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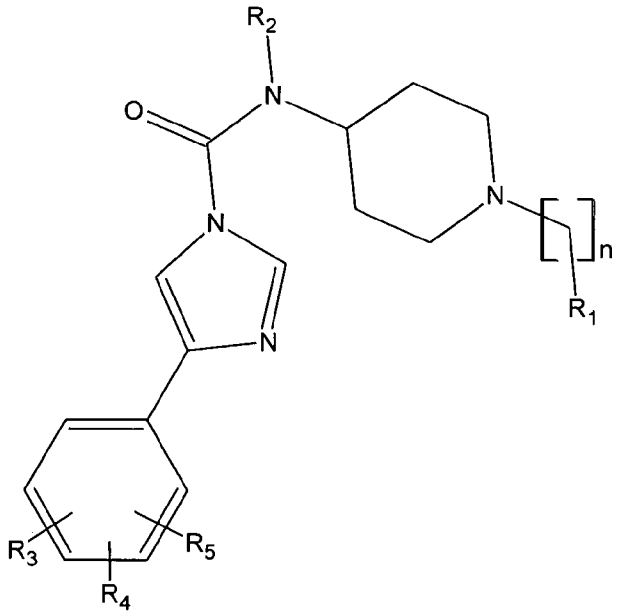
(54) **Title**: UREA COMPOUNDS AND THEIR USE AS FAAH ENZYME INHIBITORS



(I)

(57) **Abstract**: There is provided a compound having Formula I:(I) wherein: R1 is aryl which is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy, or R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy; R2 is C_{1-4} alkyl; R3 is selected from hydroxyl and OSO_2CH_3; R4 and R5 are independently selected from hydrogen, hydroxyl and halogen; and n is 0 or 1; or a pharmaceutically acceptable salt thereof; wherein when R3 is hydroxyl and R4 and R5 are not hydroxyl, the optionally substituted aryl group, second aryl group or aryloxy group of R1 is substituted with one or more hydroxyl groups or C1-4 alkoxy groups, or wherein when R3 is hydroxyl, one of R4 and R5 is hydroxyl, provided that the compound is not N-(1-benzylpiperidin-4-yl)-4-(3,4-dihydroxyphenyl)-N-methyl-1H-imidazole-1-carboxamide hydrobromide. The compound may be used as an inhibitor of fatty acid amide hydrolase.

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UREA COMPOUNDS AND THEIR USE AS FAAH ENZYME INHIBITORS

Field of the Invention

The present invention relates to urea compounds and their use. These compounds have been found to be useful in the treatment or prevention of conditions having an association with substrates, such as the neurotransmitter anandamide, which are broken down by the fatty acid amide hydrolase (FAAH) enzyme. The compounds are particularly suitable for topical administration and so can be used to treat conditions which for which topical administration is preferred. For example, such conditions include pulmonary, dermatological and gastrointestinal conditions. In particular, it has been found that the compounds may be useful in the treatment or prevention of pulmonary conditions, such as diseases of the respiratory tracts, bronchospasm, coughing, asthma, chronic bronchitis, chronic obstruction of the respiratory tract and emphysema.

Background to the Invention

FAAH enzyme breaks down fatty acid amides such as anandamide (*N*-arachidonoylethanolamine), *N*-oleoylethanolamine, *N*-palmitoylethanolamine and oleamide. Anandamide, also known as *N*-arachidonoylethanolamine or AEA, is an endogenous cannabinoid neurotransmitter found in animal and human organs, especially in the brain. It has also been found that anandamide binds to the vanilloid receptor. Anandamide is degraded by the fatty acid amide hydrolase (FAAH) enzyme to ethanolamine and arachidonic acid. Accordingly, inhibitors of FAAH lead to elevated anandamide levels.

Anandamide is a neurotransmitter in the endocannabinoid system and stimulates the cannabinoid receptors. Cannabinoid receptors, such as CB1 and CB2, are G protein-coupled receptors. CB1 is found mainly in the central nervous system whereas CB2 is found mainly in peripheral tissue. The endocannabinoid system has been implicated in a growing number of physiological functions, both in the central and peripheral nervous systems and in peripheral organs. Modulation of the activity of the endocannabinoid system has been shown to have a potentially therapeutic effect on a

wide range of disparate diseases and pathological conditions. Therefore, the endocannabinoid system, and the FAAH enzyme in particular, has become a therapeutic target for developing potential treatments for many diseases. The endocannabinoid system has been implicated in appetite regulation, obesity, metabolic disorders, cachexia, anorexia, pain, inflammation, neurotoxicity, neurotrauma, stroke, multiple sclerosis, spinal cord injury, Parkinson's disease, levodopa-induced dyskinesia, Huntington's disease, Gilles de la Tourette's syndrome, tardive dyskinesia, dystonia, amyotrophic lateral sclerosis, Alzheimer's disease, epilepsy, schizophrenia, anxiety, depression, insomnia, nausea, emesis, alcohol disorders, drug addictions such as opiates, nicotine, cocaine, alcohol and psychostimulants, hypertension, circulatory shock, myocardial reperfusion injury, atherosclerosis, asthma, glaucoma, retinopathy, cancer, inflammatory bowel disease, acute and chronic liver disease such as hepatitis and liver cirrhosis, arthritis and osteoporosis. The endocannabinoid system and the conditions with which it is associated is discussed in detail in Pacher *et al. Pharmacol. Rev.* 2006, 58, 389-462.

In order to modulate the level of endogenous FAAH substrates, such as anandamide, which in turn modulate the endocannabinoid system, inhibitors of the FAAH enzyme have been developed. This allows conditions and diseases associated with the endocannabinoid system to be at least partially treated or prevented.

Since the substrates of FAAH bind to other receptors, e.g. the vanilloid receptor, and/or are involved in other signalling pathways, inhibitors of FAAH may also allow conditions or diseases associated with other pathways or systems, e.g. the vanilloid system, to be at least partially treated or prevented.

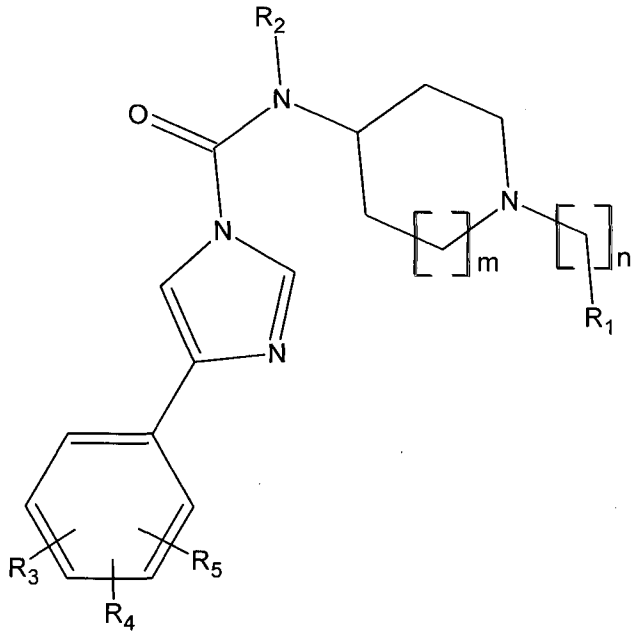
WO 2010/074588 discloses compounds which are inhibitors of FAAH.

Käsnänen et al. (Heikki Käsnänen, Mikko J. Myllymäki, Anna Minkkilä, Antti O. Kataja, Susanna M. Saario, Tapio Nevalainen, Ari M. P. Koskinen, and Antti Poso. *Chem Med Chem* 2010, 5(2), 213-231) discloses carbamate compounds which are FAAH inhibitors. In particular, compound 6b is a FAAH inhibitor which contains an imidazole structure. However, this compound is a weak FAAH inhibitor compared to

many of the other carbamate compounds described in this paper and which do not contain an imidazole structure.

Summary of the Invention

In a first aspect, the present invention provides a compound having Formula I:



Formula I

wherein:

R1 is aryl which is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy, or R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy;

R2 is C_{1-4} alkyl;

R3 is selected from hydroxyl and OSO_2CH_3;

R4 and R5 are independently selected from hydrogen, hydroxyl and halogen;

m is 0 or 1; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof;

wherein when R3 is hydroxyl and R4 and R5 are not hydroxyl, the first or second aryl group or aryloxy group of R1 is substituted with one or more hydroxyl groups or C_{1-4}

alkoxy groups, or wherein when R3 is hydroxyl, one of R4 and R5 is hydroxyl, provided that the compound is not *N*-(1-benzylpiperidin-4-yl)-4-(3,4-dihydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrobromide.

The compounds of the invention have been found to modulate the activity of the enzyme fatty acid amide hydrolase (FAAH). These compounds are particularly suitable for topical administration and have been found to be useful in the treatment of conditions for which topical administration could be advantageously used. The compounds possess one or more of the following properties that make them particularly suitable for certain conditions: they have relatively low absorption to reduce the amount of compound entering the bloodstream where it will have a peripheral/systemic effect; they are thought to have relatively high protein binding which may help to retain the compound in the tissue of interest, e.g. the lung; they are relatively potent; and they have inactive metabolites which helps to increase systemic clearance reducing systemic effects. Further, many of these compounds also display other advantages. For example, it is thought that the genotoxicity risk of at least some of these compounds is reduced so that it is relatively low. In addition, these compounds have been found to be particularly useful in the treatment of pulmonary conditions (FAAH is a potential therapeutic target for the treatment of pulmonary conditions (see Pacher *et al. Pharmacol. Rev.* 2006, 58, 389-462 and Berdyshev *et al.*, *Life Sciences*, 1998, 63: PL125-129)). The compounds of the invention have been shown to give better results relating to one or more of these properties compared to the compounds disclosed in WO 2010/074588.

The term 'C_{x-y} alkyl' as used herein refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. For example, C_{1-4} alkyl refers to a linear or branched saturated hydrocarbon group containing from 1 to 4 carbon atoms. Examples of C_{1-4} alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl. Preferably, the hydrocarbon group is linear.

The term 'C_{x-y} alkoxy' as used herein refers to an -O-C_{x-y} alkyl group wherein C_{x-y} alkyl is as defined above. Examples of such groups include methoxy, ethoxy, propoxy

and butoxy. Where adjacent atoms in a chain are both substituted with an alkoxy group, the alkyl part of each alkoxy group can be joined so as to form a ring structure such as a dioxolyl group. For example, adjacent carbon atoms in a phenyl group can both be substituted with an alkoxy group with the alkyl parts joined so as to form benzo[*d*][1,3]dioxol-5-yl.

The term 'aryl' as used herein refers to a C_{6-12} monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthalenyl and tetrahydronaphthalenyl.

The term 'aryloxy' as used herein refers to an -O-aryl group. Examples of such groups include phenoxy.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom, unless otherwise specified.

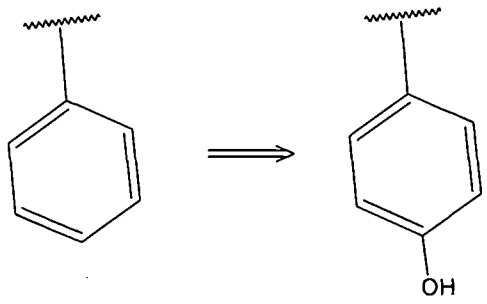
'Pharmaceutically acceptable salts' of the compound of the present invention include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Salts with acids may, in particular, be employed in some instances. Exemplary salts include hydrochloride salt, acetate salt, trifluoroacetate salt, methanesulfonate salt, 2-hydroxypropane-1,2,3-tricarboxylate salt, (2*R*,3*R*)-2,3-dihydroxysuccinate salt, phosphate salt, sulphate salt, benzoate salt, 2-hydroxy-benzoate salt, *S*-(+)-mandelate salt, *S*-(-)-malate salt, *S*-(-) pyroglutamate salt, pyruvate salt, *p*-toluenesulfonate salt, 1-*R*-(-)-camphorsulfonate salt, fumarate salt, maleate salt and oxalate salt. The compound of the present invention may be in either solvate (e.g. hydrate) or non-solvate (e.g. non-hydrate) form. When in a solvate form, additional solvents may be alcohols such as propan-2-ol.

General methods for the preparation of salts are well known to the person skilled in the art. Pharmaceutical acceptability of salts will depend on a variety of factors, including formulation processing characteristics and in vivo behaviour, and the skilled

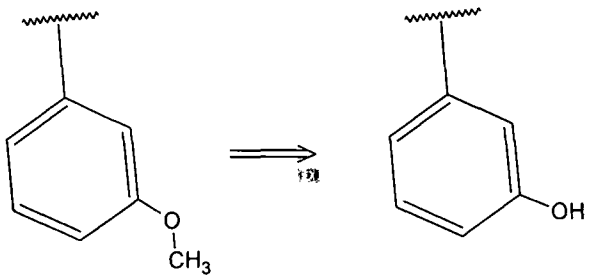
person would readily be able to assess such factors having regard to the present disclosure.

Where compounds of the invention exist in different enantiomeric and/or diastereoisomeric forms (including geometric isomerism about a double bond), these compounds may be prepared as isomeric mixtures or racemates, although the invention relates to all such enantiomers or isomers, whether present in an optically pure form or as mixtures with other isomers. Individual enantiomers or isomers may be obtained by methods known in the art, such as optical resolution of products or intermediates (for example chiral chromatographic separation (e.g. chiral HPLC)), or an enantiomeric synthesis approach. Similarly, where compounds of the invention may exist as alternative tautomeric forms (e.g. keto/enol, amide/imidic acid), the invention relates to the individual tautomers in isolation, and to mixtures of the tautomers in all proportions.

It has been found that the presence of a hydroxyl group as a substituent on the aryl ring of R1 helps to provide the compounds with good pharmacokinetic properties for topical administration. This helps to ensure that the compounds are poorly active systemically. Further, it has been found that CYP enzymes, which are responsible for drug metabolism in the human body, can metabolise at least some of the compounds of the invention to provide a hydroxyl group. For example, if R1 is aryl (e.g. phenyl), it has been found that CYP enzymes will oxidise the compound so that a hydroxyl group is added to the aryl (e.g. phenyl) ring on the right hand side of the compound. For example, see below:



Further, if R1 is aryl with a C_{1-4} alkoxy substituent, the alkoxy group is metabolised to a hydroxyl group. For example, see below:



It has also been found that having an OSO_2CH_3 group on the left hand side and a hydroxyl group on the right hand side as substituents makes the compounds particularly suitable for topical administration, for example, for use for pulmonary conditions. Similarly, it has been found that having three hydroxyl groups as substituents, one on one side of the compound and two on the other side of the compound, also makes the compounds particularly suitable for topical administration, for example, for use for pulmonary conditions. As mentioned above, the right hand side of the compound can be metabolised to provide a hydroxyl group on the right hand side of the compound.

In various embodiments, the aryl of R1 which is optionally substituted is phenyl or naphthalenyl. In some embodiments, the aryl of R1 which is optionally substituted is phenyl. In other embodiments, the aryl of R1 which is optionally substituted is naphthalenyl.

In some embodiments, R1 is aryl which is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy. The aryl of R1 may be monocyclic or bicyclic. In some embodiments, the aryl of R1 is phenyl or naphthalenyl. In particular embodiments, R1 is monocyclic aryl (such as phenyl) which is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy. In other embodiments, R1 is bicyclic aryl (such as naphthalenyl) which is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy.

In various embodiments, the aryl of R1 which is substituted with aryl or aryloxy is phenyl substituted with a second phenyl or phenoxy. The second phenyl or phenoxy group is optionally substituted.

In certain embodiments, R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy. In particular embodiments, R1 is phenyl which is substituted with a second phenyl group (to form a biphenyl structure) or a phenoxy group, wherein the second phenyl group or the phenoxy group is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy.

Preferably, R1 is aryl which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy and halogen. In particular embodiments, R1 is monocyclic aryl (such as phenyl) which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy and halogen. In other embodiments, R1 is bicyclic aryl (such as naphthalenyl) which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy and halogen.

In certain embodiments, R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy and halogen. In particular embodiments, R1 is phenyl which is substituted with a second phenyl group (to form a biphenyl structure) or a phenoxy group, wherein the second phenyl group or the phenoxy group is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy and halogen.

In particular embodiments, R1 is aryl which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl and halogen. In particular embodiments, R1 is monocyclic aryl (such as phenyl) which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl and halogen. In other embodiments, R1 is bicyclic aryl (such as naphthalenyl) which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl and halogen.

In certain embodiments, R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl and halogen. In particular embodiments, R1 is phenyl which is substituted with a second phenyl group (to form a biphenyl structure) or a phenoxy group, wherein the second phenyl group or the phenoxy group is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl and halogen.

In some embodiments, R1 is aryl which is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen. In particular embodiments, R1 is monocyclic aryl (such as phenyl) which is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen. In other embodiments, R1 is bicyclic aryl (such as naphthalenyl) which is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen.

In certain embodiments, R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen. In particular embodiments, R1 is phenyl which is substituted with a second phenyl group (to form a biphenyl structure) or a phenoxy

group, wherein the second phenyl group or the phenoxy group is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen.

It is specifically envisaged that the various embodiments described above for R1 can be combined. For example, embodiments in which the aryl of R1 is substituted with an aryl or aryloxy can be combined with embodiments in which the aryl of R1 is not substituted with an aryl or aryloxy.

The aryl structure of R1 which is optionally substituted is preferably substituted with one or two groups independently selected from hydroxyl and C_{1-4} alkoxy. This aryl structure may also be optionally substituted with one or two halogen groups such as fluorine. In some embodiments, the aryl structure of R1 is preferably substituted with one or two hydroxyl groups and may also be optionally substituted with one or two halogen groups such as fluorine.

When R1 is an aryl structure which is substituted with a hydroxyl, this aryl structure which is substituted with a hydroxyl may optionally be further substituted with one or more groups selected from hydroxyl and halogen. In some embodiments, the aryl structure may optionally be further substituted with up to two halogen groups such as fluorine and/or a hydroxyl. In a number of embodiments, the aryl structure may optionally be further substituted with a halogen such as fluorine and/or a hydroxyl. In certain embodiments, the aryl structure may optionally be further substituted with a halogen such as fluorine and a hydroxyl. In other embodiments, the aryl structure may optionally be further substituted with a halogen such as fluorine or a hydroxyl. In some embodiments, the aryl structure may optionally be further substituted with a halogen such as fluorine. In various embodiments, the aryl structure may optionally be further substituted with a hydroxyl.

In some embodiments, when R3 is hydroxyl and R4 and R5 are not hydroxyl, the first or second aryl group or aryloxy group of R1 is substituted with a hydroxyl group, or wherein when R3 is hydroxyl, one of R4 and R5 is hydroxyl. As described above, the substituted aryl structure of R1 may optionally be further substituted.

In particular embodiments, R1 is aryl which is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen.

When the aryl structure of R1 is substituted with C_{1-4} alkoxy, it is preferably substituted with C_{1-3} alkoxy, more preferably substituted with C_{1-2} alkoxy, and most preferably substituted with methoxy.

As indicated above, some compounds of the invention have at least three hydroxyl substituents. Therefore, when R3 is hydroxyl and neither of R4 and R5 is hydroxyl, the aryl structure of R1 may be substituted with two hydroxyl groups and optionally substituted with one or two halogen groups such as fluorine. However, if R3 and at least one of R4 and R5 are hydroxyl, then the aryl structure of R1 may be substituted with one hydroxyl group, and optionally substituted with one or two halogen groups such as fluorine.

In some embodiments, when R3 is OSO_2CH_3, the aryl structure of R1 may be substituted with one hydroxyl group, and optionally substituted with one or two halogen groups such as fluorine.

In particular embodiments, R2 is C_{1-3} alkyl. In some embodiments, R2 is C_{1-2} alkyl. In preferred embodiments, R2 is methyl.

R3 is selected from hydroxyl or OSO_2CH_3. In some embodiments, R3 is hydroxyl. In other embodiments, R3 is OSO_2CH_3.

R4 and R5 are independently selected from hydrogen, hydroxyl and halogen such as fluorine. In some embodiments, R4 is selected from hydroxyl and halogen such as fluorine. In various embodiments, R4 is selected from hydrogen and halogen such as fluorine. In certain embodiments, R4 is selected from hydrogen and hydroxyl. In some embodiments, R4 is hydrogen. In various embodiments, R4 is hydroxyl. In certain embodiments, R4 is halogen such as fluorine.

In some embodiments, R5 is selected from hydroxyl and halogen such as fluorine. In various embodiments, R5 is selected from hydrogen and halogen such as fluorine. In certain embodiments, R5 is selected from hydrogen and hydroxyl. In some embodiments, R5 is hydrogen. In various embodiments, R5 is hydroxyl. In certain embodiments, R5 is halogen such as fluorine.

When R3 is OSO_2CH_3, R4 and R5 are preferably independently selected from hydrogen and halogen such as fluorine. In some embodiments, when R3 is OSO_2CH_3, R4 is hydrogen and R5 is selected from hydrogen and halogen such as fluorine. In certain embodiments, when R3 is OSO_2CH_3, R4 and R5 are hydrogen. In other embodiments, when R3 is OSO_2CH_3, R4 is hydrogen and R5 is halogen such as fluorine.

When R3 is hydroxyl, R4 and R5 may be independently selected from hydrogen, hydroxyl and halogen such as fluorine. In some embodiments, when R3 is hydroxyl, R4 is selected from hydrogen and hydroxyl and R5 is selected from hydrogen and halogen such as fluorine. In various embodiments, R3 and R4 are hydroxyl and R5 is selected from hydrogen and halogen such as fluorine. In certain embodiments, R3 is hydroxyl, R4 is hydrogen and R5 is selected from hydrogen and halogen such as fluorine.

R3, R4 and R5 may be in any position on the phenyl ring.

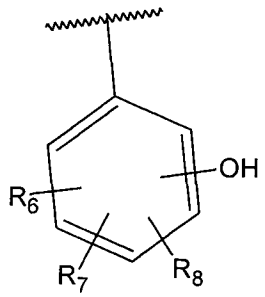
In the compound of the invention, m is 0 or 1. This means that when m is 0, the ring structure is pyrrolidinyl and when m is 1, the ring structure is piperidinyl. Preferably, m is 1. m is preferably 1 for all embodiments of the invention, including formulae I, II and III.

In the compound of the invention, n is 0 or 1. This means that when n is 0, a bond is present between the ring nitrogen atom and R1 and when n is 1, a CH_2 moiety is present between the ring nitrogen atom and R1.

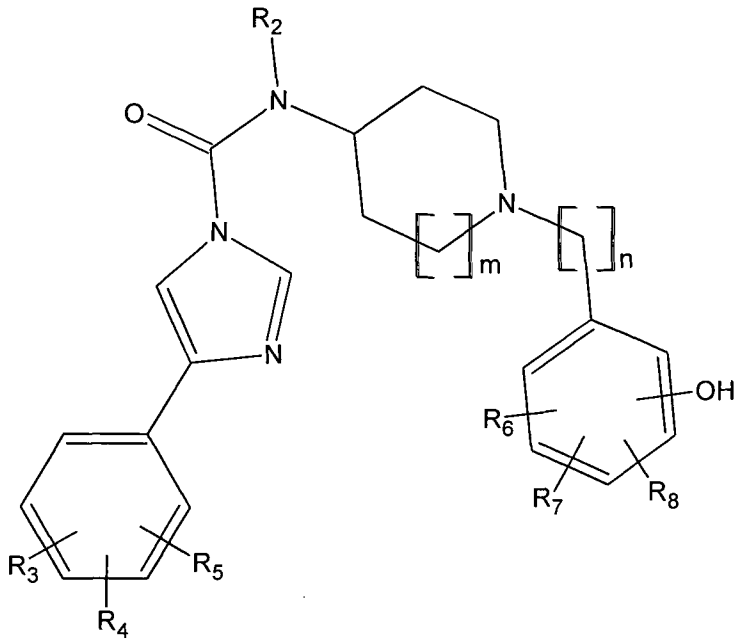
In particular embodiments, when m is 0, n is 0. In some embodiments, when m is 0, n is not 1. Further, when m is 1, n may be 0 or 1. In specific embodiments, when m is 1, n is 0. In other embodiments, when m is 1, n is 1.

It is specifically envisaged that any option described above can be combined with any other option described above. Therefore, the various options for R1, R2, R3, R4, R5, m and n can be combined in any way and all such combinations are specifically envisaged. Further, for the avoidance of doubt, it is specifically envisaged that the various options for R1 can be combined and that the various options for R3, R4 and R5 can be combined. Furthermore, it is also specifically envisaged that the various options or combinations for R1 can be combined with the various options and combinations for R3, R4 and R5.

In various embodiments, R1 has the following structure:



wherein R6, R7 and R8 are each independently selected from hydrogen, hydroxyl and halogen. For example, this means that the present invention may provide a compound having Formula II:



Formula II

wherein:

R2 is C_{1-4} alkyl;

R3 is selected from hydroxyl and OSO_2CH_3;

R4, R5, R6, R7 and R8 are each independently selected from hydrogen, hydroxyl and halogen;

m is 0 or 1; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof,

wherein when R3 is hydroxyl, one of R4, R5, R6, R7 or R8 is hydroxyl.

The options described above for Formula I for R2, R3, R4, R5, m and n also apply to above Formula II. Further, the options for the substituents of R1 when R1 is a substituted phenyl in Formula I are equally applicable to R6, R7 and R8 described above for Formula II.

R6, R7, R8 and the hydroxyl substituent may be in any position on the phenyl ring.

R6, R7 and R8 are independently selected from hydrogen, hydroxyl and halogen such as fluorine. In some embodiments, R6 is selected from hydroxyl and halogen such as fluorine. In various embodiments, R6 is selected from hydrogen and halogen such as

fluorine. In certain embodiments, R6 is selected from hydrogen and hydroxyl. In some embodiments, R6 is hydrogen. In various embodiments, R6 is hydroxyl. In certain embodiments, R6 is halogen such as fluorine.

In some embodiments, R7 is selected from hydroxyl and halogen such as fluorine. In various embodiments, R7 is selected from hydrogen and halogen such as fluorine. In certain embodiments, R7 is selected from hydrogen and hydroxyl. In some embodiments, R7 is hydrogen. In various embodiments, R7 is hydroxyl. In certain embodiments, R7 is halogen such as fluorine.

In some embodiments, R8 is selected from hydroxyl and halogen such as fluorine. In various embodiments, R8 is selected from hydrogen and halogen such as fluorine. In certain embodiments, R8 is selected from hydrogen and hydroxyl. In some embodiments, R8 is hydrogen. In various embodiments, R8 is hydroxyl. In certain embodiments, R8 is halogen such as fluorine.

In some embodiments, R6 and R7 are independently selected from hydrogen and halogen such as fluorine and R8 is selected from hydrogen and hydroxyl.

In some embodiments, R6 is halogen such as fluorine, R7 is selected from hydrogen and halogen such as fluorine and R8 is selected from hydrogen and hydroxyl.

In various embodiments, R6 and R7 are independently selected from hydrogen and halogen such as fluorine and R8 is hydroxyl. This can be combined with R3 being hydroxyl, preferably when neither of R4 and R5 are hydroxyl.

In several embodiments, R6 is hydrogen, R7 is selected from hydrogen and halogen such as fluorine, and R8 is hydroxyl. This can be combined with R3 being hydroxyl, preferably when neither of R4 and R5 are hydroxyl.

In some embodiments, when R3 is hydroxyl and neither of R4 and R5 is hydroxyl, at least one of R6, R7 and R8 is hydroxyl.

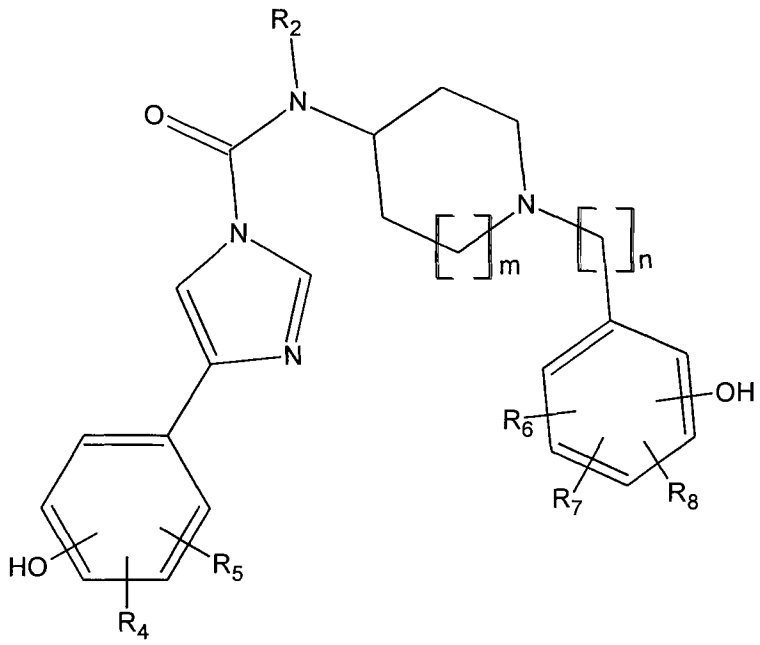
In particular embodiments, R3 and R4 are hydroxyl, R5 is selected from hydrogen and halogen such as fluorine, R6 is hydrogen, and R7 and R8 are independently selected from hydrogen and halogen such as fluorine; or R3 is hydroxyl, R4 is hydrogen, R5 is selected from hydrogen and halogen such as fluorine, R6 and R7 are independently selected from hydrogen and halogen such as fluorine, and R8 is hydroxyl.

In various embodiments, R3 and R4 are hydroxyl, R5 is selected from hydrogen and halogen such as fluorine, R6 is hydrogen, and R7 and R8 are independently selected from hydrogen and halogen such as fluorine.

In some embodiments, R3 is hydroxyl, R4 is hydrogen, R5 is selected from hydrogen and halogen such as fluorine, R6 and R7 are independently selected from hydrogen and halogen such as fluorine, and R8 is hydroxyl.

In some embodiments, R3 is OSO_2CH_3, R4 is hydrogen, and R5 is selected from hydrogen and halogen such as fluorine. In certain embodiments, R3 is OSO_2CH_3, and R4 and R5 are hydrogen. In these embodiments, preferably R6 and R7 are hydrogen, and R8 is selected from hydrogen, hydroxyl and halogen such as fluorine.

In certain embodiments, the present invention provides a compound having Formula III:



Formula III

wherein:

R2 is C_{1-4} alkyl;

one of R4 and R8 is hydroxyl and the other is hydrogen;

R5, R6 and R7 are each independently selected from hydrogen and halogen;

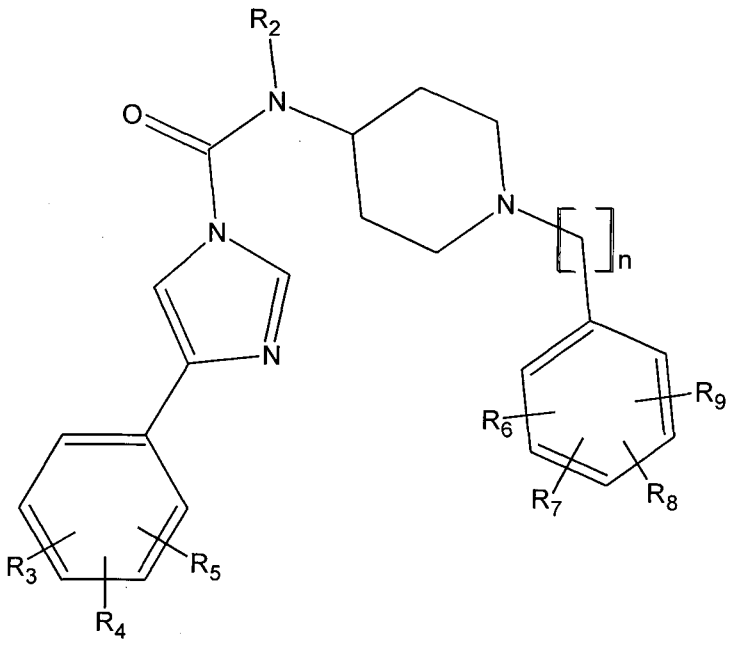
m is 0 or 1; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

The options described above for Formula I and Formula II for R2, R5, R6, R7, m and n also apply to above Formula III.

In particular embodiments, the present invention provides a compound having Formula IV:



Formula IV

wherein:

R2 is C_{1-4} alkyl;

R3 is selected from hydroxyl and OSO_2CH_3;

R4 is selected from hydrogen and hydroxyl;

R5 is selected from hydrogen and halogen;

R6 and R7 are each independently selected from hydrogen and halogen;

R8 and R9 are each independently selected from hydrogen, hydroxyl and C_{1-4} alkoxy; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof,

wherein, if R3 is hydroxyl, at least one of R4, R8 and R9 is hydroxyl.

In some embodiments of Formula IV:

R2 is C_{1-4} alkyl;

R3 is hydroxyl;

R4 is selected from hydrogen and hydroxyl;

R5 is selected from hydrogen and halogen;

R6 is hydrogen;

R7 is selected from hydrogen and halogen;

R8 is selected from hydrogen, hydroxyl and C_{1-4} alkoxy;

R9 is selected from hydroxyl and C_{1-4} alkoxy; and
n is 0 or 1;
or a pharmaceutically acceptable salt thereof,
wherein at least one of R4 and R8 is hydroxyl.

In other embodiments of Formula IV:
R2 is C_{1-4} alkyl;
R3 is hydroxyl;
R4 is selected from hydrogen and hydroxyl;
R5 is selected from hydrogen and halogen;
R6 is hydrogen;
R7 is selected from hydrogen and halogen;
R8 is selected from hydrogen, hydroxyl and C_{1-4} alkoxy;
R9 is hydroxyl; and
n is 0 or 1;
or a pharmaceutically acceptable salt thereof,
wherein at least one of R4 and R8 is hydroxyl.

In certain embodiments of Formula IV:
R2 is C_{1-4} alkyl;
R3 is hydroxyl;
R4 is selected from hydrogen and hydroxyl;
R5 is selected from hydrogen and halogen;
R6 is hydrogen;
R7 is selected from hydrogen and halogen;
R8 is selected from hydrogen and hydroxyl;
R9 is hydroxyl; and
n is 0 or 1;
or a pharmaceutically acceptable salt thereof,
wherein at least one of R4 and R8 is hydroxyl.

The options described above for Formula I and II for R2, R3, R4, R5, R6, R7, R8 and n also apply to above Formula IV. Further, the options for the substituents of R1

when R1 is a substituted phenyl in Formula I are equally applicable to R6, R7 and R8 described above for Formula IV.

In accordance with a second aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect of the invention, together with one or more pharmaceutically acceptable excipients.

Pharmaceutical compositions of this invention comprise the compound of the first aspect of the present invention with any pharmaceutically acceptable carrier, adjuvant or vehicle. The pharmaceutical compositions may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, intravenously, topically or by inhalation. Administration by inhalation is preferred.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, powders, granules, and aqueous suspensions and solutions. These dosage forms are prepared according to techniques well-known in the art of pharmaceutical formulation. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn

starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavouring and/or colouring agents may be added.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as that described in Ph. Helv, or a similar alcohol.

For purposes of topical administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration) may be prepared. The composition can take the form of an emulsion (e.g., water/oil, oil/water, water/silicone, silicone/water, water/oil/water, water/silicone/water, oil/water/oil, silicone/water/silicone) a cream, a lotion, a solution, an anhydrous stick, a serum, etc. The composition can include the active ingredient from about 0.001% to about 5% by weight. The composition can further include a moisturization agent, an antioxidant, a structuring or thickening agent, and/or an emulsifier. Alternatively, suspensions of the compounds may be prepared.

The pharmaceutical compositions of this invention may be administered by inhalation, including nasal aerosol, liquid bolus instillation, intrapulmonary aerosolizer and

aerosol inhalation/ventilation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

The compounds of the present invention may be administered in a dose of around 1 to around 20,000 μg/kg per dose, for example, around 1 to around 10,000 μg/kg, around 1 to around 5,000 μg/kg, around 1 to around 3,000 μg/kg, around 1 to around 2,000 μg/kg, around 1 to around 1,500 μg/kg, around 1 to around 1,000 μg/kg, around 1 to around 500 μg/kg, around 1 to around 250 μg/kg, around 1 to around 100 μg/kg, around 1 to around 50 μg/kg or around 1 to around 25 μg/kg per dose depending on the condition to be treated or prevented, and the characteristics of the subject being administered with the compound. In many instances, the dose may be around 1 to around 10 μg/kg per dose. In particular embodiments, the dose may be around 250 μg/kg per dose, around 100 μg/kg, around 50 μg/kg or around 10 μg/kg per dose. The dosing regimen for a given compound could readily be determined by the skilled person having access to this disclosure.

In one particular embodiment, the pharmaceutical composition of the invention additionally comprises one or more additional active pharmaceutical ingredients. The compound of the invention may be administered with one or more additional active pharmaceutical ingredients, such as anandamide, *N*-oleoylethanolamine, *N*-palmitoylethanolamine. This may be in the form of a single composition comprising the compound of the invention and one or more additional active pharmaceutical ingredients. Alternatively, this may be in two or more separate compositions where the compound of the invention is contained in one composition and the one or more additional active pharmaceutical ingredients are contained in one or more separate compositions.

Administration of the compounds of the present invention may therefore be simultaneous with, or staggered with respect to, the one or more additional active pharmaceutical ingredient.

In a third aspect, the present invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in therapy.

In a fourth aspect, the invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in the treatment or prevention of a condition, for example a pulmonary condition, whose development or symptoms are linked to a substrate of the FAAH enzyme.

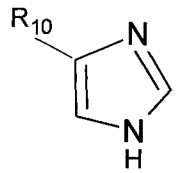
The invention also provides the use of a compound according to the first aspect of the invention, or a composition according to the second aspect, in the manufacture of a medicament for the treatment or prevention of a condition, for example a pulmonary condition, whose development or symptoms are linked to a substrate of the FAAH enzyme.

A number of conditions whose development or symptoms are linked to a substrate of the FAAH enzyme are known to the skilled person. For example, such conditions include pulmonary, dermatological and gastrointestinal conditions. Particular pulmonary conditions include diseases of the respiratory tracts, bronchospasm, coughing, asthma, chronic bronchitis, chronic obstruction of the respiratory tract, emphysema and Acute Respiratory Distress Syndrome (ARDS).

In a fifth aspect, the invention also provides a method of treatment or prevention of a condition, for example a pulmonary condition, whose development or symptoms are linked to a substrate of the FAAH enzyme, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to the first aspect of the invention, or a composition according to the second aspect.

A compound according to the fourth aspect, or a method according to the fifth aspect, wherein the condition, for example pulmonary condition, is a disorder associated with the endocannabinoid system.

In a sixth aspect, there is provided a process for the the preparation of an imidazolyl derivative of the formula:



wherein R10 is selected from C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R10a, halogen, OH, OR10a, SH, SR10a, OCOR10a, SCOR10a, NH_2, NO_2, NHR10a, $NHSO_2NH_2$, $NHSO_2R10a$, NR10aCOR10b, NHCOR10a, $NHC(NH)NH_2$, NR10aR10b, COR10a, CSR10a, CN, COOH, COOR10a, $CONH_2$, CONHOH, CONHR10a, CONHOR10a, $C(NOH)NH_2$, CONR10aR10b, SO_2R10a, SO_3H, SO_2NH_2, $SO_2NR10aR10b$, wherein R10a and R10b are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R10a and R10b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R10 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R10 is C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R10c, C_{1-6} alkyl, C_{1-6} alkynyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl C_{1-6} alkoxy, heterocyclyl C_{1-6} alkoxy, OH, OR10c, OCOR10c, SH, SR10c, SCOR10c, NH_2, NO_2, NHR10c, $NHSO_2NH_2$, $NHC(NH)NH_2$, $NHSO_2R10c$, NR10cCOR10d, NHCOR10c, NR10cR10d, COR10c, CSR10c, CN, COOH, COOR10c, $CONH_2$, CONHR10c, CONHOR10c, CONHOH, $C(NOH)NH_2$, CONR10cR10d, SO_2R10c, SO_3H, SO_2NH_2, $SO_2NR10cR10d$, wherein R10c and R10d are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R10c and R10d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R10 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R10 is C_{1-6} alkyl, C_{1-6} alkynyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl C_{1-6} alkoxy, heterocyclyl C_{1-6} alkoxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R10e, C_{1-6} alkyl, C_{1-4} alkoxy, OH, OR10e, OCOR10e, SH, SR10e, SCOR10e, NH_2, NO_2, NHR10e, $NHSO_2NH_2$, $NHC(NH)NH_2$, $NHSO_2R10e$, NR10eCOR10f, NHCOR10e, NR10eR10f, COR10e, CSR10e, CN, COOH, COOR10e, $CONH_2$, CONHOH, CONHR10e, CONHOR10e, $C(NOH)NH_2$, CONR10eR10f, SO_2R10e, SO_3H, SO_2NH_2, $SO_2NR10eR10f$, wherein R10e and R10f are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R10e and R10f, together with the heteroatom to which they are joined, can form heterocyclyl;

the process comprising the reaction of a bromoacetyl derivative of R10: R10-$COCH_2Br$, with diformylamide or a salt thereof, followed by reaction of the resulting oxoethyl-N-formylformamide derivative with ammonia or a salt thereof in the presence of an acid catalyst, thereby forming the imidazolyl derivative.

The process of the sixth aspect provides a novel means for producing imidazolyl derivatives which are of use, for example, in the synthesis of compounds of the first aspect.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such bicyclic aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl,

naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridyl, furopyridyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and imidazopyridyl.

The term 'heteroaryl substituted with one or more oxygen atoms' refers to a heteroaryl ring which has one or more oxygen atoms bonded to the ring. It does not mean that the heteroaryl ring contains one or more oxygen atoms as ring atoms, although in some embodiments, this may be the case. Preferably, the one or more oxygen atoms is bonded to a nitrogen heteroatom in the heteroaryl ring. A heteroaryl substituted with an oxygen atom may contain an N-oxide. An example of a heteroaryl substituted with one or more oxygen atoms is 1-oxidopyridyl in which the pyridyl nitrogen is oxidised.

The term 'heterocyclyl' refers to a 3-8 (preferably 4-8 and, more preferably, 4-7) membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated, which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen, silicon or sulphur. Examples of such monocyclic rings include oxaziridinyl, oxiranyl, dioxiranyl, aziridinyl, pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl and azepanyl. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1H-3-benzazepine, 4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl, and, tetrahydroisoquinolinyl.

The term 'heterocyclyl substituted with one or more oxygen atoms' refers to a heterocyclyl ring which has one or more oxygen atoms bonded to the ring. It does not mean that the heterocyclyl ring contains one or more oxygen atoms as ring atoms, although in some embodiments, this may be the case. Preferably, the one or more oxygen atoms is bonded to a heteroatom, such as nitrogen or sulphur, in the

heterocyclyl ring. An example of a heterocyclyl substituted with one or more oxygen atoms is 1,1-dioxido-1,3-thiazolidinyl.

The term 'C_{x-y} cycloalkyl' as used herein refers to a saturated hydrocarbon ring of x to y carbon atoms which can be mono, bi or tricyclic. For example, C_{3-10} cycloalkyl refers to a saturated mono, bi or tricyclic hydrocarbon ring of 3 to 10 carbon atoms. Examples of C_{3-10} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and adamantyl.

The term 'aryl C_{x-y} alkyl' as used herein refers to an aryl group as defined above attached to a C_{x-y} alkyl as defined above. For example, aryl C_{1-6} alkyl refers to an aryl group attached to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of aryl C_{1-6} alkyl groups include benzyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl and phenylhexyl.

The terms 'heteroaryl C_{x-y} alkyl', 'heterocyclyl C_{x-y} alkyl' and 'C_{x-y} cycloalkyl C_{x-y} alkyl' as used herein refers to a heteroaryl, heterocyclyl or C_{x-y} cycloalkyl group as defined above attached to a C_{x-y} alkyl as defined above.

The term 'aryloxy' as used herein refers to an -O-aryl group. Examples of such groups include phenoxy. The terms 'heteroaryloxy' and 'heterocyclyloxy' as used herein refer to an -O-heteroaryl and -O-heterocyclyl group respectively.

In embodiments of the sixth aspect, R10 is an optionally substituted aryl or heteroaryl group. Particular substituents thereon include OH or O-alkyl, which may be further substituted. In certain embodiments, R10 is phenyl, which may be substituted with one or more O-benzyl groups. In another embodiment, R10 is the phenyl-R3R4R5 group depicted in Formula I above.

In particular embodiments of the process of the sixth aspect, a salt of diformylamide is used, for example the Na salt. A salt of ammonia may also be used, for example the ammonium salt of an organic acid, such as ammonium acetate. The first step of the process may, for example, be conducted in acetonitrile. The second step, conversion of the formylformamide to the imidazole, may for example be performed in acetic acid. In this instance, the acetic acid may function as both solvent and acid catalyst.

Detailed Description of the Invention

The invention will now be described in more detail by way of example only:

1. Synthetic Methodologies

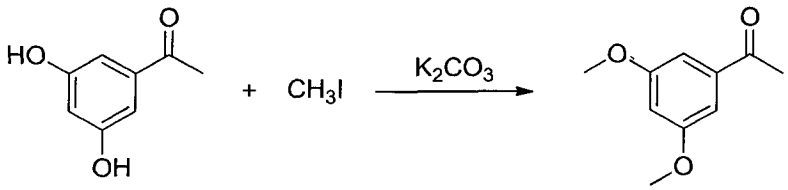
The methods used for synthesis of the compounds of the invention are illustrated by the general schemes below. The starting materials and reagents used in preparing these compounds are available from commercial suppliers or can be prepared by methods obvious to those skilled in the art. These general schemes are merely illustrative of methods by which the compounds of this invention can be synthesised, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

All compounds and intermediates were characterised by nuclear magnetic resonance (NMR). NMR spectra were recorded on a Bruker Avance III 600MHz spectrometer with solvent used as internal standard. 13C spectra were recorded at 150 MHz and 1H spectra were recorded at 600 MHz. Data are reported in the following order: approximate chemical shift (ppm), number of protons, multiplicity (br, broad; d, doublet; m, multiplet; s, singlet, t; triplet) and coupling constant (Hz).

Room temperature in the following scheme means the temperature ranging from 20°C to 25°C.

Intermediate 1: 4-(3,5-dimethoxyphenyl)-1*H*-imidazole

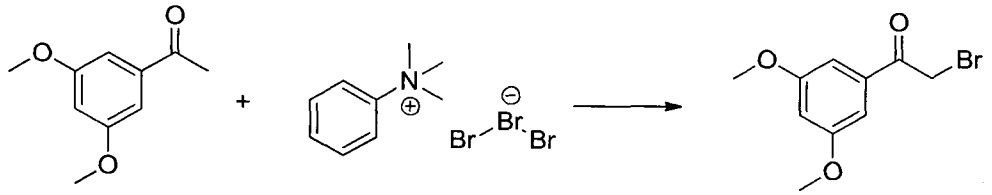
Step1: 1-(3,5-dimethoxyphenyl)ethanone



To a clear solution of 1-(3,5-dihydroxyphenyl)ethanone (10 g, 65.7 mmol) in acetone (130 mL) was added potassium carbonate (23.62 g, 171 mmol) and methyl iodide (16.44 mL, 263 mmol). The reaction mixture was stirred at gentle reflux for 18 h, and then the reaction mixture was filtered through a short pad of silica/celite and washed

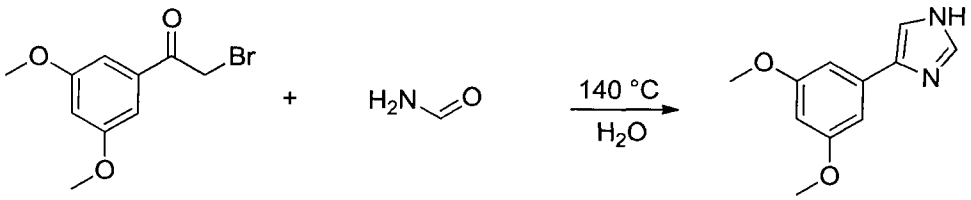
with acetone. The filtrate was concentrated to give 1-(3,5-dimethoxyphenyl)ethanone (12.78 g, quantitative yield).

Step2: 2-bromo-1-(3,5-dimethoxyphenyl)ethanone



To a stirred clear yellow solution of 1-(3,5-dimethoxyphenyl)ethanone (14.45 g, 80 mmol) in terahydrofuran (150 mL) was added portionwise phenyltrimethylammonium tribromide (31.7 g, 84 mmol) at room temperature for 1h. Then, the ammonium salts were filtered off and the filter cake was washed with ether. The filtrate was concentrated under reduced pressure and the resultant oily product was used without further purification.

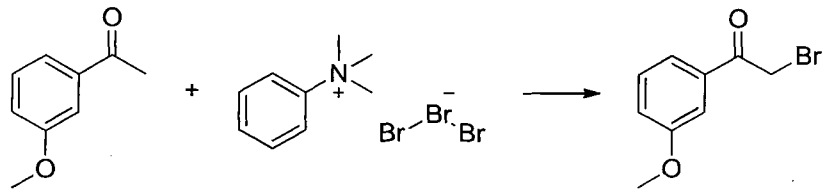
Step 3: 4-(3,5-dimethoxyphenyl)-1H-imidazole



Water (1.4 mL) was added to a stirred suspension of 2-bromo-1-(3,5-dimethoxyphenyl)ethanone (20.73 g, 80 mmol) and formamide (38.3 mL, 960 mmol). The mixture was allowed to stir at 140 °C for 5h. The dark reaction mixture was poured into *ca* 200 mL of crushed ice and the resultant solid (brown gum) was filtered off. The filtrate was set to pH=12 upon addition of aqueous NaOH (3 M). The obtained white turbid solution was transferred into separatory funnel and extracted with a mixture of dichloromethane/isopropanol 7/3 several times. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography (DCM/MeOH 9/1), followed by recrystallization from isopropanol. Yielded 4-(3,5-dimethoxyphenyl)-1*H*-imidazole (0.868 g, 5% yield).

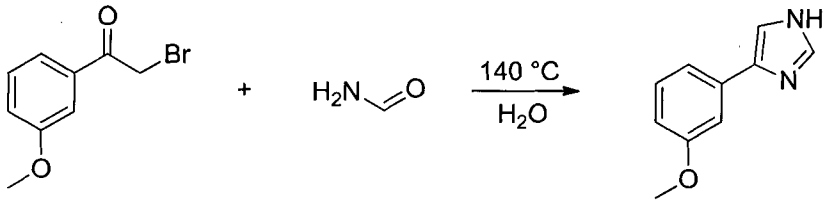
Intermediate 2: 4-(3-methoxyphenyl)-1*H*-imidazole

Step1: 2-bromo-1-(3-methoxyphenyl)ethanone



To a stirred clear yellow solution of 1-(3-methoxyphenyl)ethanone (20 mL, 139 mmol) in tetrahydrofuran (250 mL) was added portionwise phenyltrimethylammonium tribromide (54.7 g, 145 mmol) at room temperature and stirred for 1h. Then, the ammonium salts were filtered off and the filter cake was washed with ether. The filtrate was concentrated under reduced pressure and the resultant oily product was used without further purification Yielded 2-bromo-1-(3-methoxyphenyl)ethanone (32.6 g, 142 mmol, quantitative yield).

Step2: 4-(3-methoxyphenyl)-1H-imidazole



A white suspension of 2-bromo-1-(3-methoxyphenyl)ethanone (32.6 g, 142 mmol), formamide (68.1 mL, 1708 mmol) and water (2.56 mL, 142 mmol) was heated at 140 °C for 5 h. The reaction mixture was poured onto 200 mL crushed ice and filtered. The filtrate was set to pH 12 upon addition of aqueous NaOH (3 M), transferred into separatory funnel and extracted into dichloromethane (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. Recrystallization from isopropanol afforded 4-(3-methoxyphenyl)-1*H*-imidazole (11.2 g, 48% yield).

Intermediate 3: 4-(4-methoxyphenyl)-1*H*-imidazole

The title compound was prepared by analogous manner to intermediate 2 from 1-(4-methoxyphenyl)ethanone.

Intermediate 4: 4-(3,4-dimethoxyphenyl)-1*H*-imidazole

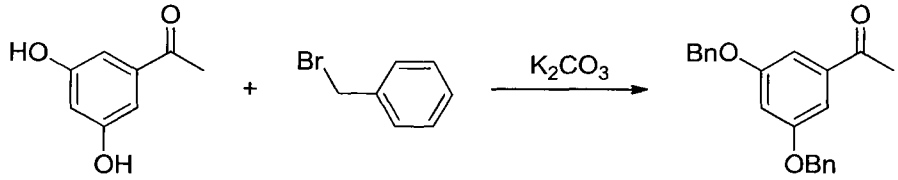
The title compound was prepared by analogous manner to intermediate 2 from 1-(3,4-dimethoxyphenyl)ethanone.

Intermediate 5: 4-(2,4-*bis*(benzyloxy)phenyl)-1*H*-imidazole

The title compound was prepared by analogous manner to intermediate 2 from 1-(2,4-bis(benzyloxy)phenyl)ethanone.

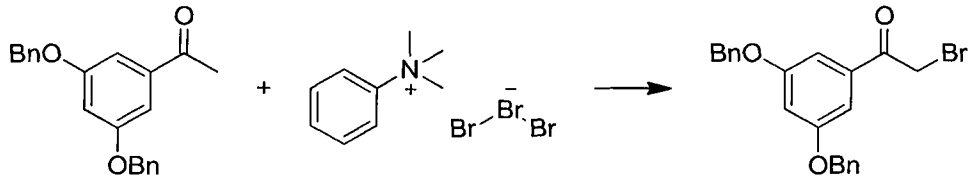
Intermediate 6: 4-(3,5-*bis*(benzyloxy)phenyl)-1*H*-imidazole

Step1: 1-(3,5-bis(benzyloxy)phenyl)ethanone



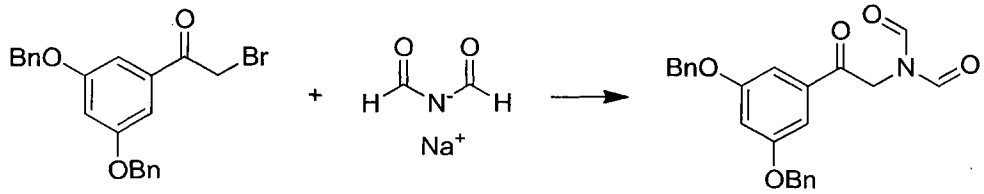
To a clear solution of 1-(3,5-dihydroxyphenyl)ethanone (20 g, 131 mmol) in acetone (260 mL) was added potassium carbonate (47.2 g, 342 mmol) and benzyl bromide (35.9 mL, 302 mmol). The reaction mixture was stirred at gentle reflux for 18 h, then the mixture was filtered through a short pad of silica/celite and washed with acetone. The filtrate was concentrated to furnish 1-(3,5-*bis*(benzyloxy)phenyl)ethanone as a white solid (41.6 g, 86% yield).

Step2: 1-(3,5-bis(benzyloxy)phenyl)-2-bromoethanone



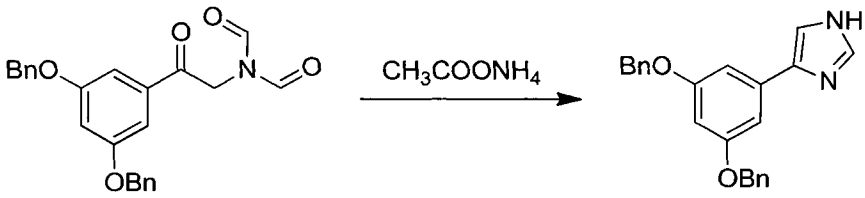
To a stirred clear yellow solution of 1-(3,5-*bis*(benzyloxy)phenyl)ethanone (41.6 g, 125 mmol) in dichloromethane (500 mL) was added portionwise over a period of 1h phenyltrimethylammonium tribromide (49.4 g, 131 mmol) The reaction was allowed to stir at room temperature for 3h. Then, the mixture was transferred into a separatory funnel and washed with water several times. The organic phase was evaporated to dryness. Column chromatography in toluene afforded 1-(3,5-bis(benzyloxy)phenyl)-2-bromoethanone as a white solid (24.72 g, 38% yield).

Step3: N-(2-(3,5-bis(benzyloxy)phenyl)-2-oxoethyl)-N-formylformamide



To a suspension of 1-(3,5-*bis*(benzyloxy)phenyl)-2-bromoethanone (24.72 g, 60.1 mmol) in acetonitrile (120 mL) was added sodium diformylamide (8.57 g, 90 mmol) and heated at reflux for 3 h. Upon cooling the salts were filtered off, washed with acetonitrile and concentrated. The residue was crystallized on standing and afforded *N*-(2-(3,5-*bis*(benzyloxy)phenyl)-2-oxoethyl)-*N*-formylformamide (13.08 g, 51% yield).

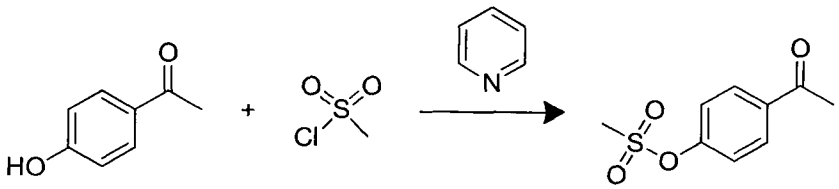
Step4: 4-(3,5-bis(benzyloxy)phenyl)-1H-imidazole



To a solution of *N*-(2-(3,5-*bis*(benzyloxy)phenyl)-2-oxoethyl)-*N*-formylformamide (13.08 g, 32.4 mmol) in acetic acid (125 mL) was added ammonium acetate (10.00 g, 130 mmol). The reaction was allowed to stir at reflux for 5 h, then acetic acid was removed under reduced pressure. The residue was taken up in dichloromethane, transferred into separatory funnel and extracted with water (3 times). The combined aqueous layers were basified (till pH≈8-9) upon addition of solid sodium bicarbonate. The resultant weakly basic aqueous layer was extracted with a mixture of dichloromethane/isopropanol 7/3 (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through celite, concentrated and purified by column chromatography (gradient DCM to DCM/MeOH 95/5) to afford 4-(3,5-*bis*(benzyloxy)phenyl)-1*H*-imidazole as brown oil. (6.5 g, 45% yield).

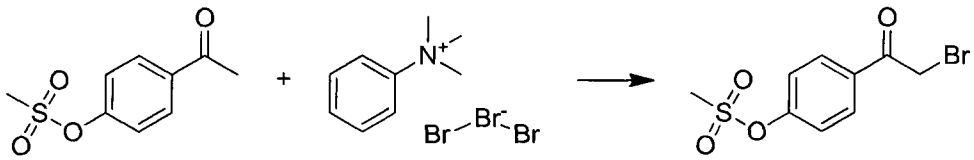
Intermediate 7: 4-(1*H*-imidazol-4-yl)phenyl methanesulfonate

Step1: 4-acetylphenyl methanesulfonate



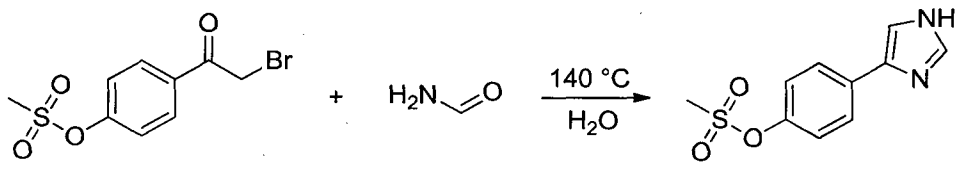
To a chilled solution of 1-(4-hydroxyphenyl)ethanone (10 g, 73.4 mmol) in dichloromethane (250 mL) was added pyridine (7.72 mL, 95 mmol), followed by dropwise addition of methanesulfonyl chloride (6.87 mL, 88 mmol). The reaction was stirred at room temperature until its completion, then was transferred into separatory funnel and washed with dilute acid (HCl), water and brine, respectively. The organic layer was then dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated to yield 4-acetylphenyl methanesulfonate (9.93 g, 59% yield).

Step2: 4-(2-bromoacetyl)phenyl methanesulfonate



To a clear solution of 4-acetylphenyl methanesulfonate (9.93 g, 46.4 mmol) in tetrahydrofuran (200 mL) was added portionwise phenyltrimethylammonium tribromide (18.30 g, 48.7 mmol) and allowed to stir at room temperature for 1h. The inorganic salts were filtered off, washed with a small amount of diethyl ether and then the filtrate was concentrated. The obtained oil was taken up in ethyl acetate, washed with water, dried over anhydrous Na_2SO_4, filtered through a pad of silica/celite and then concentrated. The resultant oil was suspended in a mixture of methyl *tert*-butyl ether and petroleum ether, sonicated for few minutes and then, the obtained solid was filtered off and dried under vacuum. Yielded 4-(2-bromoacetyl)phenyl methanesulfonate (10.95 g, 81% yield).

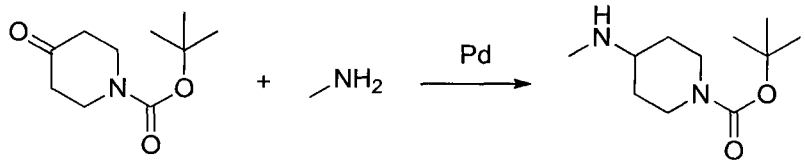
Step3: 4-(1H-imidazol-4-yl)phenyl methanesulfonate



A suspension of 4-(2-bromoacetyl)phenyl methanesulfonate (10.95 g, 37.4 mmol) in formamide (17.87 mL, 448 mmol) and water (1.346 mL, 74.7 mmol) was heated at 140 °C for 5h. Then, the reaction was cooled to room temperature and poured onto *ca* 100 g of crushed ice and the resultant orange/brown solid was discarded by filtration. The filtrate was basified (till pH 8-9) upon addition of aqueous NaOH (3 M). The resultant cloudy solution was extracted with ethyl acetate (3 times). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite, and concentrated. The resultant oily product was suspended in a mixture of methyl *tert*-butyl ether and petroleum ether, sonicated until a white solid was formed, then filtered and dried. Yielded 4-(1*H*-imidazol-4-yl)phenyl methanesulfonate (5.62 g, 53% yield).

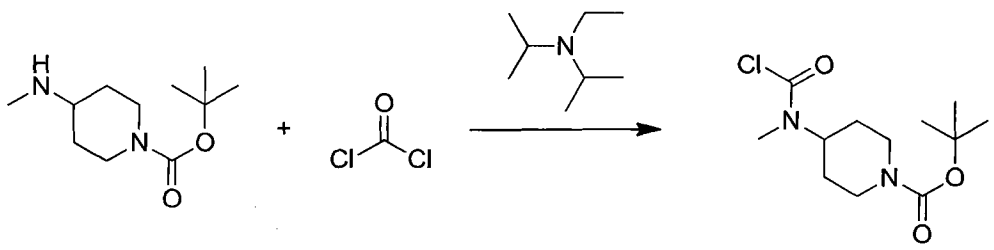
Intermediate 8: *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate

Step1: tert-butyl 4-(methylamino)piperidine-1-carboxylate



To a well purged solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (20 g, 100 mmol) in methanol (100 mL) and methanamine (40% in water) (38.0 mL, 442 mmol) was added palladium (10 wt% on activated charcoal) (1.602 g, 1.506 mmol) and placed in Parr reactor. The reaction mixture was allowed to stir under H_2 atmosphere (20 atm) at 50 °C for 2h. The reaction was then allowed to slowly cool down to room temperature, purged with N_2 and filtered. Evaporation of the filtrate afforded *tert*-butyl 4-(methylamino)piperidine-1-carboxylate as yellowish oil (20 g, 93% yield).

Step2: tert-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate

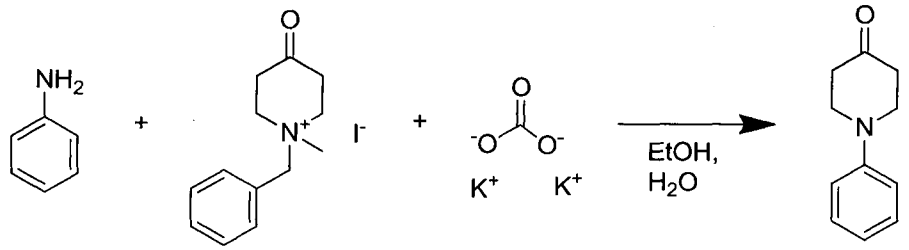


To a chilled phosgene solution (20% in toluene, 60.9 g, 123 mmol) was added dropwise a solution of *tert*-butyl 4-(methylamino)piperidine-1-carboxylate (21.98 g,

103 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (36.8 mL, 26.5 g, 205 mmol) in tetrahydrofuran (160 mL). The reaction was allowed to stir for 3 h (yellow suspension) in the cold. Then, the mixture was quenched upon addition of crushed ice and transferred into a separatory funnel. The organic phase was washed with aqueous 1M HCl solution and water, respectively. Then, the organic layer was dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated to give *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate (8.7 g, 31% yield) as white solid.

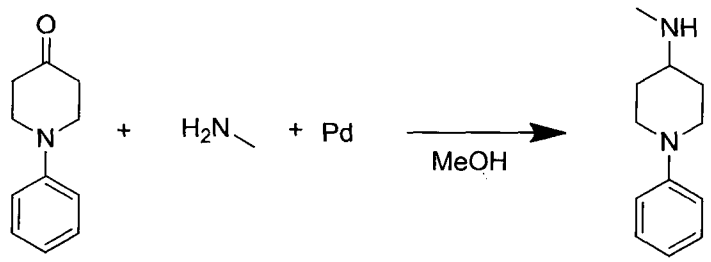
Intermediate 9: *N*-methyl-1-phenylpiperidin-4-amine

Step1: 1-phenylpiperidin-4-one



In a 250 mL round-bottomed flask aniline (2.84 mL, 31.1 mmol), potassium carbonate (0.603 g, 4.36 mmol) and ethanol (57 mL) were placed. The mixture was heated at reflux and a suspension of 1-benzyl-1-methyl-4-oxopiperidinium iodide (15.69 g, 47.4 mmol) in water (43 mL) was added over a period of 1 h. The reaction mixture was stirred at reflux for 45 min. Then, it was quenched with water (175 mL) and the solution was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered and evaporated. The obtained yellow oil was separated by column chromatography (petroleum ether/ethyl acetate, 9:1, 4:1) to give 1-phenylpiperidin-4-one (4.67 g, 81% yield).

Step2: N-methyl-1-phenylpiperidin-4-amine



In a 50 mL pear flask, 1-phenylpiperidin-4-one (1.52g, 8.67 mmol) and methanol (15.2 mL) were placed under inert atmosphere. Methanamine (40% in water) (3.78 mL, 38.2 mmol) was added, followed by palladium (10% on charcoal, 0.138 g, 0.130 mmol). The reaction flask was placed in an autoclave, charged with 20 atm of hydrogen, heated at 50 °C and stirred for 2 h. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure. The resultant pale yellow oil crystallized on standing, to give *N*-methyl-1-phenylpiperidin-4-amine (1.58 g, 91% yield).

Intermediate 10: 1-(3-methoxyphenyl)-*N*-methylpiperidin-4-amine

The title compound was prepared by analogous manner to intermediate 9 from 3-methoxyaniline.

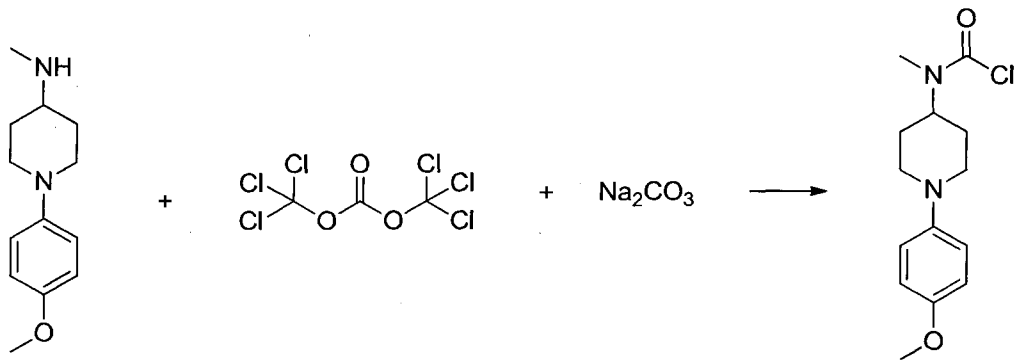
Intermediate 11: 4-(3-fluoro-4-methoxyphenyl)-1*H*-imidazole

The title compound was prepared by analogous manner to intermediate 2 from 1-(3-fluoro-4-methoxyphenyl)ethanone

Intermediate 12: 1-(4-methoxyphenyl)-*N*-methylpiperidin-4-amine

The title compound was prepared by analogous manner to intermediate 9 from 4-methoxyaniline.

Intermediate 13: 1-(4-methoxyphenyl)piperidin-4-yl(methyl)carbamic chloride



To a cold solution of triphosgene (3.07 g, 10.35 mmol) in dichloromethane (51.7 mL) added a solution of 1-(4-methoxyphenyl)-*N*-methylpiperidin-4-amine (intermediate 12) (5.7 g, 25.9 mmol) in dichloromethane (51.7 mL), followed by portionwise addition of Na_2CO_3 (5.48 g, 51.7 mmol) (gas evolution). The reaction mixture was

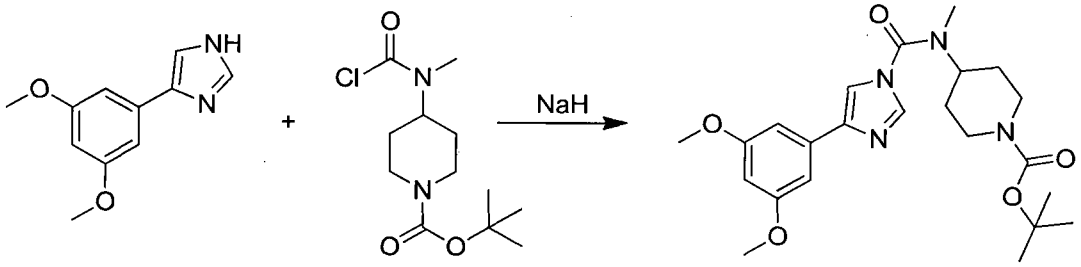
allowed to warm to room temperature and, after stirring for 3 hours, reaction was quenched with water. Transferred the mixture into a separatory funnel and partitioned between water and dichloromethane; separated layers and the organic phase was dried over MgSO4 and concentrated under reduced pressure to yield 1-(4-methoxyphenyl)piperidin-4-yl(methyl)carbamic chloride (2.114 g, 82 % yield) as a pale beige solid.

Intermediate 14: 4-(4-fluoro-3-methoxyphenyl)-1*H*-imidazole

The title compound was prepared by analogous manner to intermediate 2 from 1-(4-fluoro-3-methoxyphenyl)ethanone.

Example 1: 4-(3,5-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride

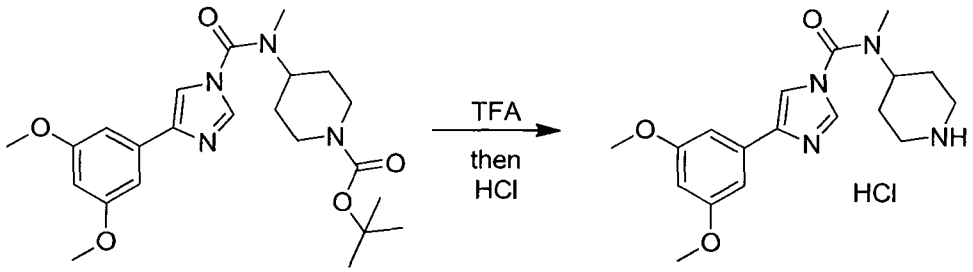
Step1: tert-butyl 4-(4-(3,5-dimethoxyphenyl)-N-methyl-1H-imidazole-1-carboxamido)piperidine-1-carboxylate



To a chilled suspension of 4-(3,5-dimethoxyphenyl)-1*H*-imidazole (Intermediate 1) (568 mg, 2.78 mmol) in tetrahydrofuran (10 mL) was added sodium hydride (60% in mineral oil dispersion) (133 mg, 3.34 mmol). After stirring the reaction mixture for *ca* 10 min., *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate (Intermediate 8) (924 mg, 3.34 mmol) was added and stirring was continued at room temperature for 3h. The reaction was quenched upon addition of water, transferred into a separatory funnel and partitioned between water and a mixture of dichloromethane/isopropanol 7/3. The biphasic mixture was separated and the aqueous phase was further extracted into mixture of dichloromethane/isopropanol 7/3 (twice). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. The residue was recrystallized from isopropanol. Further trituration with a mixture of diethyl ether and petroleum

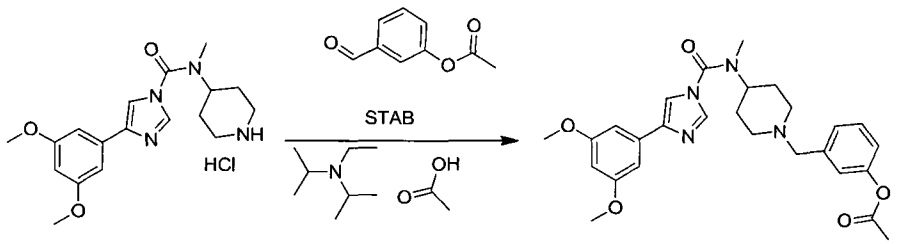
ether. afforded *tert*-butyl 4-(4-(3,5-dimethoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (1.28 g, 77 % yield).

Step2: 4-(3,5-dimethoxyphenyl)-N-methyl-N-(piperidin-4-yl)-1H-imidazole-1-carboxamide hydrochloride



To a chilled portion of *tert*-butyl 4-(4-(3,5-dimethoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (1.28 g, 2.88 mmol) was added trifluoroacetic acid (8.87 mL, 115 mmol) and stirred in the cold for 45 min. Then, trifluoroacetic acid was removed under reduced pressure. The residue was dissolved in methanol and treated with excess of hydrogen chloride (2 M solution in diethyl ether). The reaction was stirred until a thick white suspension was formed. Removal of the solvents under reduced pressure resulted in a sticky oil. Recrystallization from isopropanol afforded 4-(3,5-dimethoxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrochloride (0.8 g, 69% yield) as white solid.

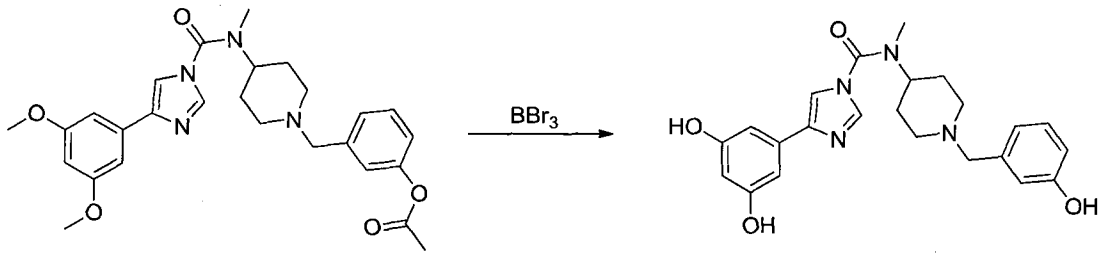
Step3: 3-((4-(4-(3,5-dimethoxyphenyl)-N-methyl-1H-imidazole-1-carboxamido)piperidin-1- yl)methyl)phenyl acetate



To a suspension of 4-(3,5-dimethoxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrochloride (393 mg, 1.032 mmol) in 1,2-dichloroethane (9 mL) was added *N*,*N*-diisopropylethylamine (0.72 mL, 4.13 mmol), followed by addition of 3-formylphenyl acetate (339 mg, 2.064 mmol). After stirring for *ca* 30 min, sodium triacetoxyhydroborate (656 mg, 3.10 mmol) was added, followed by addition of acetic acid (59.0 µL, 1.032 mmol). The reaction was allowed to stir at

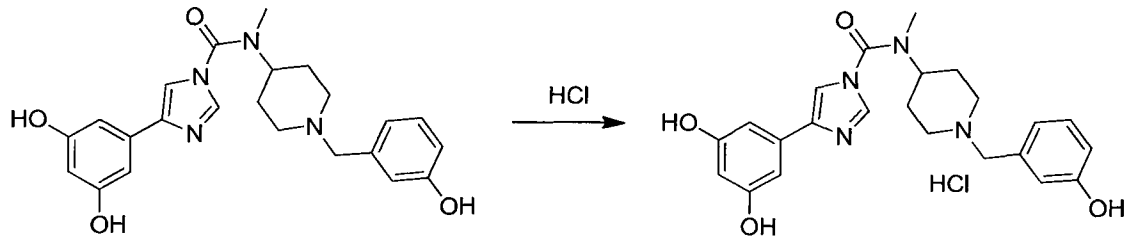
room temperature for 16h, and then was quenched upon addition of crushed ice. The resultant mixture was partitioned between water and a mixture of dichloromethane/methanol 9/1. The layers were separated and the aqueous phase was further extracted into a mixture of dichloromethane/methanol 9/1. The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a pad of silica/celite and concentrated. Purification by column chromatography (dichloromethane-methanol 95/5) afforded 3-((4-(4-(3,5-dimethoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidin-1-yl)methyl)phenyl acetate (393 mg, 70% yield).

Step4: 4-(3,5-dihydroxyphenyl)-N-(1-(3-hydroxybenzyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide



To a suspension of 3-((4-(4-(3,5-dimethoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidin-1-yl)methyl)phenyl acetate (310 mg, 0.629 mmol) in dry dichloromethane (2.1 mL) was added boron tribromide (357 µL, 3.78 mmol) at -78 °C. The reaction was allowed to stir in the cold for 15 min., then at room temperature overnight. Thereupon, the mixture was cooled to 0 °C, carefully quenched with crushed ice and allowed to stir for a couple of hours. The resultant mixture was partitioned between water and a mixture of dichloromethane/methanol 9/1. The layers were separated and the aqueous phase was further extracted into a mixture of dichloromethane/methanol 9/1. The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a pad of silica/celite and concentrated. The residue was purified by column chromatography (dichloromethane/methanol 9/1). Yielded 4-(3,5-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (61 mg, 23% yield).

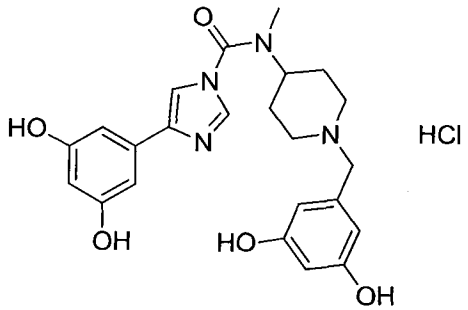
Step5: 4-(3,5-dihydroxyphenyl)-N-(1-(3-hydroxybenzyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide hydrochloride



To a chilled slightly turbid solution of 4-(3,5-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (61 mg, 0.144 mmol) in methanol (3 mL) was added fast dropwise hydrogen chloride (2 M in diethyl ether) (0.289 mL, 0.578 mmol). The stirring was continued at room temperature until a thick suspension was formed, and then the solvents were removed under reduced pressure to give a white solid. Recrystallization from isopropanol afforded 4-(3,5-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride as a white solid (65 mg, 88% yield).

^{1}H NMR (DMSO-d_6): 10.92 (1H, s br), 9.75 (1H, br), 9.48 (2H, br), 8.79 (1H, s br), 8.06 (1H, s), 7.24 (1H, t, J = 8.0 Hz), 7.03 (1H, d, J = 7.6 Hz), 6.98 (1H, m), 6.85 (1H, dd, J = 2.0, 8.0 Hz), 6.70 (2H, d, J = 2.0 Hz), 6.27 (1H, t, J = 2.0 Hz), 4.19 (1H, br), 4.15 (2H, d, J = 4.8 Hz), 3.39 (2H, d, J = 12.0 Hz), 3.07 (2H, q, J = 11.5 Hz), 2.94 (3H, s), 2.36 (2H, dq, J = 3.0, 13.0 Hz), 1.95 (2H, d, J = 12.5 Hz).
^{13}C NMR (DMSO-d_6): 158.8, 157.6, 149.8, 137.5, 137.3, 131.6, 131, 129.8, 121.7, 118.1, 116.4, 115, 103.6, 102.7, 58.8, 52.3, 50.2, 31.6, 24.7.

Example 2: *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3,5-dihydroxyphenyl)-*N*-methyl-1*H*- imidazole-1-carboxamide hydrochloride



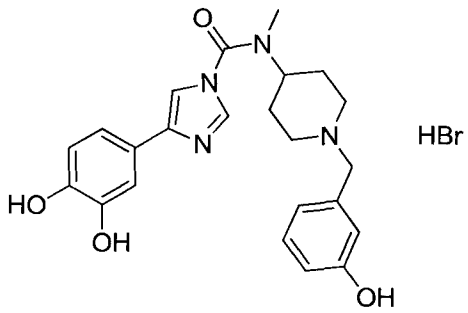
The title compound was prepared by analogous manner to Example 1 from Intermediate 1, Intermediate 8 and 3,5-dimethoxy benzaldehyde.

Appearance: white solid.

^{1}H NMR (DMSO-d_6): 10.60 (1H, s br), 9.54 (4H, br), 8.94 (1H, s br), 8.12 (1H, s), 6.70 (2H, d, J = 2Hz), 6.41 (2H, d, J = 2Hz), 6.32 (1H, t, J = 2.0 Hz), 6.30 (1H, t, J = 2.0 Hz), 4.17 (1H, s br), 4.04 (2H, d, J = 4.8 Hz), 3.40 (2H, m), 3.07 (2H, m), 2.94 (3H, s), 2.33 (2H, dq, J = 2.7, 13.5 Hz), 1.96 (2H, d, J = 11.5Hz).

^{13}C NMR (DMSO-d_6): 158.9, 158.7, 137.3, 131.4, 115.2, 109.2, 103.7, 103.5, 102.9, 59, 52.4, 50.2, 31.6, 24.7.

Example 3: 4-(3,4-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrobromide



The title compound was prepared by analogous manner to Example 1 from Intermediate 4, Intermediate 8 and 3-methoxy benzaldehyde.

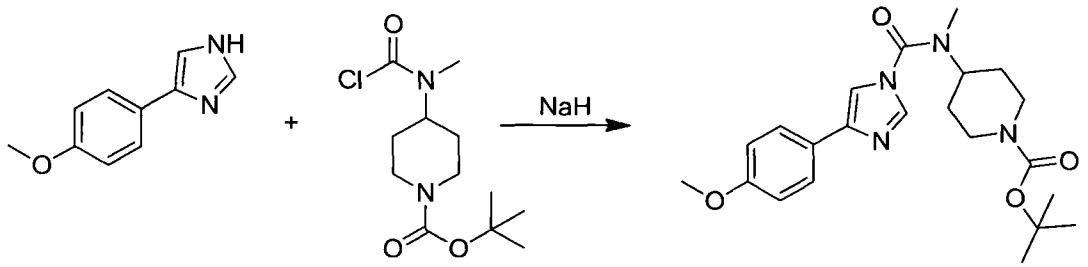
Appearance: white solid.

^{1}H NMR (DMSO-d_6): 9.70 (1H, s br), 9.52 (1H, br), 8.95 (1H, s), 8.90 (1H, s), 8.05 (1H, s), 7.71 (1H, s), 7.25 (1H, m), 7.27 (1H, s, J = 2 Hz), 7.10 (1H, dd, J = 2.0, 8.0 Hz), 6.98-6.80 (3H, m), 6.73 (1H, d, J = 8.0 Hz), 4.15 (3H, m), 3.40 (2H, br), 3.10 (2H, br), 2.92 (3H, s), 2.13 (2H, br), 1.96 (2H, br).

^{13}C NMR (DMSO-d_6): 157.6, 151.2, 145.3, 144.8, 141.3, 137.3, 131.2, 129.9, 124.9, 121.5, 117.8, 116.4, 116.2, 115.7, 112.6, 112.4, 59.3, 52.3, 50.7, 31.7, 25.3.

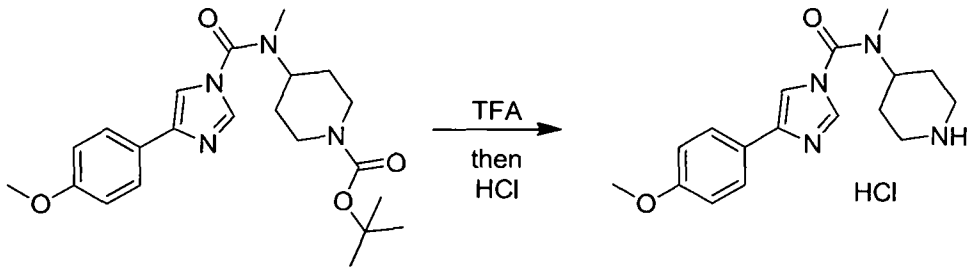
Example 4: *N*-(1-(3,4-dihydroxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride

Step1: tert-butyl 4-(4-(4-methoxyphenyl)-N-methyl-1H-imidazole-1-carboxamido)piperidine-1-carboxylate



To a chilled suspension of 4-(4-methoxyphenyl)-1*H*-imidazole (intermediate 3) (8.03 g, 46.1 mmol) in tetrahydrofuran (200 mL) was added sodium hydride (60% in mineral oil dispersion) (2.212 g, 55.3 mmol). After stirring the reaction mixture for *ca* 15 min, *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate (Intermediate 8) (14.03 g, 50.7 mmol) was added and stirring was continued at room temperature for 4 h. The reaction was quenched upon addition of water, transferred into a separatory funnel and partitioned between water and mixture of dichloromethane/isopropanol 7/3. The biphasic mixture was separated and the aqueous phase was further extracted into mixture of dichloromethane/isopropanol 7/3 (twice). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. The residue was triturated with hot ethyl acetate to yield *tert*-butyl 4-(4-(4-methoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (19 g, 99% yield).

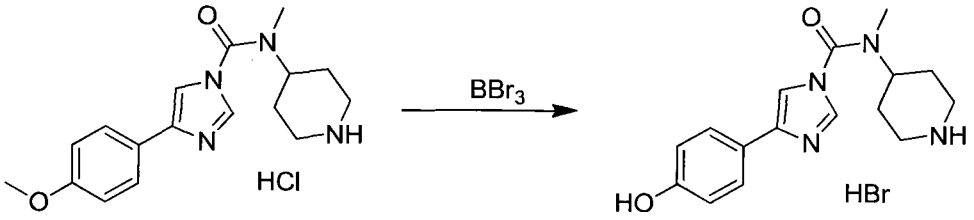
Step2: 4-(4-methoxyphenyl)-N-methyl-N-(piperidin-4-yl)-1H-imidazole-1-carboxamide hydrochloride



To a chilled portion of *tert*-butyl 4-(4-(4-methoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (19 g, 45.8 mmol) was added trifluoroacetic acid (141 mL, 1834 mmol) and stirred in the cold for 1h. Then, trifluoroacetic acid was removed under reduced pressure and the residue was dissolved in methanol and treated with excess of hydrogen chloride (2 M solution in diethyl ether). The reaction was stirred until a thick white suspension was formed. Removal of the solvents under

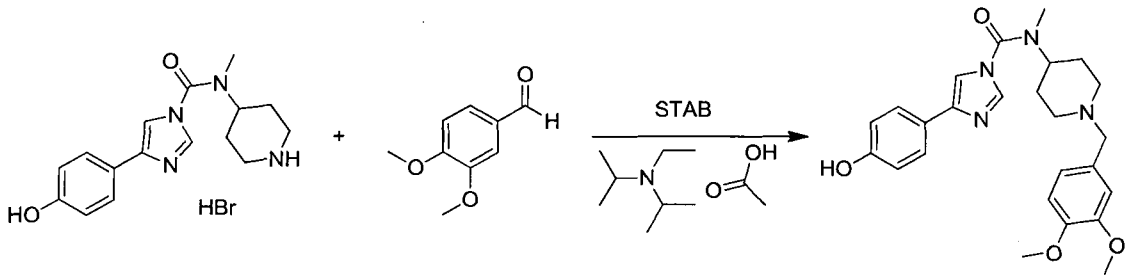
reduced pressure resulted in a sticky oil. Recrystallization from isopropanol afforded 4-(4-methoxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrochloride (17.52 g, 109% yield) as white solid.

Step3: 4-(4-hydroxyphenyl)-N-methyl-N-(piperidin-4-yl)-1H- imidazole-1-carboxamide hydrobromide



To a suspension of 4-(4-methoxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrochloride (5 g, 14.25 mmol) in dry dichloromethane (190 mL) was added dropwise boron tribromide (5.39 mL, 57.0 mmol) at -78 °C. The reaction was allowed to stir in the cold for 1h, then at room temperature until its completion. Thereupon, the mixture was cooled to 0 °C, carefully quenched with crushed ice and stirred for a while. The obtained white solid was filtered off and dried under vacuum. Purification by column chromatography (dichloromethane/methanol 95/5, then dichloromethane/methanol/25% aq. ammonia 7/1/0.2) afforded 4-(4-hydroxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrobromide (4.91 g, 81% yield).

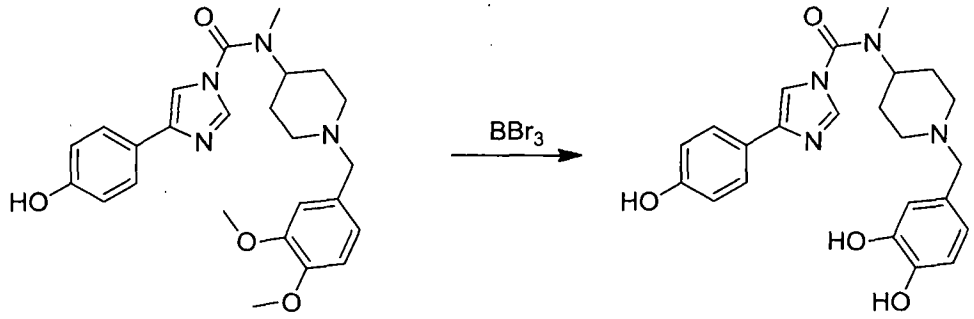
Step4: N-(1-(3,4-dimethoxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-N-methyl-1H-imidazole-1-carboxamide



To a suspension of 4-(4-hydroxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrobromide (0.607 g, 1.592 mmol) in 1,2-dichloroethane (13.84 mL) was added *N*,*N*-diisopropylethylamine (1.11 mL, 6.37 mmol), followed by addition of 3,4-dimethoxybenzaldehyde (0.529 g, 3.18 mmol). After stirring for *ca* 30

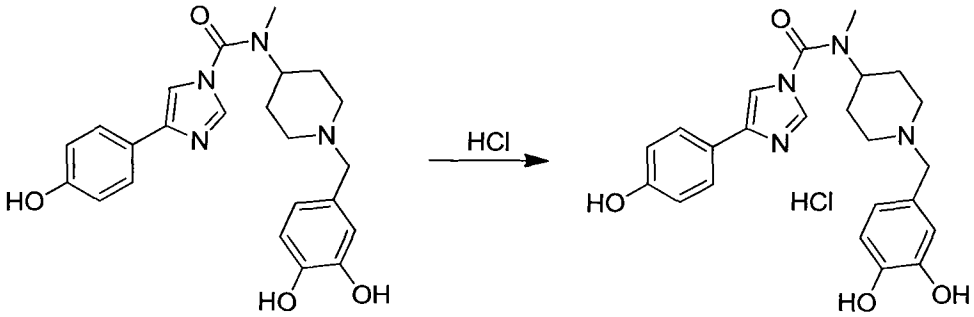
min sodium triacetoxyhydroborate (0.675 g, 3.18 mmol) was added, followed by addition of acetic acid (0.091 mL, 1.592 mmol). The reaction was allowed to stir at room temperature for 18 h, and then was quenched upon addition of crushed ice. The resultant mixture was partitioned between water and a mixture of dichloromethane/methanol 9/1. The layers were separated and the aqueous phase was further extracted into a mixture of dichloromethane/methanol 9/1 (twice). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a pad of silica/celite and concentrated. Recrystallization from hot isopropanol afforded *N*-(1-(3,4-dimethoxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (390 mg, 52% yield).

Step5: N-(1-(3,4-dihydroxybenzyl)piperidin-4-yl)-4-(4- hydroxyphenyl)-N-methyl-1H-imidazole-1-carboxamide



To a suspension of *N*-(1-(3,4-dimethoxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.3 g, 0.666 mmol) in dry dichloromethane (6.66 mL) was added slowly boron tribromide (0.378 mL, 4.00 mmol) at -78 °C. The reaction was allowed to stir in the cold for 30 min, then at room temperature for 48 h. Thereupon, the mixture was cooled to 0 °C, carefully quenched with crushed ice and allowed to stir for a couple of hours. The resultant very hygroscopic solid was isolated by filtration and further purified by column chromatography (dichloromethane/methanol, then dichloromethane/methanol/25% aq. ammonia (7/1/0.2) to give *N*-(1-(3,4-dihydroxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.155 g, 52% yield).

Step6: N-(1-(3,4-dihydroxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-N-methyl-1H-imidazole-carboxamide hydrochloride

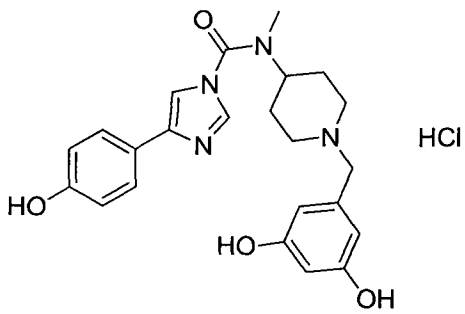


To a cold suspension of *N*-(1-(3,4-dihydroxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.164 g, 0.388 mmol) in a mixture of diethyl ether (1.94 mL) and ethyl acetate (1.94 mL) was added dropwise hydrogen chloride (2 M in diethyl ether) (0.776 mL, 1.553 mmol). The resultant solution was stirred for couple of hours, then the solvents were removed under reduced pressure to give an oily residue. Recrystallization from isopropanol afforded *N*-(1-(3,4-dihydroxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride (0.135 g, 68% yield) as beige solid.

^{1}H NMR (DMSO-d_6): 10.8 (1H, s br), 10.2-8.3 (3H, br), 8.16 (1H, s), 7.72 (2H, md, J = 8.9 Hz), 6.95 (1H, d, J = 2 Hz), 6.87 (2H, md, J = 8.9 Hz), 6.84 (1H, dd, J = 2.0, 8.1 Hz), 6.78 (1H, d, J = 8.1 Hz), 4.18 (1H, br), 4.05 (2H, d, J = 4.8 Hz), 3.37 (2H, d, J = 11 Hz), 3.02 (2H, m), 2.95 (3H, s), 2.35 (2H, dq, J = 3.0, 12.7 Hz), 1.95 (2H, d, J = 12.0 Hz).

^{13}C NMR (DMSO-d_6): 158.2, 149.3, 146.6, 145.3, 136.9, 136, 127, 122.7, 120.1, 119.3, 118.7, 115.8, 115.6, 113.9, 58.8, 52.4, 49.8, 31.6, 24.7.

Example 5: *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride



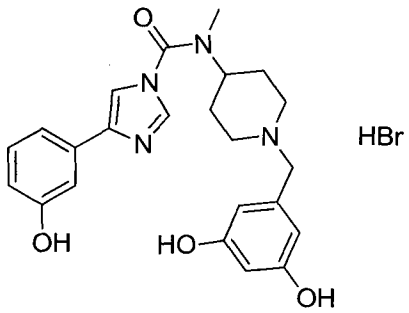
The title compound was prepared by analogous manner to Example 4 from Intermediate 3, Intermediate 8 and 3,5-dimethoxy benzaldehyde.

Appearance: white solid.

^{1}H NMR (DMSO-d_6): 10.66 (1H, s br), 9.86 (1H, br), 9.58 (2H, br), 9.03 (1H, s br), 8.12 (1H, s), 7.71 (2H, md, J = 8.7 Hz), 6.86 (2H, md, J = 8.7 Hz), 6.41 (2H, d, J = 2.0 Hz), 6.32 (1H, t, J = 2.0 Hz), 4.19 (1h, s br), 4.04 (2H, d, J = 5.1 Hz), 3.39 (2H, d, J = 11 Hz), 3.06 (2H, m), 2.96 (3H, s), 2.34 (2H, q, J = 13.0 Hz), 1.96 (2H, d, J = 12.0 Hz).

^{13}C NMR (DMSO-d_6): 158.7, 158, 149.6, 137, 136.7, 131.4, 126.9, 120, 115.7, 113.7, 109.2, 103.5, 59, 52.4, 50.2, 31.7, 24.7.

Example 6: *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-hydroxyphenyl)-*N*-methyl-1*H*-imidazole- 1-carboxamide hydrobromide



The title compound was prepared by analogous manner to Example 4 from Intermediate 2, Intermediate 8 and 3,5-dimethoxy benzaldehyde.

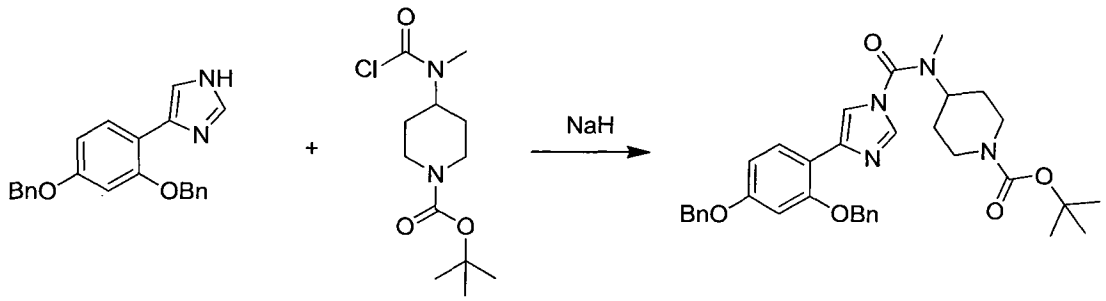
Appearance: white solid.

^{1}H NMR (DMSO-d_6): 9.56 (1H, s), 9.41 (1H, s), 9.27 (1H, s br), 8.11 (1H, s), 7.91 (1H, s), 7.29-7.23 (2H, m), 7.16 (1H, t, J = 7.8 Hz), 6.66 (1H, dd, J = 2.2, 8.0 Hz), 6.36-6.30 (3H, m), 4.14 (1H, m), 4.09 (2H, d, J = 4.8 Hz), 3.44 (2H, d, J = 10.5 Hz), 3.12 (2H, m), 2.92 (3H, s), 2.13 (2H, q, J = 12.5 Hz), 2.0 (2H, d, J = 12.0 Hz).

^{13}C NMR (DMSO-d_6): 158.7, 157.6, 151.1, 140.8, 137.6, 134.5, 131.4, 129.6, 115.7, 114.3, 114.2, 111.7, 109, 103.6, 59.3, 52.2, 50.6, 31.8, 25.1.

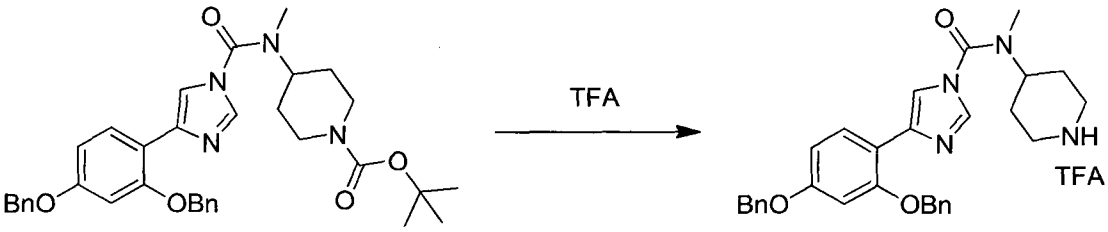
Example 7: 4-(2,4-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrobromide

Step1: tert-butyl 4-(4-(2,4-bis(benzyloxy)phenyl)-N-methyl-1H-imidazole-1-carboxamido)piperidine-1-carboxylate



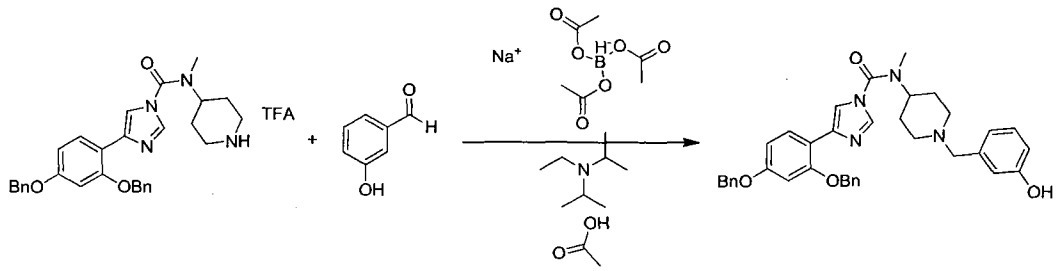
To a clear chilled, dark brown solution of 4-(2,4-*bis*(benzyloxy)phenyl)-1*H*-imidazole (Intermediate 5) (4.19 g, 11.76 mmol) in tetrahydrofuran (58.8 mL) was carefully added sodium hydride (60% in mineral oil dispersion) (0.611 g, 15.28 mmol). After stirring the reaction for 10 min, *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate (Intermediate 8) (3.90 g, 14.11 mmol) was added and the reaction was stirred for 1h. Thereupon, the reaction was quenched with crushed ice and then partitioned between water and ethyl acetate. The organic layer was washed with dilute HCl and brine, respectively. Then the organic layer was dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. Recrystallization from hot isopropanol afforded *tert*-butyl 4-(4-(2,4-*bis*(benzyloxy)phenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (4.66 g, 63% yield).

Step2: 4-(2,4-bis(benzyloxy)phenyl)-N-methyl-N-(piperidin-4-yl)-1H-imidazole-1-carboxamide 2,2,2-trifluoroacetate



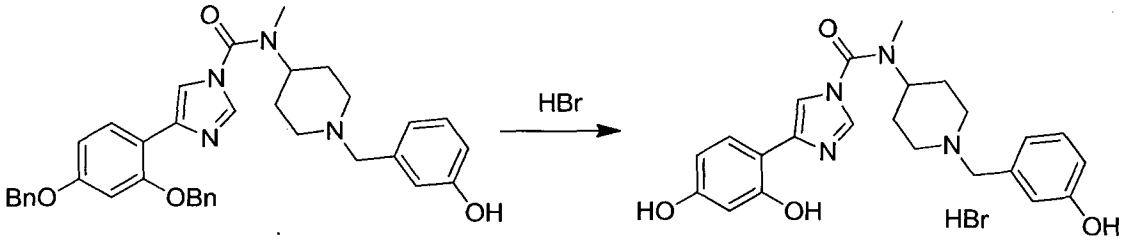
To a chilled portion of *tert*-butyl 4-(4-(2,4-*bis*(benzyloxy)phenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (4.66 g, 7.81 mmol) was added trifluoroacetic acid (24.07 mL, 312 mmol). After stirring the reaction for 10 min, the excess of trifluoroacetic acid was removed under reduced pressure. The oil residue was suspended in hot methanol and upon cooling yielded 4-(2,4-*bis*(benzyloxy)phenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide 2,2,2-trifluoroacetate (3.8 g, 84% yield) as white solid.

Step3: 4-(2,4-bis(benzyloxy)phenyl)-N-(1-(3-hydroxybenzyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide



To a suspension of 4-(2,4-*bis*(benzyloxy)phenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide 2,2,2-trifluoroacetate (0.750 g, 1.228 mmol) in 1,2-dichloroethane (10.7 mL) was added *N*,*N*-diisopropylethylamine (0.86 mL, 4.91 mmol) and 3-hydroxybenzaldehyde (0.300 g, 2.457 mmol). The reaction was allowed to stir at room temperature for *ca* 30 min and then was treated with sodium triacetoxyhydroborate (0.521 g, 2.457 mmol) followed by addition of acetic acid (0.070 mL, 1.228 mmol). The stirring was continued at room temperature for 48 h and then quenched upon addition of crushed ice. The resultant mixture was partitioned between water and dichloromethane/methanol 9/1 mixture. The two phases were separated and the aqueous phase was further extracted into dichloromethane/methanol 9/1 mixture until no further material could be observed by TLC in the aqueous phase. The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. Recrystallization from isopropanol yielded 4-(2,4-*bis*(benzyloxy)phenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.635 g, 73% yield).

Step4: 4-(2,4-dihydroxyphenyl)-N-(1-(3- hydroxybenzyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide hydrobromide



To a chilled solution of 4-(2,4-*bis*(benzyloxy)phenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.630 g,

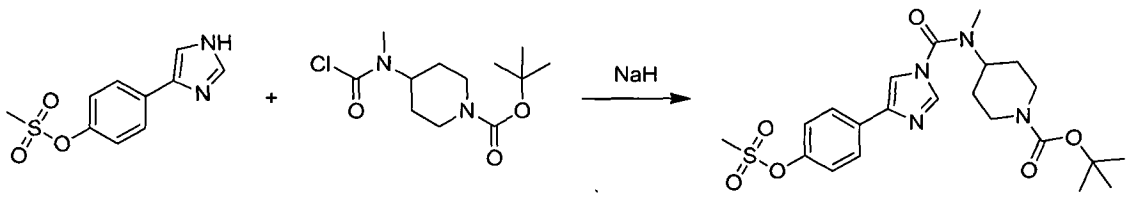
1.045 mmol) in dichloromethane (8.4 mL) was added dropwise hydrogen bromide (33% in acetic acid) (1.42 mL, 7.84 mmol). The reaction was allowed to stir at 0° C and then slowly warm up to room temperature and stirred for additional 16 h. Thereupon, the reaction was quenched with water and neutralized upon careful addition of a saturated aqueous solution of Na_2CO_3 (gas evolution). The obtained mixture was extracted with dichloromethane/methanol 9/1 mixture until no further material could be extracted. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Recrystallization from hot isopropanol afforded 4-(2,4-dihydroxyphenyl)-*N*-(1-(3-hydroxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrobromide (0.932 g, 16% yield) as a white solid.

^{1}H NMR (DMSO-d_6): 10.78 (1H, s), 9.75 (1H, s), 9.39 (2H, m), 8.18 (1H, s), 7.76 (1H, d, J = 1.3 Hz), 7.63 (1H, d, J = 8.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 6.89 (2H, m), 6.32 (1H, d, J = 2.3 Hz), 6.29 (1H, dd, J = 2.3, 8.5 Hz), 4.20 (2H, d, J = 4.5 Hz), 4.13 (1H, m), 3.44 (2H, d, J = 11Hz), 3.12 (2H, m), 2.91 (3H, s), 2.11 (2H, q, J = 13 Hz), 2.0 (2H, d, J = 12.5 Hz).

^{13}C NMR (DMSO-d_6): 157.7, 157.6, 156, 151.1, 138.9, 135.9, 131, 130, 127.1, 121.7, 118, 116.6, 113.3, 109.5, 107, 102.8, 59.1, 52.2, 50.6, 31.7, 25.1.

Example 8: 4-(1-((1-(3,5-dihydroxybenzyl)piperidin-4-yl)(methyl)carbamoyl)-1*H*-imidazol-4-yl)phenyl methanesulfonate

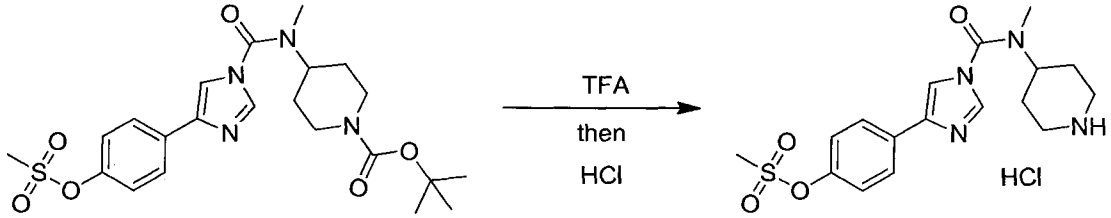
Step1: tert-butyl 4-(N-methyl-4-(4-(methylsulfonyloxy)phenyl)-1H-imidazole-1-carboxamido)piperidine-1-carboxylate



To a chilled cloudy solution of 4-(1*H*-imidazol-4-yl)phenyl methanesulfonate (Intermediate 7) (2.49 g, 10.45 mmol) in dry tetrahydrofuran (41.8 mL) was added portionwise sodium hydride (60% in mineral oil dispersion) (0.543 g, 13.59 mmol). The reaction was allowed to stir in the cold for a while and then *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate (Intermediate 8) (3.47 g,

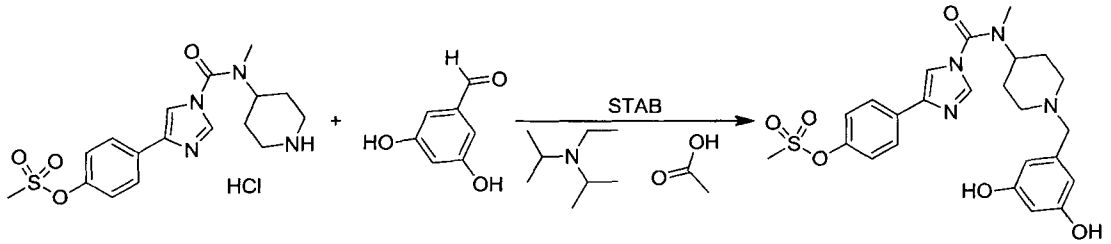
12.54 mmol) was added resulting in a very thick suspension. After completion, the reaction was quenched with crushed ice; the insoluble product was collected by filtration, washed with water and dried under vacuum. Recrystallization from isopropanol afforded *tert*-butyl 4-(*N*-methyl-4-(4-(methylsulfonyloxy)phenyl)-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (4.34 g, 82% yield).

Step2: 4-(1-(methyl(piperidin-4-yl)carbamoyl)-1H-imidazol-4-yl)phenyl methanesulfonate hydrochloride



To a chilled portion of *tert*-butyl 4-(*N*-methyl-4-(4-(methylsulfonyloxy)phenyl)-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (4.34 g, 9.07 mmol) was added trifluoroacetic acid (27.9 mL, 363 mmol) and the reaction was stirred at 0 °C for 1 h. Thereupon, the excess of trifluoroacetic acid was removed under reduced pressure and the oily residue was taken up in methanol (36.3 mL), chilled in ice/water bath and treated with hydrogen chloride (2 M in diethyl ether) (13.60 mL, 27.2 mmol) resulting in a suspension. After stirring for couple of hours, the solvent was removed under reduced pressure affording 4-(1-(methyl(piperidin-4-yl)carbamoyl)-1*H*-imidazol-4-yl)phenyl methanesulfonate hydrochloride (3.87 g, 93% yield).

Step3: 4-(1-((1-(3,5-dihydroxybenzyl)piperidin-4-yl)(methyl)carbamoyl)-1H-imidazol-4-yl)phenyl methanesulfonate



To a stirred suspension of 4-(1-(methyl(piperidin-4-yl)carbamoyl)-1*H*-imidazol-4-yl)phenyl methanesulfonate hydrochloride (0.5 g, 1.205 mmol) in 1,2-dichloroethane (10.5 mL) was added 3,5-dihydroxybenzaldehyde (0.333 g, 2.410 mmol) and *N*,*N*-disopropylethylamine (0.84 mL, 4.82 mmol) The reaction was allowed to stir for

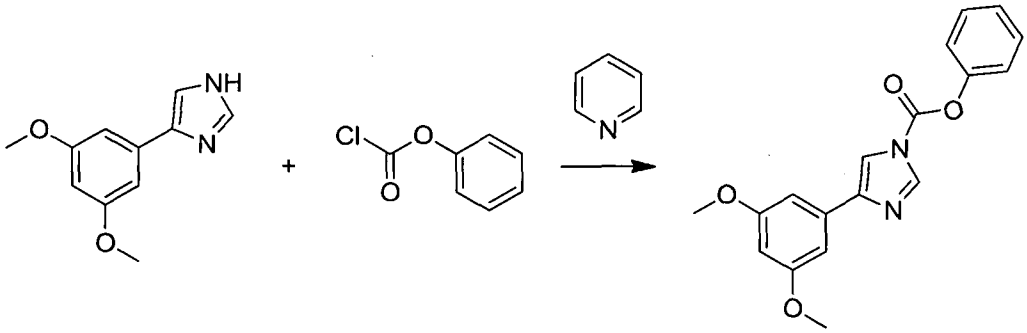
couple of hours, then sodium triacetoxyhydroborate (0.511 g, 2.410 mmol) was added followed by addition of acetic acid (0.071 mL, 1.205 mmol). The stirring was continued at room temperature over 72 h. Thereupon, the reaction was quenched with water and then partitioned between aqueous $NaHCO_3$ and dichloromethane/methanol 9/1 mixture. The layers were separated and the aqueous phase was extracted with dichloromethane/methanol 9/1 mixture (3 times). The combined organic phases were dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. The residue was purified by column chromatography (silica gel H; gradient dichloromethane/methanol 95/5 to 90/10) affording 4-(1-((1-(3,5-dihydroxybenzyl)piperidin-4-yl)(methyl)carbamoyl)-1*H*-imidazol-4-yl)phenyl methanesulfonate (0.180 g, 28% yield) as off-white solid.

^{1}H NMR (DMSO-d_6): 9.12 (2H, s), 8.14 (1H, d, J = 1.3 Hz), 8.08 (1H, s), 7.94 (2H, md, J = 8.6 Hz), 7.37 (2H, md, J = 8.6 Hz), 6.17 (2H, s), 6.08 (1H, s br), 3.82 (1H, s br), 3.39 (3H, s), 3.26 (2H, br), 2.94 (3H, s), 2.90 (2H, br), 1.95 (2H, m br), 1.82 (2H, m br), 1.73 (2H, m br).

^{13}C NMR (DMSO-d_6): 158.2, 150.9, 148, 140.5, 139.5, 137.9, 132.6, 126.2, 122.5, 115, 106.7, 101.1, 62.1, 55.6, 52.3, 37.3, 31.5, 28.2.

Example 9: 4-(3,5-dihydroxyphenyl)-N-methyl-N-(1-phenylpiperidin-4-yl)-1H-imidazole-1- carboxamide hydrochloride

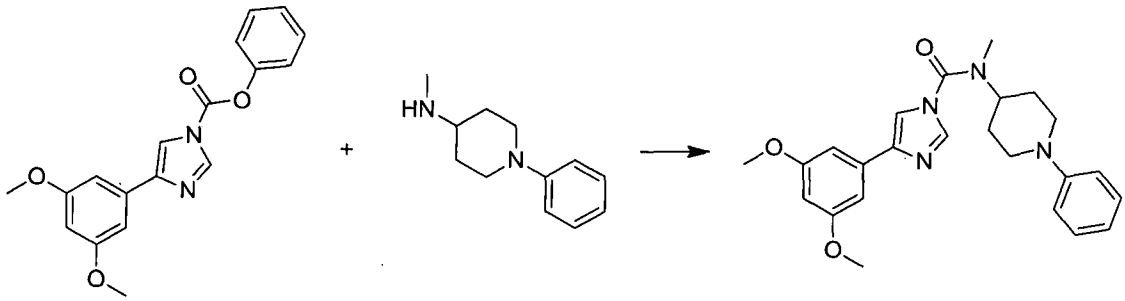
Step1: Phenyl 4-(3,5-dimethoxyphenyl)-1H-imidazole-1-carboxylate



To a clear chilled solution of 4-(3,5-dimethoxyphenyl)-1*H*-imidazole (Intermediate 1) (2.5 g, 12.24 mmol) in dichloromethane (46.1 mL) was added pyridine (1.19 mL, 14.69 mmol), followed by dropwise addition of a solution of phenyl carbonochloridate (1.84 mL, 14.69 mmol) in dichloromethane (12 mL). The reaction was allowed to stir at room temperature for 1 h, then was quenched with crushed ice and transferred into a

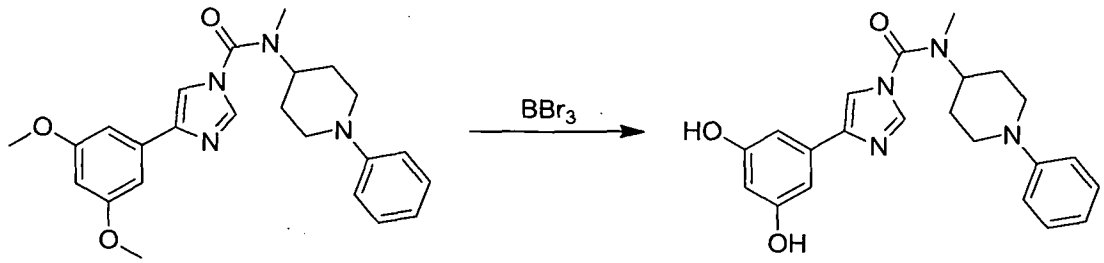
separatory funnel. The organic phase was separated and washed with dilute acid. The organic layer was dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. The residue was triturated with a mixture of petroleum ether and traces of diethyl ether yielding of phenyl 4-(3,5-dimethoxyphenyl)-1*H*-imidazole-1-carboxylate (3.23 g,81 % yield).

Step2: 4-(3,5-dimethoxyphenyl)-N-methyl-N-(1-phenylpiperidin-4-yl)-1H-imidazole-1-carboxamide



To a clear solution of phenyl 4-(3,5-dimethoxyphenyl)-1*H*-imidazole-1-carboxylate (220 mg, 0.678 mmol) in tetrahydrofuran (2.7 mL) was added *N*-methyl-1-phenylpiperidin-4-amine (Intermediate 9) (258 mg, 1.357 mmol) and stirred at room temperature overnight. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography (gradient elution with a mixture of dichloromethane/ethyl acetate). Recrystallization from isopropanol yielded 4-(3,5-dimethoxyphenyl)-*N*-methyl-*N*-(1-phenylpiperidin-4-yl)-1*H*-imidazole-1-carboxamide (151 mg, 47% yield).

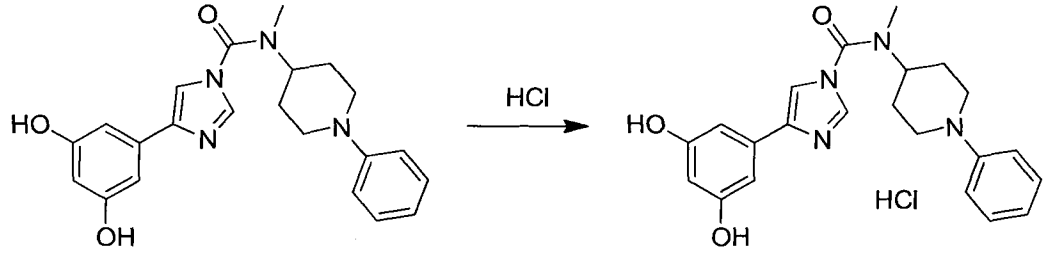
Step3: 4-(3,5-dihydroxyphenyl)-N-methyl-N-(1-phenylpiperidin-4-yl)-1H-imidazole-1-carboxamide



To a clear solution of 4-(3,5-dimethoxyphenyl)-*N*-methyl-*N*-(1-phenylpiperidin-4-yl)-1*H*-imidazole-1-carboxamide (151 mg, 0.359 mmol) in dry dichloromethane (4.8 mL)

was added boron tribromide (0.204 mL, 2.155 mmol) at -78 °C. After stirring 10 min in the cold, the stirring was continued at room temperature for 18 h. Thereupon, the reaction mixture was cooled in a crushed ice/water bath and quenched with crushed ice followed by stirring for additional 1 h. Recrystallization from a mixture of isopropanol and diethyl ether afforded of 4-(3,5-dihydroxyphenyl)-*N*-methyl-*N*-(1-phenylpiperidin-4-yl)-1*H*-imidazole-1-carboxamide (132 mg, 94% yield).

Step4: 4-(3,5-dihydroxyphenyl)-N-methyl-N-(1-phenylpiperidin-4-yl)-1H-imidazole-1-carboxamide hydrochloride

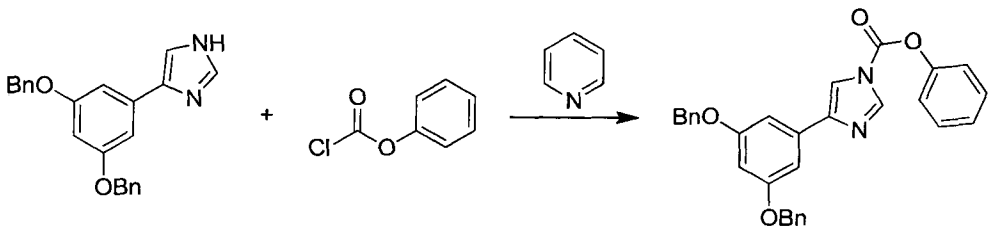


To a chilled solution of 4-(3,5-dihydroxyphenyl)-*N*-methyl-*N*-(1-phenylpiperidin-4-yl)-1*H*-imidazole-1-carboxamide (36 mg, 0.092 mmol) in methanol (1 mL) was added hydrogen chloride (2 M in diethyl ether) (0.46 mL, 0.917 mmol). The reaction mixture was stirred at room temperature until a thick white suspension was formed. Then, the solvents were removed under reduced pressure and the residue was triturated with methanol affording 4-(3,5-dihydroxyphenyl)-*N*-methyl-*N*-(1-phenylpiperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrochloride as a white solid (30 mg, 69% yield).

^{1}H NMR (DMSO-d_6): 9.55 (2H, br), 9.0 (1H, s br), 8.18 (1H, s), 7.74 (2H, s br), 7.52 (2H, m), 7.38 (1H, s br), 6.72 (2H, d, J = 2.2 Hz), 6.30 (1H, t, J = 2.2 Hz), 4.39 (1H, br), 3.69 (4H, m), 3.01 (3H, s), 2.58 (2H, m), 2.02 (2H, d, J = 11.5 Hz).
^{13}C NMR (DMSO-d_6): 158.9, 149.7, 144.4, 137.3, 137, 131, 129.9, 129.9, 120.4, 115.3, 103.7, 102.9, 53, 52.5, 31.6, 25.8.

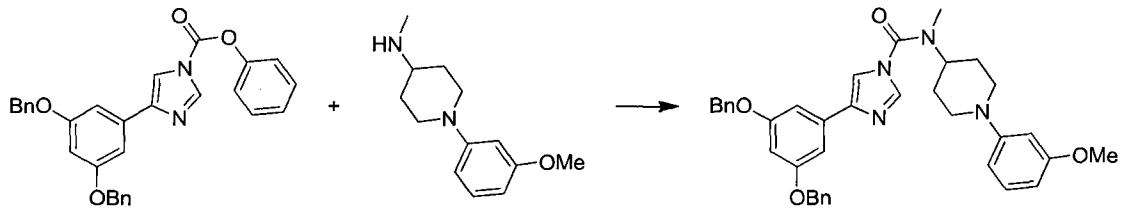
Example 10: 4-(3,5-dihydroxyphenyl)-*N*-(1-(3-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrobromide

Step1: Phenyl 4-(3,5-bis(benzyloxy)phenyl)-1H-imidazole-1-carboxylate



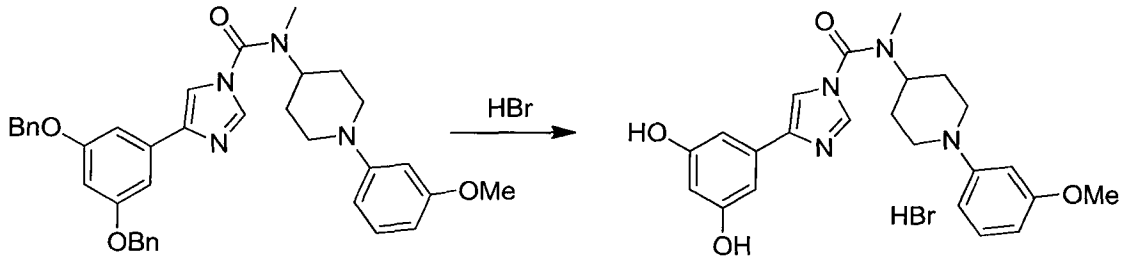
To a chilled clear solution of 4-(3,5-*bis*(benzyloxy)phenyl)-1*H*-imidazole (6.5 g, 18.24 mmol) in dichloromethane (87 mL) was added pyridine (1.766 mL, 21.88 mmol), followed by fast dropwise addition of phenyl carbonochloridate (2.75 mL, 21.88 mmol). The reaction mixture was stirred in the cold and monitored for 1 h. Thereupon, the reaction was washed with water twice, dried over anhydrous Na_2SO_4, filtered through a pad of silica/celite and evaporated. The resultant yellow/orange oil was triturated with a mixture of petroleum ether and small amount of toluene, filtered and dried under high vacuum at room temperature yielding phenyl 4-(3,5-*bis*(benzyloxy)phenyl)-1*H*-imidazole-1-carboxylate (6.9 g, 72% yield).

Step2: 4-(3,5-bis(benzyloxy)phenyl)-N-(1-(3-methoxyphenyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide



To a clear solution of phenyl 4-(3,5-*bis*(benzyloxy)phenyl)-1*H*-imidazole-1-carboxylate (2.34 g, 4.91 mmol) in tetrahydrofuran (19.7 mL) was added portionwise 1-(3-methoxyphenyl)-*N*-methylpiperidin-4-amine (Intermediate 10) (1.623 g, 7.37 mmol). The reaction was allowed to stir at room temperature overnight. Then, the solvent was removed under reduced pressure and the residue purified by column chromatography (gradient dichloromethane/ethyl acetate 98/2, 95/5, 9/1,7/3, 1/1) to afford an oil, which was crystallized from isopropanol. Yielded 4-(3,5-*bis*(benzyloxy)phenyl)-*N*-(1-(3-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.848 g, 27% yield).

Step3: 4-(3,5-dihydroxyphenyl)-N-(1-(3-methoxyphenyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide hydrobromide



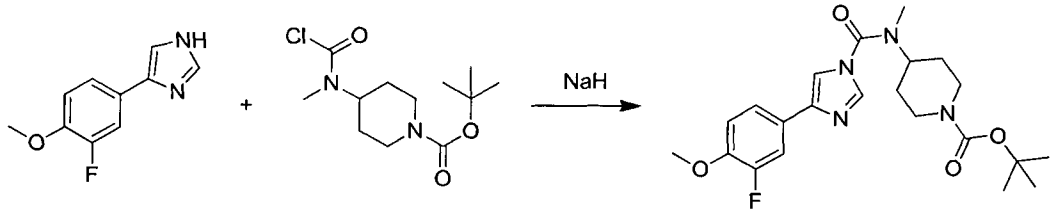
To a chilled solution of 4-(3,5-*bis*(benzyloxy)phenyl)-*N*-(1-(3-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.848 g, 1.407 mmol) in dichloromethane (11.2 mL) was added dropwise hydrogen bromide (33% in acetic acid) (1.74 mL, 10.55 mmol). The reaction was allowed to stir at 0 °C and then slowly warm up to room temperature and stirred for additional few hours. The obtained solid was filtered off and dried under vacuum. Recrystallization from methanol afforded 4-(3,5-dihydroxyphenyl)-*N*-(1-(3-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrobromide (0.313 g, 40% yield) as a white solid.

^{1}H NMR (DMSO-d_6): 9.50 (2H, br), 9.0 (1H, s br), 8.17 (1H, s), 7.30 (1H, s br), 7.1-6.5 (3H, br), 6.70 (2H, d, J = 2Hz), 6.28 (1H, t, J = 2Hz), 4.23 (1H, s br), 3.77 (3H, s), 3.75 (2H, d, J = 11.5 Hz), 3.50 (2H, br), 3.0 (3H, s), 2.19 (2H, s br), 2.0 (2H, d, J = 10 Hz).

^{13}C NMR (DMSO-d_6): 160.2, 158.9, 149.2, 137.3, 135.9, 130.7, 130.1, 115.6, 111.6, 105.3, 103.8, 103.2, 55.5, 53.3, 52.2, 31.9, 26.3.

Example 11: *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride

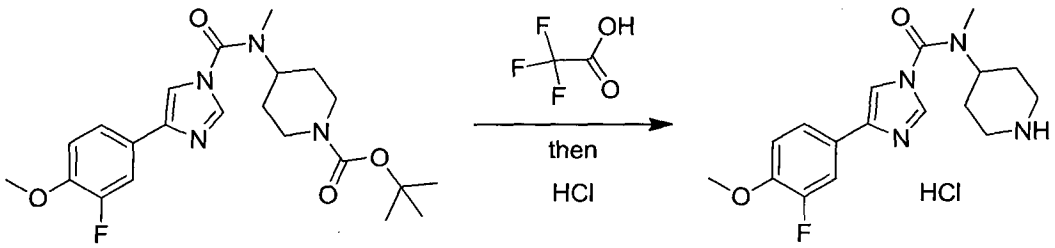
Step1: tert-butyl 4-(4-(3-fluoro-4-methoxyphenyl)-N-methyl-1H-imidazole-1-carboxamido)piperidine-1-carboxylate



To a solution of 4-(3-fluoro-4-methoxyphenyl)-1*H*-imidazole (5.32 g, 27.7 mmol) (intermediate 11) in tetrahydrofuran (111 mL) added portionwise sodium hydride

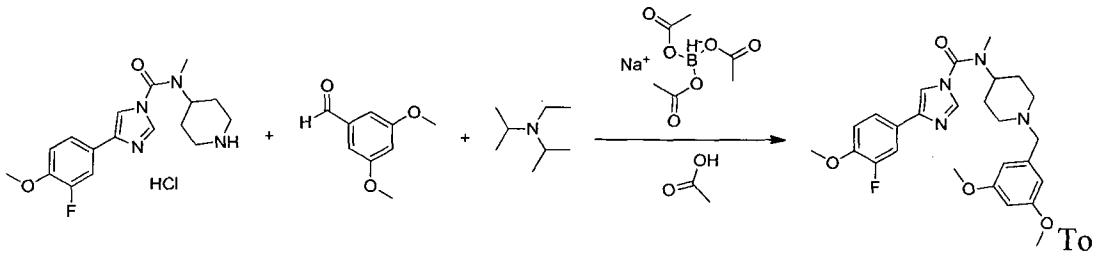
(60% in oil dispersion) (1.550 g, 38.8 mmol). After the gas evolution subsided added *tert*-butyl 4-(chlorocarbonyl(methyl)amino)piperidine-1-carboxylate (8.64 g, 31.2 mmol) (intermediate 8) and continued stirring. Monitored reaction by TLC; once complete conversion is observed quenched reaction upon addition of crushed ice. Transferred reaction mixture into separatory funnel and extracted into ethyl acetate until no more product is observed by TLC. The organic layer was washed with aqueous HCl (1 M), water and dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. Yielded *tert*-butyl 4-(4-(3-fluoro-4-methoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (11.65 g, 97 % yield)

Step 2: 4-(3-fluoro-4-methoxyphenyl)-N-methyl-N-(piperidin-4-yl)-1H-imidazole-1-carboxamide hydrochloride



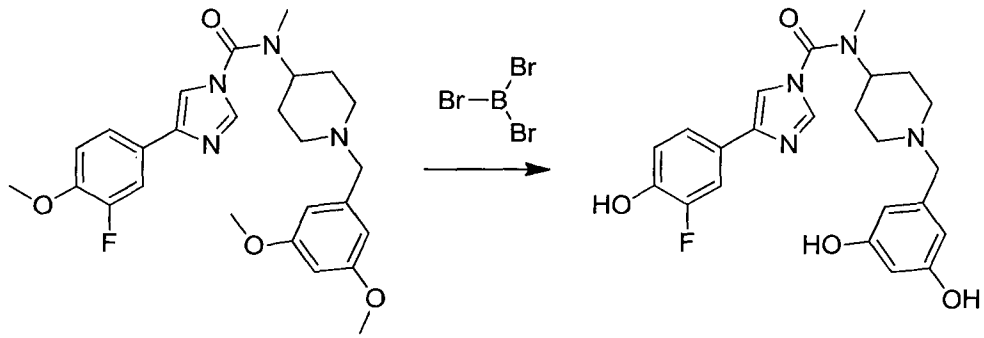
To an ice/water cold solution of *tert*-butyl 4-(4-(3-fluoro-4-methoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamido)piperidine-1-carboxylate (11.65 g, 26.9 mmol) in ice/water bath added trifluoroacetic acid (31.1 mL, 404 mmol); after 10 min TLC shows complete conversion. Removed trifluoroacetic acid under reduced pressure; and, the residue was diluted in methanol (108 mL), chilled in ice/water bath and added hydrogen chloride (2 M in ether) (26.9 mL, 53.9 mmol). Quickly a white suspension was formed; continued stirring at room temperature and, after 1 hr, removed solvents under reduced pressure. The white solid was triturated from isopropanol, collected in glass fritted funnel and allowed to air dry. Yielded 4-(3-fluoro-4-methoxyphenyl)-N-methyl-N-(piperidin-4-yl)-1H-imidazole-1-carboxamide hydrochloride (8.96 g, 90 % yield) as an off-white solid.

Step 3: N-(1-(3,5-dimethoxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-methoxyphenyl)-N-methyl-1H-imidazole-1-carboxamide



a suspension of 4-(3-fluoro-4-methoxyphenyl)-*N*-methyl-*N*-(piperidin-4-yl)-1*H*-imidazole-1-carboxamide hydrochloride (0.75 g, 2.033 mmol) in 1,2-dichoroethane (17.68 mL) added *N,N*-diisopropylethylamine (1.421 mL, 8.13 mmol), followed by 3,5-dimethoxybenzaldehyde (0.676 g, 4.07 mmol). Stirred at room temperature for 15 min and then added sodium triacetoxyhydroborate (0.862 g, 4.07 mmol), followed by acetic acid (0.116 mL, 2.033 mmol). Continued stirring at room temperature under inert atmosphere and monitored reaction by TLC. Once reaction is complete, quenched upon addition of cold water; transferred reaction mixture into separatory funnel and partitioned between water and dichloromethane/methanol (9/1). Separated layers and the aqueous layer was further extracted into dichloromethane/methanol (9/1). Combined the organic extracts and dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. The residue was precipitated from ether to afford *N*-(1-(3,5-dimethoxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-methoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.741 g, 64.2 % yield).

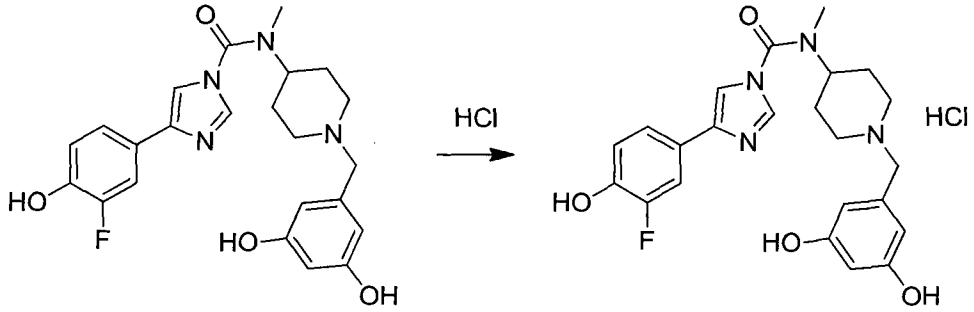
Step 4: -(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-hydroxyphenyl)-N-methyl-1H-imidazole-1-carboxamide



To a -78 °C chilled clear solution of *N*-(1-(3,5-dimethoxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-methoxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.724 g, 1.500 mmol) in dry dichloromethane (30.0 mL) added boron tribromide (1.277 mL, 13.50 mmol). A thick suspension quickly formed. Stirred at -78 °C for 15 min and then removed cold bath and continued stirring at room temperature for 18 h. Chilled

reaction mixture in ice/water bath and slowly added an aqueous solution of trimethylolpropane (2 M) (3 mL) – exothermic reaction. Allowed to stir in the cold for ca 1 h: decanted brown gum. Partitioned the filtrate between water and dichloromethane/methanol (9/1). Separated layers and the aqueous layer was further washed with dichloromethane/methanol (9/1) three times. The aqueous layer was neutralized with saturated aqueous sodium hydrideCO_3 until pH 8-9 and a white suspension was formed. Collected the solid and washed with water. The solid was then triturated in isopropanol/dichloromethane/ether and collected in glass fritted funnel. Yielded *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.163 g, 23.43 % yield) as a beige solid.

Step 5: N-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-hydroxyphenyl)-N-methyl-1H-imidazole-1-carboxamide hydrochloride



To a clear chilled solution of *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.155 g, 0.352 mmol) in ethyl acetate (1.759 mL)/methanol (1.759 mL) added hydrogen chloride (2 M in ether) (0.704 mL, 1.408 mmol) and allowed to stir at room temperature for a couple of hours. The solvents were removed under reduced pressure and the residue was triturated from ether and ethyl acetate, the solid collected in glass fritted funnel and dried under vacuum at 50 °C. Yielded *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(3-fluoro-4-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride (0.1605 g, 81 % yield) as an off-white solid.

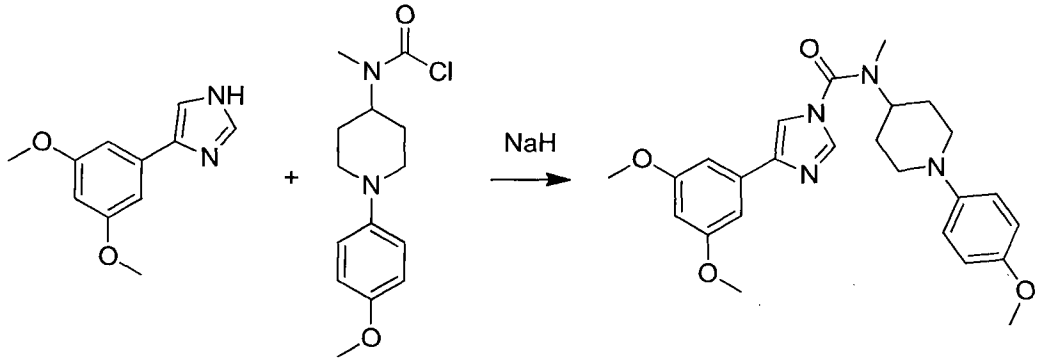
^{1}H NMR (DMSO-d_6):. 10.75 (1H, s), 10.27 (1H, br), 9.57 (1H, br), 8.86 (1H, s br), 8.15 (1H, s), 7.71 (1H, dd, J = 2.2, 12.7 Hz), 7.55 (1H, dd, J = 1.5, 8.3 Hz), 7.05 (1H,

t, J = 8.9 Hz), 6.42 (2H, d, J = 1.9 Hz), 6.33 (1H, t, J = 1.9 Hz), 4.17 (1H, br), 4.03 (2H, m), 3.38 (2H, m), 3.06 (2H, m), 2.95 (3H, s), 2.35 (2H, m), 1.95 (2H, m).

^{13}C NMR (DMSO-d_6):. 158.7, 151.9, 150.3, 149.7, 145.3, 145.2, 137.3, 136.4, 131.4, 121.8, 121.5, 118.1, 114.4, 113.3, 113.2, 109.2, 103.5, 59, 52.3, 50.2, 31.6, 24.7.

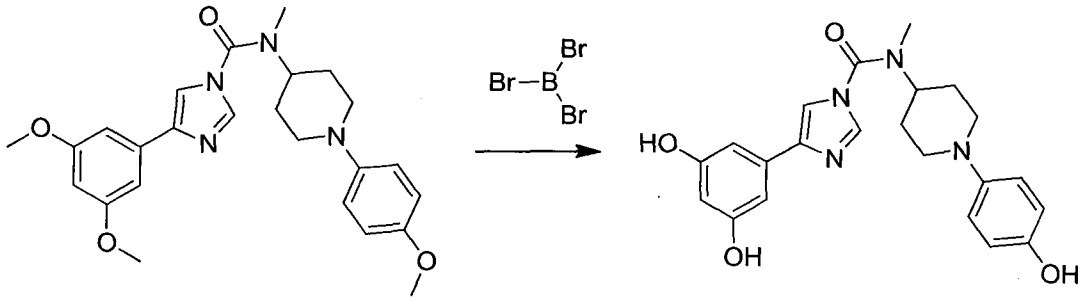
Example 12: 4-(3,5-dihydroxyphenyl)-*N*-(1-(4-hydroxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride

Step1: 4-(3,5-dimethoxyphenyl)-N-(1-(4-methoxyphenyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide



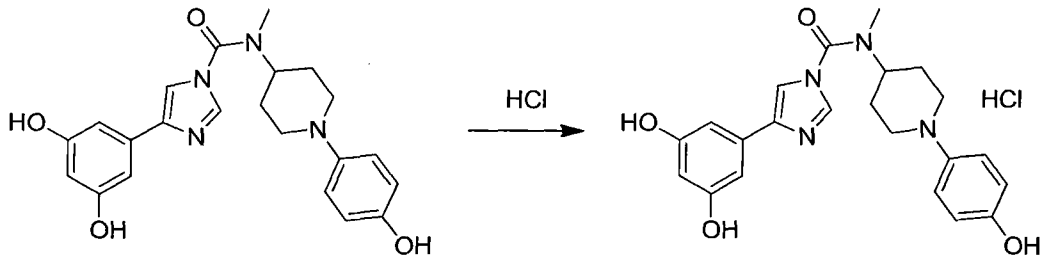
To a clear chilled solution of 4-(3,5-dimethoxyphenyl)-1*H*-imidazole (Intermediate 1) (0.75 g, 3.67 mmol) in DMF (14.69 mL) added sodium hydride (60% in oil dispersion) (0.176 g, 4.41 mmol). Once gas evolution subsided added 4-(3,5-dimethoxyphenyl)-*N*-(1-(4-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (1.246 g, 4.41 mmol) (Intermediate 13) and monitored reaction by TLC. Once reaction is complete quenched it upon addition of crushed ice and transferred mixture into separatory funnel; partitioned between water/dichloromethane and separated layers. The organic layers was dried over anhydrous Na_2SO_4, filtered through a short pad of silica/celite and concentrated. The residue was purified by column chromatography (Silica gel H; dichloromethane/methanol 95/5 to 9/1); the isolated product was further triturated from isopropanol/methyl *tert*-butyl ether to afford 4-(3,5-dimethoxyphenyl)-*N*-(1-(4-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (1.35 g, 78 % yield).

Step 2: 4-(3,5-dihydroxyphenyl)-N-(1-(4-hydroxyphenyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide



To a -78 °C cold clear solution of 4-(3,5-dimethoxyphenyl)-*N*-(1-(4-methoxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (1.35 g, 3.00 mmol) in dichloromethane (30.0 mL) added boron tribromide (2.55 mL, 27.0 mmol), stirred for *ca* 5 min and then removed cold bath. Continued stirring at room temperature and monitored reaction by TLC. Once reaction is complete, cooled reaction mixture in ice/water bath and quenched it with crushed ice; allowed to stir at room temperature overnight. The reaction mixture was transferred into separatory funnel and neutralized upon careful addition of saturated aqueous sodium hydrogencarbonate. The product was extracted into dichloromethane/methanol (9/1) until no more product could be observed on TLC. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (Si gel H; dichloromethane/methanol 9/1) to afford 4-(3,5-dihydroxyphenyl)-*N*-(1-(4-hydroxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (1.04 g, 81 % yield).

Step 3: -(3,5-dihydroxyphenyl)-N-(1-(4-hydroxyphenyl)piperidin-4-yl)-N-methyl-1H-imidazole-1-carboxamide hydrochloride



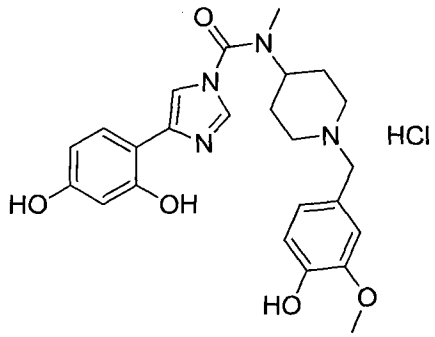
To a chilled (0 °C) solution of 4-(3,5-dihydroxyphenyl)-*N*-(1-(4-hydroxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide (0.212 g, 0.519 mmol) in methanol (5.19 mL) added hydrogen chloride (2 M in ether) (0.519 mL, 1.038 mmol); a thick white suspension was quickly formed. After *ca* 30 min removed solvents under reduced pressure and the residue was then triturated in

isopropanol and collected in pore 4 glass fritted funnel to afford 4-(3,5-dihydroxyphenyl)-*N*-(1-(4-hydroxyphenyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride (0.217 g, 89% yield) as a white solid.

^{1}H NMR (DMSO-d_6):. 13.0 (1H, s), 10.12 (1H, s br), 9.55 (2H, s br), 9.03 (1H, s), 8.19 (1H, s), 7.71 (2H, d, J = 8.3 Hz), 6.91 (2H, d, J = 8.9 Hz), 6.72 (2H, d, J = 2.0 Hz), 6.31 (1H, t, J = 1.8 Hz), 4.44 (1H, s br), 3.79 (2H, br), 3.54 (2H, d, J = 10.3 Hz), 3.02 (3H, s), 2.72 (2H, m, J = 11.5 Hz), 2.03 (2H, d, J = 11.8 Hz).

^{13}C NMR (DMSO-d_6):. 158.9, 158.2, 149.6, 137.3, 136.8, 133.8, 131, 122.7, 116.2, 115.3, 103.7, 102.9, 54.6, 51.5, 31.5, 25.2

Example 13: 4-(2,4-dihydroxyphenyl)-*N*-(1-(4-hydroxy-3-methoxybenzyl)piperidin-4-yl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride



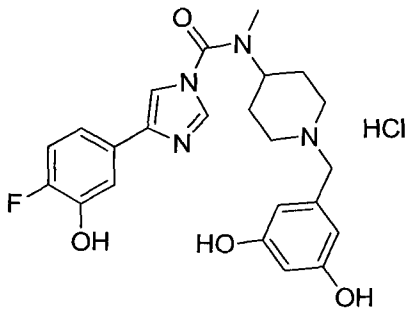
The title compound was prepared by analogous manner to Example 1 from Intermediate 5, Intermediate 8 and 4-hydroxy-3-methoxybenzaldehyde.

Appearance: white solid.

^{1}H NMR (DMSO-d_6):. 10.95 (1H, s), 9.79 (1H, s br), 9.37 (1H, s br), 9.12 (2H, m), 7.96 (1H, s), 7.62 (1H, d, J = 8.5 Hz), 7.32 (1H, d, J = 1.7 Hz), 6.90 (1H, dd, J = 1.6, 8.0 Hz), 6.81 (1H, d, J = 8.0 Hz), 6.48 (1H, d, J = 2.1 Hz), 6.35 (1H, dd, J = 2.3, 8.5 Hz), 4.18 (1H, br), 4.11 (2H, d, J = 4.7 Hz), 3.8 (3H, s), 3.37 (2H, d, J = 11.5 Hz), 3.02 (2H, m), 2.93 (3H, s), 2.37 (2H, m), 1.95 (2H, d, J = 12.1 Hz).

^{13}C NMR (DMSO-d_6):. 159.1, 156.1, 149.4, 147.6, 135.7, 127.9, 124.1, 120.2, 115.3, 115.2, 115.0, 107.3, 106.1, 102.9, 59.0, 55.7, 52.5, 49.9, 31.6, 24.7.

Example 14: *N*-(1-(3,5-dihydroxybenzyl)piperidin-4-yl)-4-(4-fluoro-3-hydroxyphenyl)-*N*-methyl-1*H*-imidazole-1-carboxamide hydrochloride



The title compound was prepared by analogous manner to Example 1 from Intermediate 14, Intermediate 8 and 3,5-dimethoxy benzaldehyde.

Appearance: white solid.

^{1}H NMR (DMSO-d_6):. 10.93 (1H, s br), 10.11 (1H, br), 9.59 (2H, br), 8.67 (1H, s br), 8.08 (1H, s), 7.49 (1H, dd, J = 1.7, 8.5 Hz), 7.29 (1H, m), 7.19 (1H, dd, J = 8.6, 11.0 Hz), 6.43 (2H, m), 6.33 (1H, m), 4.18 (1H, s br), 4.02 (2H, d, J = 4.5 Hz), 3.37 (2H, m), 3.05 (2H, m), 2.94 (3H, s), 2.38 (2H, m), 1.95 (2H, m).

^{13}C NMR (DMSO-d_6):. 158.6, 151.7, 150.1, 150.1, 145.1, 145.1, 137.5, 137.5, 131.4, 127.7, 116.5, 116.5, 116.4, 116.4, 114.8, 114.8, 109.1, 103.5, 58.9, 52.2, 50.2, 31.5, 24.7.

2. Biological Efficacy of Compounds of the Invention

In vitro/ex vivo Protocol for FAAH Activity Determination

To evaluate the selectivity of BIA 13 compounds in inhibiting FAAH activity, male NMRI mice were administrated following instillation with 1 mg/kg compound and were sacrificed after 8 h treatment. Liver, brain and lung fragments were removed and processed for enzymatic activity determination.

FAAH activity was measured as the amount of ^{3}H-ethanolamine formed, by liquid scintillation counting, from the hydrolysis of the substrate anandamide (AEA, labeled with ^{3}H on the ethanolamine part of the molecule). The percentage of remaining enzymatic activity was calculated in respect to controls and after blank subtraction.

Therefore, a low value for the test compounds indicates a strong inhibitor. A value of 100 indicates that no measureable inhibition took place.

Experiments in Mice

Animal Treatment

Male NMRI mice (body weight range: 25-35 g) were obtained from Harlan Laboratories (Barcelona, Spain). Animals were kept 10 per cage, under controlled environmental conditions (12 hr light [8 am] / 12 hr dark [8 pm] cycle; room temperature 22±1°C). Food and tap water were allowed *ad libitum*. Animals were habituated to the animal facilities at least for a week prior to experiments. The experiments were all carried out during daylight hours.

Animals were fasted overnight before administration of compounds. Animals were administered with test compounds (1 mg/kg) by intra-tracheal instillation (2 mL/kg in milliQ water) using an Introcan® Certo cannula after intra-peritoneal (ip) anaesthesia with a mixture of ketamine (150 mg/kg) + medetomidine (1 mg/kg) + butorphanol (1 mg/kg). After administration the animals were given atipamezole (1 mg/kg) to reverse the sedative and analgesic effects induced by the anaesthesia.

Fifteen minutes before sacrifice, animals were anesthetized with pentobarbital 60 mg/kg administrated intra-peritoneally. The brain (without cerebellum), lungs and a fragment of liver were collected into plastic vials containing membrane buffer (3 mM $MgCl_2$, 1 mM EDTA, 50 mM Tris HCl, pH 7.4). Glass beads (2.5 mm BioSpec Products, Bartlesville, OK, USA) were added to the vials containing the brain and liver tissues. Tissues were stored at -20°C until analysis.

FAAH Activity Determination

Reagents and Solutions

Anandamide [ethanolamine-1-^{3}H-] was obtained from American Radiochemicals – with a specific activity of 60 Ci/mmol. All other reagents were obtained from Sigma-Aldrich. Optiphase Supermix was obtained from Perkin Elmer.

Tissue preparation

Brain and liver tissues were thawed and homogenized in 10 volumes of membrane buffer (3 mM $MgCl_2$, 1 mM EDTA, 50 mM Tris HCl, pH 7.4) with homogenizer Precellys 24 Dual Tissue Homogenizer (Bertin Technologies) for 2 cycles of 5 sec (5000 rpm). Lung samples were homogenized with a probe homogenizer.

Total protein in the tissue homogenates was determined with the BioRad Protein Assay (BioRad) using a standard curve of BSA (50-250 µg/mL). Tissue homogenates were diluted to appropriate concentration for enzymatic determination in assay buffer (1 mM EDTA, 10 mM Tris HCl, pH 7.6).

Enzymatic assay

Reaction mix (total volume 200 µL) contained 2 µM AEA (2 µM AEA + 5 nM ^{3}H-AEA), 0.1% fatty acid free BSA, 15 µg (brain), 5 µg (liver) or 50 µg (lung) protein, in assay buffer (1 mM EDTA, 10 mM Tris pH 7.6).

After 15 minutes pre-incubation at 37 °C of the protein sample, reaction was started by the addition of the substrate solution (cold AEA + radiolabelled AEA + BSA). Reaction was carried out for 12 minutes for brain and liver tissues, and 10 minutes for lung samples. Reaction was terminated by addition of 400 µL chloroform:methanol (1:1, v/v) solution. Reaction samples were vortex twice, left on ice for 5 minutes and then centrifuged in the microfuge for 7 minutes, 7000 rpm. 200 µL of the obtained supernatants were added to 800 µL Optiphase Supermix scintillation cocktail previously distributed in 24-well plates.

Counts per minute (cpm) were determined in a Microbeta TriLux scintillation counter. In each assay blank samples (without protein) were prepared.

Experiments in Rats

Animal treatment

Male Wistar rats (body weight range: 190-230 g) were obtained from Harlan (Spain). Rats were kept 5 per cage, under controlled environmental conditions (12 hr light/dark cycle and room temperature 22±1°C). Food and tap water were allowed ad libitum and the experiments were all carried out during daylight hours.

Rats were administered the appropriate dose of compound of the invention via gavage (administration volume = 4 ml/kg body weight) using animal feeding stainless steel curve needles (Perfectum, U.S.A.). Vehicle was 0.5% CMC in Milli Q water. Rats were fasted at least 15 h before experiments.

Fifteen minutes before sacrifice animals were anesthetized with pentobarbital i.p. 60 mg/kg body weight. Liver biopsies and brain samples (without cerebellum) were collected and placed in a plastic vial containing membrane buffer (3 mM MgCl2, 1 mM EDTA, 50 mM Tris HCl pH 7.4) and, in the case of liver samples, glass beads (2.5 mm BioSpec Products). Tissues were stored at -20°C until analysis.

Reagents and Solutions

Anandamide [ethanolamine-1-3H-] was obtained from American Radiochemicals (specific activity of 60 Ci/mmol). All other reagents were obtained from Sigma-Aldrich. Optiphase Supermix was obtained from Perkin Elmer.

Tissue Preparation

Tissues were thawed on ice; livers were homogenized in a Precellys 24 Dual Tissue Homogenizer (Bertin Technologies) for 2 cycles of 5 sec with an interval of 5 min in ice and brains were homogenized with Heidolph Silent Crusher M (probe 8 F/M) for about 45 sec at maximum velocity. Total protein in homogenates was determined with the BioRad Protein Assay (BioRad) using a standard curve of BSA (50-250 µg/ml).

Enzymatic assay

Reaction mix (total volume of 200 µl) contained: 2 µM AEA (2 µM AEA + 5 nM 3H-AEA), 0.1 % fatty acid free BSA, 15 µg (brain) or 1.5 µg (liver) protein, in 1 mM EDTA, 10 mM Tris pH 7.6. After 15 minutes pre-incubation at 37°C reaction was started by the addition of the substrate solution (cold AEA + radiolabelled AEA + BSA). Reaction was carried out for 7 minutes for liver samples and for 10 min for brain samples and terminated by addition of 400 µL chloroform:methanol (1:1, v/v) solution. Reaction samples were vortex twice, left on ice for 5 minutes and then centrifuged in microfuge (7 minutes, 7000 rpm). Two-hundred µl of supernatants were

added to 800 µl Optiphase Supermix scintillation cocktail previously distributed in 24-well plates. Counts per minute (cpm) were determined in a Microbeta TriLux scintillation counter. In each assay blank samples (without protein) were prepared. The percentage of remaining enzymatic activity was calculated in respect to controls and after blank subtraction.

3. CYPs Metabolic Stability Assay

Stability of the test compounds was performed in HLM (human liver microsomes) in the presence and in the absence of NADPH.

The stability was measured using the incubation mixture (100 µl total volume) contained 1mg/ml total protein, $MgCl_2$ 5mM and 50mM K-phosphate buffer. Samples were incubated in the presence and in the absence of NADPH 1mM. Reactions were pre-incubated 5 min and the reaction initiated with the compound under test (at a concentration of 5µM). Samples were incubated for 60 min in a shaking water bath at 37°C. The reaction was stopped by adding 100 µl of acetonitrile. Samples were then centrifuged, filtered and supernatant injected in HLPC-MSD. Test compounds were dissolved in DMSO and the final concentration of DMSO in the reaction was below 0.5% (v/v). At T_0 acetonitrile was added before adding the compound. All experiments were performed with samples in duplicate.

4. Permeability assay

MDCK cells protocol

MDCK-II cells (canine) were grown in MEM supplemented with 100 U/ml penicillin G, 0.25 µg /ml amphotericin B, 100µg /ml streptomycin, 10% fetal bovine serum and 25 mM Hepes and maintained in a humified atmosphere of 5% CO_2-95% air at 37°C for 5 days. Transport experiments are performed in collagen treated 0.4 µm polycarbonate filter supports (12 mm ID, transwell, Costar-Corning) with compounds being applied from the apical (AP) cell border. The upper and lower chambers contained 400 and 1000 µl of HBSS, respectively. On the day of the experiment, cells were washed with Hank's Balance Salt Solution (HBSS), pH 7.4 and after a 5 min pre-incubation period under gentle agitation, experiments were started by the addition of compounds. Compounds are diluted in HBSS in order to have a final concentration

of 50 μM with less than 1% DMSO. After 30 min incubation, 250 μl of medium was taken, from the lower side to determine the apical transport. Samples were mixed with equal volume of acetonitrile 0.1 % formic acid and injected directly onto the LC-MS column.

Apparent permeability coefficients (Papp) were calculated using the following equation:

$$P_{app} = \frac{V}{AC_0} x \frac{dC}{dt}$$

Where V is the volume of the solution in the receiving compartment, A is the membrane surface area, C_0 is the initial concentration and dC/dt is the change in the drug concentration in the receiver solution over the time (Balimane, Chong *et al.* 2000).

Results

Table 1

The following table shows the FAAH activity in brain, lung and liver samples from mice for the compounds:

Compound - Example No.	FAAH Activity - Brain itc (%C)	FAAH Activity - Lung itc (%C)	FAAH Activity - Liver itc (%C)
1	104.7	53.9	90.8
2	77.8	53.4	81.1
3	103.1	45.8	81.1
4	160.1	52	78.2
5	96.6	33.9	74.4
6	83.1	41	73.9
7	114.7	46.3	84
8	86.1	43.3	77.3
9	98.3	45.5	78.6
10	119.7	49.2	80.3
11	88.2	40.7	80.1
12	110.3	36.0	79.9
13	94.8	58.8	95.8
14	101.1	55.5	111.6

As can be seen from the above table, all the compounds cause a significant amount of FAAH inhibition in the lung whereas the compounds cause less FAAH inhibition in the brain and liver. This shows that the compounds have advantageous properties for FAAH inhibition in the lung.

Table 2

Additional data relating to the activity of FAAH in mice at various doses for the compounds are given in the tables below:

Tissue	Brain	Brain	Brain	Lung	Lung	Lung	Liver	Liver	Liver
Dose (mg/kg)	1	1	1	1	1	1	1	1	1
Time (h)	1	8	24	1	8	24	1	8	24
Compound 1		104.7			53.9			90.8	
Compound 5	79.5	96.6	92.1	47	33.9	53.4	91.5	74.4	85.1

Tissue	Brain	Lung	Liver
Dose (mg/kg)	3	3	3
Time (h)	8	8	8
Compound 1	120.2	33.1	80.3
Compound 5	120.9	52.2	82.8

As can be seen above, compounds 1 and 5 show good properties for lung administration as FAAH inhibition is greater in the lung than in the brain or liver.

Table 3

Further, similar experiments were conducted in rats which gave the following results:

Tissue	Brain	Brain	Brain	Lung	Lung	Lung	Liver	Liver	Liver
Dose (mg/kg)	1	1	1	1	1	1	1	1	1
Time (h)	0.5	2	8	0.5	2	8	0.5	2	8
Compound 5	96.3	96.3	99	27.7	66.3	40.9	91.3	113.6	103.9

Again, as can be seen above, compound 5 shows good properties for lung administration as FAAH inhibition is greater in the lung than in the brain or liver.

Table 4

The following table shows the metabolic stability of the compounds:

Compound - Example No.	CYP+ (%remain)
1	78.6
5	93.9

The above table shows that the two compounds are metabolised, to a relatively small extent, by CYP enzymes. A value of 100 would demonstrate no metabolism. Compounds may be metabolised into inactive compounds which can help to improve systemic clearance. Further, compounds may be metabolised into an alternative form which has good pharmacokinetic properties.

Table 5

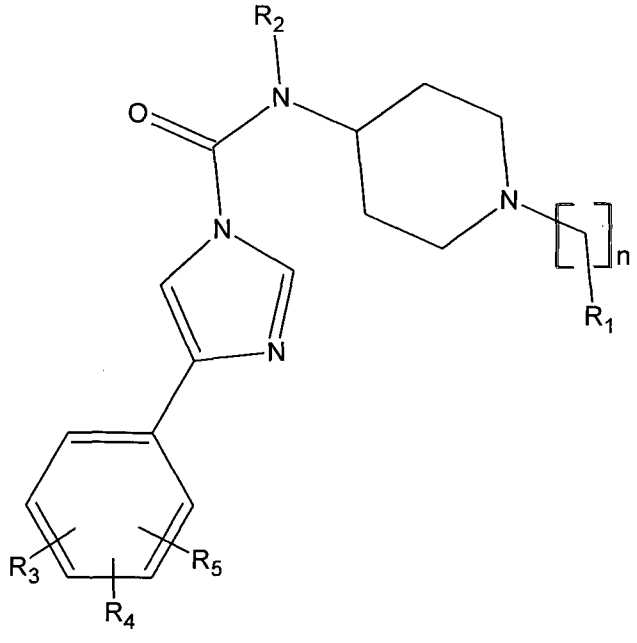
The permeability of the compounds was also tested. The results are as follows:

	Papp (Log cm/s)
Propranolol	-4.2
Atenolol	-6.4
Compound 1	-5.4
Compound 5	-6.8

In this experiment, a value of -6 is indicative of a compound which is not permeable whilst a value of -4 is indicative of a compound which is permeable. These results show that both the compounds are not significantly permeable. This means that the compounds have a low absorption. In comparison with the highly permeable (propranolol) and poorly permeable (atenolol) standards, compounds 1 and 5 showed a significantly different permeability with compound 1 30 fold more permeable than compound 5 in the assay. This shows that the compounds have good properties for topical administration.

Claims

1. A compound having Formula I:



Formula I

wherein:

R1 is aryl which is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy, or R1 is aryl which is substituted with a second aryl group or an aryloxy group, wherein the second aryl group or the aryloxy group is optionally substituted with one or more groups selected from hydroxyl, halogen and C_{1-4} alkoxy;

R2 is C_{1-4} alkyl;

R3 is selected from hydroxyl and OSO_2CH_3;

R4 and R5 are independently selected from hydrogen, hydroxyl and halogen; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof;

wherein when R3 is hydroxyl and R4 and R5 are not hydroxyl, the optionally substituted aryl group, second aryl group or aryloxy group of R1 is substituted with one or more hydroxyl groups or C_{1-4} alkoxy groups, or wherein when R3 is hydroxyl, one of R4 and R5 is hydroxyl,

provided that the compound is not N-(1-benzylpiperidin-4-yl)-4-(3,4-dihydroxyphenyl)-N-methyl-1H-imidazole-1-carboxamide hydrobromide.

2. The compound of claim 1, wherein R1 is aryl which is substituted with a hydroxyl group or a C_{1-4} alkoxy group and which is optionally further substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy and halogen.

3. The compound of claim 1 or claim 2, wherein R1 is aryl which is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen.

4. The compound of any preceding claim, wherein R1 is phenyl which is optionally substituted.

5. The compound of any preceding claim, wherein R1 is phenyl which is substituted with a hydroxyl group and optionally further substituted with one or more groups selected from hydroxyl and halogen.

6. The compound of any preceding claim, wherein R1 is aryl which is substituted with a hydroxyl group and which is optionally further substituted with up to two halogen groups such as fluorine and/or one hydroxyl group.

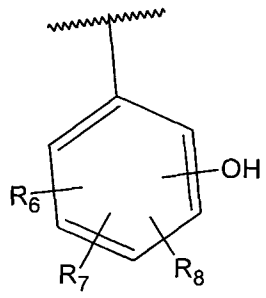
7. The compound of claim 1, wherein R1 is phenyl which is substituted with a second phenyl group or a phenoxy group, wherein the second phenyl group or the phenoxy group is optionally substituted.

8. The compound of any preceding claim, wherein R2 is methyl.

9. The compound of any preceding claim, wherein R3 is hydroxyl.

10. The compound of any preceding claim, wherein R4 is selected from hydrogen and hydroxyl and R5 is selected from hydrogen and halogen such as fluorine.

11. The compound of any preceding claim, wherein R1 has the following structure:



wherein R6, R7 and R8 are each independently selected from hydrogen, hydroxyl and halogen.

12. The compound of claim 11, wherein R6 and R7 are independently selected from hydrogen and halogen such as fluorine and R8 is selected from hydrogen and hydroxyl.

13. The compound of claim 11 or claim 12, wherein R6 and R7 are independently selected from hydrogen and halogen such as fluorine and R8 is hydroxyl.

14. The compound of claim 13, wherein R3 is hydroxyl and neither of R4 and R5 are hydroxyl.

15. The compound of claim 11, wherein R3 and R4 are hydroxyl, R5 is selected from hydrogen and halogen such as fluorine, R6 is hydrogen, and R7 and R8 are independently selected from hydrogen and halogen such as fluorine; or
R3 is hydroxyl, R4 is hydrogen, R5 is selected from hydrogen and halogen such as fluorine, R6 and R7 are independently selected from hydrogen and halogen such as fluorine, and R8 is hydroxyl.

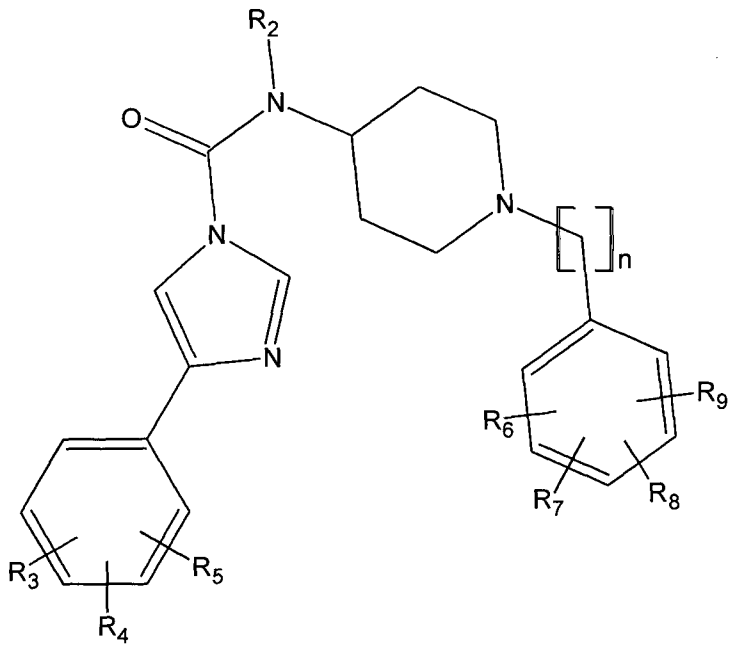
16. The compound of claim 11, wherein R3 and R4 are hydroxyl, R5 is selected from hydrogen and halogen such as fluorine, R6 is hydrogen, and R7 and R8 are independently selected from hydrogen and halogen such as fluorine.

17. The compound of claim 11, wherein R3 is hydroxyl, R4 is hydrogen, R5 is selected from hydrogen and halogen such as fluorine, R6 and R7 are independently selected from hydrogen and halogen such as fluorine, and R8 is hydroxyl.

18. The compound of claim 11, wherein R3 is OSO_2CH_3, R4 is hydrogen, and R5 is selected from hydrogen and halogen such as fluorine.

19. The compound of claim 18, wherein R6 and R7 are hydrogen, and R8 is selected from hydrogen, hydroxyl and halogen such as fluorine.

20. The compound of claim 1, having Formula IV:



Formula IV

wherein:

R2 is C_{1-4} alkyl;

R3 is hydroxyl;

R4 is selected from hydrogen and hydroxyl;

R5 is selected from hydrogen and halogen;

R6 is hydrogen;

R7 is selected from hydrogen and halogen;

R8 is selected from hydrogen, hydroxyl and C_{1-4} alkoxy;

R9 is hydroxyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof,

wherein at least one of R4 and R8 is hydroxyl.

21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20, together with one or more pharmaceutically acceptable excipients.

22. The pharmaceutical composition of claim 21, further comprising one or more additional active pharmaceutical ingredients such as anandamide, *N*-oleoylethanolamine or *N*-palmitoylethanolamine.

23. The pharmaceutical composition of claim 21 or claim 22, wherein the composition is for administration by inhalation.

24. A compound according to any one of claims 1 to 20 or a composition according to any one of claims 21 to 23 for use in therapy.

25. A compound according to any one of claims 1 to 20 or a composition according to any one of claims 21 to 23 for use in the treatment or prevention of a condition whose development or symptoms are linked to a substrate of the FAAH enzyme.

26. A method of treatment or prevention of a condition whose development or symptoms are linked to a substrate of the FAAH enzyme, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a composition according to any one of claims 21 to 23.

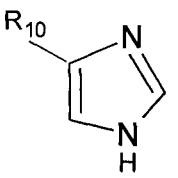
27. The method of claim 26, wherein the compound or the composition is administered by inhalation.

28. A compound for use according to claim 25 or a method according to claim 26, wherein the condition is a disorder associated with the endocannabinoid system.

29. A compound or a method according to claim 28, wherein the condition is a pulmonary condition.

30. A compound or a method according to claim 28, wherein the disorder is selected from diseases of the respiratory tracts, bronchospasm, coughing, asthma, chronic bronchitis, chronic obstruction of the respiratory tract, emphysema and Acute Respiratory Distress Syndrome (ARDS).

31. A process for the preparation of an imidazolyl derivative of the formula:



wherein R10 is selected from C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R10a, halogen, OH, OR10a, SH, SR10a, OCOR10a, SCOR10a, NH_2, NO_2, NHR10a, $NHSO_2NH_2$, $NHSO_2R10a$, NR10aCOR10b, NHCOR10a, $NHC(NH)NH_2$, NR10aR10b, COR10a, CSR10a, CN, COOH, COOR10a, $CONH_2$, CONHOH, CONHR10a, CONHOR10a, $C(NOH)NH_2$, CONR10aR10b, SO_2R10a, SO_3H, SO_2NH_2, $SO_2NR10aR10b$, wherein R10a and R10b are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R10a and R10b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R10 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R10 is C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R10c, C_{1-6} alkyl, C_{1-6} alkynyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl C_{1-6} alkoxy, heterocyclyl C_{1-6} alkoxy, OH, OR10c, OCOR10c, SH, SR10c, SCOR10c, NH_2, NO_2, NHR10c,

$NHSO_2NH_2$, $NHC(NH)NH_2$, $NHSO_2R10c$, NR10cCOR10d, NHCOR10c, NR10cR10d, COR10c, CSR10c, CN, COOH, COOR10c, $CONH_2$, CONHR10c, CONHOR10c, CONHOH, $C(NOH)NH_2$, CONR10cR10d, SO_2R10c, SO_3H, SO_2NH_2, $SO_2NR10cR10d$, wherein R10c and R10d are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R10c and R10d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R10 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R10 is C_{1-6} alkyl, C_{1-6} alkynyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl C_{1-6} alkoxy, heterocyclyl C_{1-6} alkoxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R10e, C_{1-6} alkyl, C_{1-4} alkoxy, OH, OR10e, OCOR10e, SH, SR10e, SCOR10e, NH_2, NO_2, NHR10e, $NHSO_2NH_2$, $NHC(NH)NH_2$, $NHSO_2R10e$, NR10eCOR10f, NHCOR10e, NR10eR10f, COR10e, CSR10e, CN, COOH, COOR10e, $CONH_2$, CONHOH, CONHR10e, CONHOR10e, $C(NOH)NH_2$, CONR10eR10f, SO_2R10e, SO_3H, SO_2NH_2, $SO_2NR10eR10f$, wherein R10e and R10f are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R10e and R10f, together with the heteroatom to which they are joined, can form heterocyclyl;

the process comprising the reaction of a bromoacetyl derivative of R10: R10-$COCH_2Br$, with diformylamide or a salt thereof, followed by reaction of the resulting oxoethyl-N-formylformamide derivative with ammonia or a salt thereof in the presence of an acid catalyst, thereby forming the imidazolyl derivative.

32. A process according to claim 31, wherein R10 is an aryl or heteroaryl group, optionally substituted with one or more aryl-C_{1-6} alkoxy groups.

33. A process for preparing a compound according to claim 1, in which a process according to claim 31 or 32 is comprised.

INTERNATIONAL SEARCH REPORT

International application No
PCT/PT2014/000052

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/454 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/074588 A2 (BIAL - PORTELA & CO. S.A., PORT.) 1 July 2010 (2010-07-01) cited in the application the whole document in particular; compounds 454, 523, 555	1-33
X	WO 2012/015324 A1 (BIAL - PORTELA & CA, S.A., PORT.) 2 February 2012 (2012-02-02) the whole document	1-33

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 2014	13/10/2014

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PT2014/000052

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