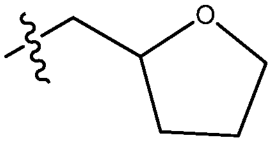
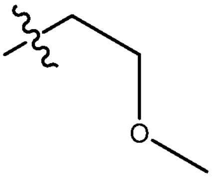
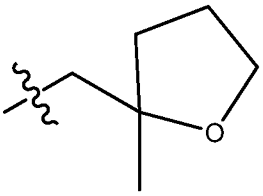
R^1 is C-i-Ce alkoxy optionally substituted by one or more halogen atoms; or halogen;;

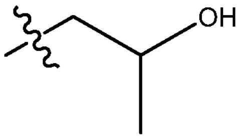
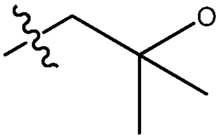
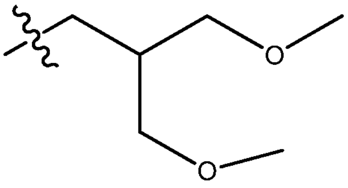
R_3 is H or CH_3;

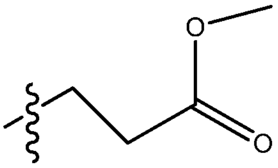
R^{101} is , , ,

, , ,

, , ,

, , ,

, , ,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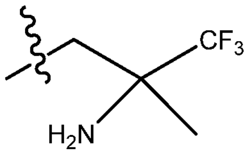
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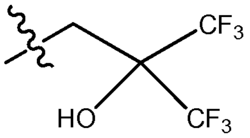
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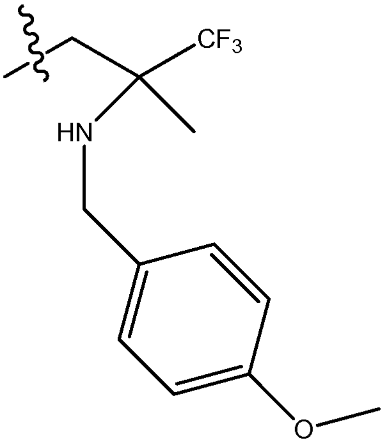
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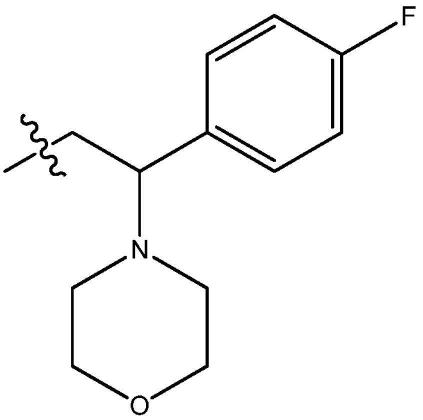
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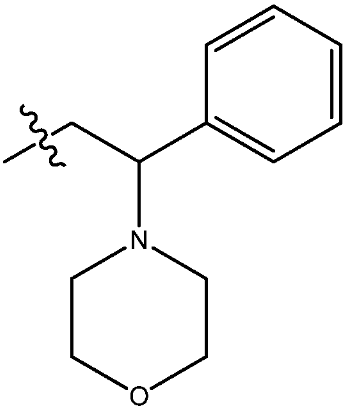
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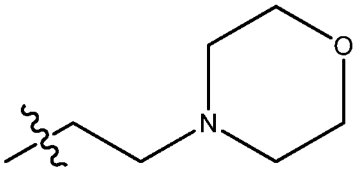
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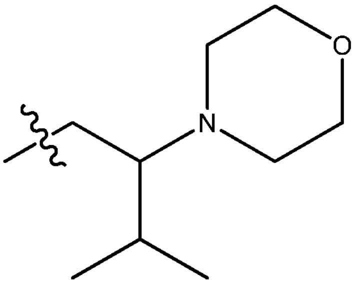
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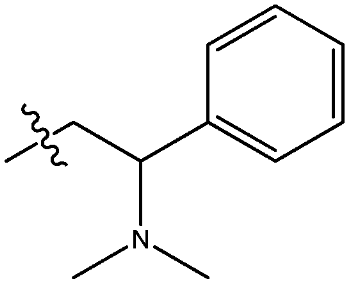
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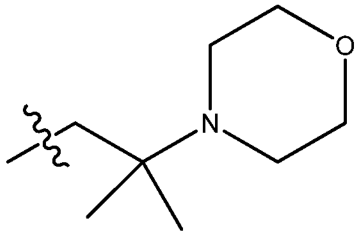

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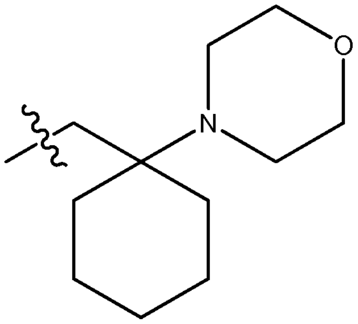

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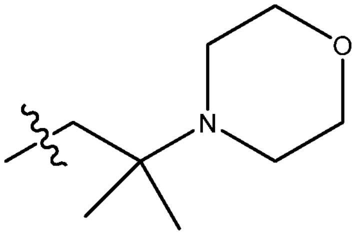

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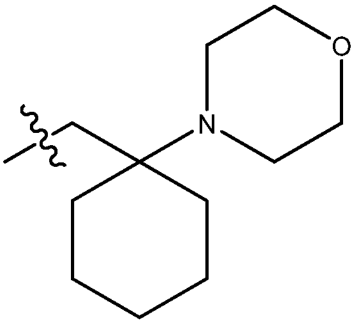

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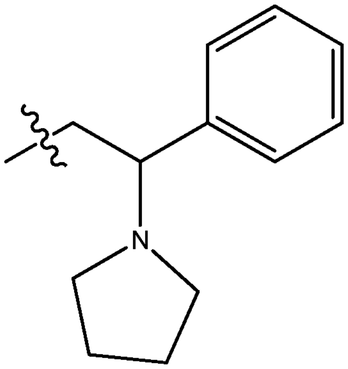

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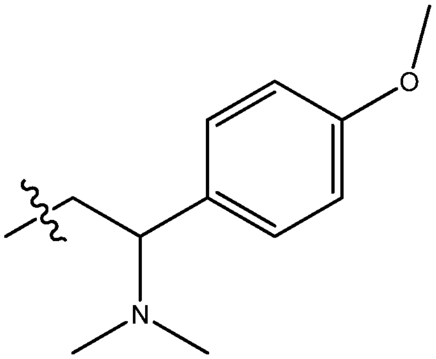

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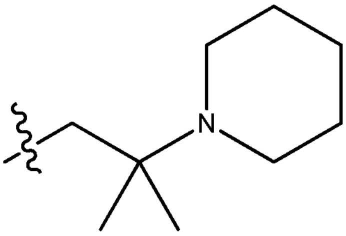

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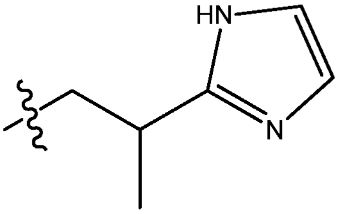

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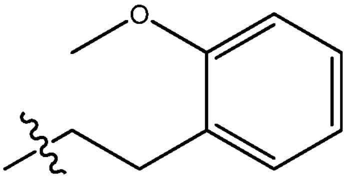

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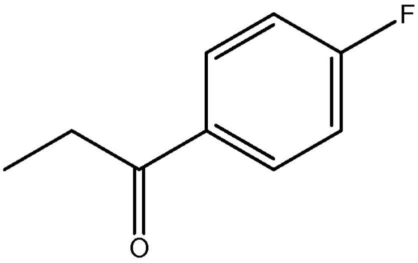

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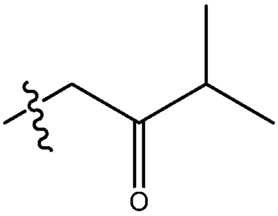

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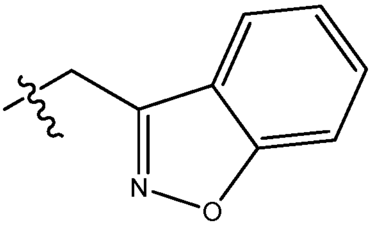

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10. The compound according to any one of claims 1 to 10 selected from
(S)-3-Amino-4-chloro-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoromethyl)picolinamide;
(S)-3-Amino-6-methoxy-N-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-5-(trifluoro methyl)-4-vinylpicolinamide; and
3-Amino-6-methoxy-4-phenyl-5-trifluoromethyl-pyridine-2-carboxylic acid ((S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)-amide.

11. A compound according to any of Claims 1 to 10 for use as a pharmaceutical.

12. A compound according to any of Claims 1 to 10 for use in the treatment of an inflammatory or obstructive airways disease or mucosal hydration.

13. Use of a compound according to any of Claims 1 to 10 in the manufacture of a medicament for use in the treatment of an inflammatory or obstructive airways disease or mucosal hydration.

14. A pharmaceutical composition, comprising:
the compound according to any of Claims 1 to 10 and
one or more pharmaceutically acceptable excipients.

15. A pharmaceutical combination, comprising:
a first active comprising the compound according to any of Claims 1 to 10 and
a second active selected from osmotic agents, ENaC blockers, anti-inflammatory agents, bronchodilatory agents, antihistamine agents, anti-tussive agents, antibiotic agents and DNase drug substances, wherein the first and second actives may be in the same or different pharmaceutical composition.

16. A pharmaceutical combination, comprising:
a first active comprising the compound according to any of Claims 1 to 10 and
a second active which is a CFTR corrector, wherein the first and second actives may be in the same or different pharmaceutical composition.

17. A method for treating CFTR mediated condition or disease, comprising:
administering an effective amount of at least one compound according to any of claims 1 to 10 to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/054801

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 A61K31/44 A61P11/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 2011/113894 A1 (NOVARTIS AG [CH]; BAETTIG URS [GB]; BALA KAMLESH JAGDIS [GB]; BUDD EMM) 22 September 2011 (2011-09-22) claims 1, 15 -----	1-17
A	WO 2008/141119 A2 (VERTEX PHARMA [US]; HADIDA RUAH SARA [US]; GROOTENHUIS PETER D J [US];) 20 November 2008 (2008-11-20) claim 1 -----	1-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 19 November 2012	Date of mailing of the international search report 27/11/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/054801

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		WO 2008141119 A2	20-11-2008