(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 June 2012 (28.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/085935 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IN2011/000870

(22) International Filing Date:
19 December 2011 (19.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3487/MUM/2010 22 December 2010 (22.12.2010) IN

(71) Applicant *(for all designated States except US)*: **CADILA HEALTHCARE LIMITED** [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DESAI, Jigar** [IN/IN]; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat (IN). **THOMBARE, Pravin** [IN/IN]; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat (IN). **JAIN, Mukul, R.** [IN/IN]; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat (IN).

(74) Agents: **SUBRAMANIAM, Hariharan** et al.; Subramaniam, Nataraj & Associates, E- 556, Greater Kailash-II, New Delhi 110048 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

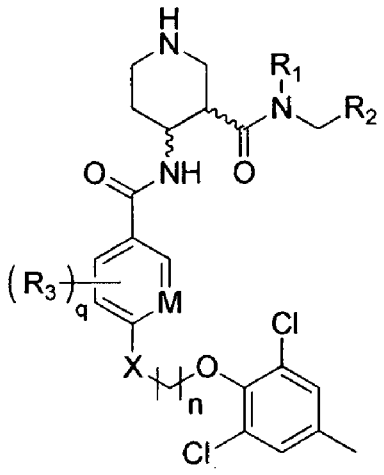
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: COMPOUNDS AS INHIBITORS OF RENIN



(I)

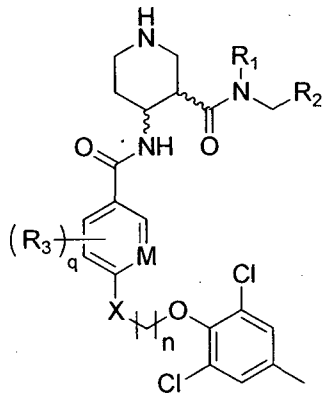
(57) Abstract: The present invention relates to novel renin inhibitors of general formula (1), novel intermediates involved in their synthesis, their pharmaceutically acceptable salts and pharmaceutical compositions containing them. The present invention also relates to a process of preparing compounds of general formula (1), wherein all the symbols are as defined in the specification, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, and novel intermediates involved in their synthesis.

WO 2012/085935 A2

COMPOUNDS AS INHIBITORS OF RENIN

FIELD OF INVENTION

The present invention relates to novel renin inhibitors of general formula **(1)**, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts and pharmaceutical compositions containing them. The present invention also relates to a process of preparing compounds of general formula **(1)**, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, and novel intermediates involved in their synthesis.



(I)

BACKGROUND TO THE INVENTION

The biologically active angiotension II (Ang II) is generated by two step mechanism in the renin-angiotensin system (RAS). The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the action of less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT1 and AT2. AT1 seems to transmit most of the known functions of Ang II, the role of AT2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT1 blockers have been accepted to treat hypertension (Waeber B. *et* al, "The renin-angiotensin system: role in experimental and human hypertension", in Birkenhager W. H., Reid J. L. (eds): *Hypertension, Amsterdam, Elsevier Science Publishing Co,* **1986**, *489-519; Weber M. A., Am. J. Hypertens.,* **1992**, *5, 247S*). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et* al, *Kidney International,* **1994**, *45, 403*; Breyer J. A. *et* al. *Kidney International,* **1994**, *45, S156*), in the prevention of congestive heart failure. (Vaughan

D. E. *et al*, *Cardiovasc. Res.*, **1994**, *28, 159*; Fouad-Tarazi F. *et al.*, *Am. J. Med*, **1988**, *84 (Suppl. 3A), 83*) and myocardial infarction (Pfeffer M. A. *et* al, *N. Engl. J. Med.*, **1992**, *327, 669*).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, 9, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, 11, 1 155). In patients, inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et* al, *Annals of Internal Medicine*, **1992**, 117, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT1 receptor (e.g. using losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT_2) to Ang II, whose concentration is significantly increased by the blockade of AT1 receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT1 blockers with regard to efficacy in blocking the RAS and in safety aspects. Only limited clinical experience (Azizi M. *et al.*, J. *Hypertens.*, **1994**, 12, 419; Neutel J. M. *et al*, *Am. Heart*, **1991**, 122, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, 9, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only few compounds containing three to four chiral centers has entered clinical trials (Rahuel J. *et* al. *Chem. Biol.*, **2000**, 7, 493; Mealy N. E., *Drugs of the Future*, **2001**, 26, 1139). Thus, renin inhibitors with good oral bioavailability and long duration of action are required. The first class of non-peptide renin inhibitors were described in Oefner C. *et* al, *Chem. Biol*, **1999**, 6, 127; Patent Application WO97/0931 1 ; Marki H. P. *et* al., 11 *Farmaco*, **2001**, 56, 21 which showed high *in vitro* activity.

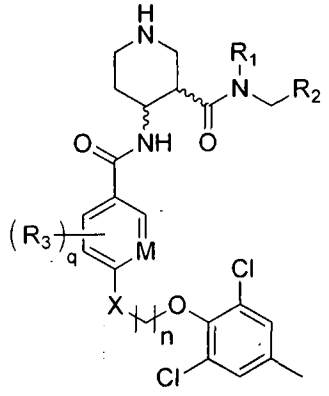
3,4-Disubstituted piperidine as renin inhibitors are reported in the literature (for e.g. in WO2008058387, WO2007088514). Our earlier patent application reported 3-carboxamide-4-benzamido piperdines as renin inhibitors (WO2010122580). The *in-vitro* IC_{50} of most of the compounds reported in this specification are in the range of 25-

100 nM in *in-vitro* fluorogenic substrate assay. Some of the reported compounds showed poor pharmacokinetic properties.

The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Described are orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis. The aim of the present invention is to improve *in- vitro* potency and also to overcome some of the problems in the earlier reported renin inhibitors such as problems with pharmacokinetics.

SUMMARY OF THE INVENTION

The present invention describes a group of novel compounds as renin inhibitors useful for the treatment cardiovascular events, renal insufficiency and other related diseases. The novel compounds are defined by the general formula **(1)** below:



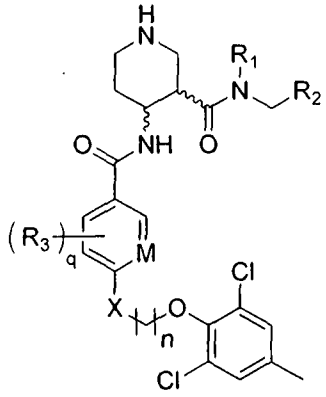
(I)

The compounds of the present invention are useful in the treatment of the human or animal body, by regulating renin levels. The compounds of this invention are therefore suitable for the treatment of cardiovascular events, renal insufficiency other related diseases. The present invention also discloses processes for the preparation of the compounds of formula (I) and also pharmaceutical compositions containing them and their use in medicine.

EMBODIMENTS OF THE PRESENT INVENTION

The main objective of the present invention thus is to provide novel compounds of general formula **(1)**, their stereoisomers, tautomers, solvates, novel intermediates

involved in their synthesis, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them or their mixtures as therapeutic agents.



(I)

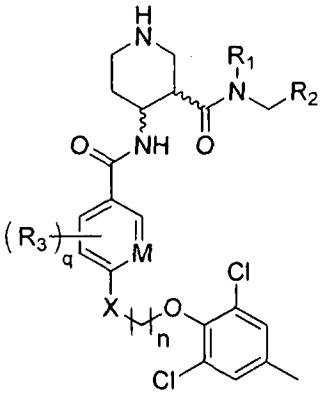
In an embodiment is provided processes for the preparation of novel compounds of general formula **(1)**, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

In another embodiment is provided pharmaceutical compositions containing compounds of general formula **(1)**, their pharmaceutically acceptable salts, comprising pharmaceutically acceptable carriers, solvents, diluents, excipients and other media normally employed in their manufacture.

In a further embodiment is provided the use of the novel compounds of the present invention as blood pressure regulating agents, by administering a therapeutically effective & non-toxic amount of the compounds of formula **(1)** or their pharmaceutically acceptable compositions to the mammals.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of the present invention are defined by the general formula **(I)** below:



(I)

wherein 'X' is independently selected from the group comprising of -CH_2-, O, and $S(O)_p$; p in each instance when it occurs is independently selected from the integers 0,1,2.

'n' is an integer selected from 1,2. 'M' is nitrogen or carbon atom;

R_3 at each occurrence is independently selected from the group comprising of OH, CN, halogen, N_3, NO_2, COOH, OCF_2H, CF_3, $C_{(1-6)}$ alkyl, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkoxy, $C(O)C_1$-C_6 alkyl, $C(O)OC_1$-C_6 alkyl, $S(O)_p$ $C_{(1-6)}$ alkyl or $(CH_2)_{1-2}O$-alkyl groups; Preferred groups may be selected from halogen, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy groups.

'q' represents an integer from 1-4 & 'p' is as defined earlier; In an embodiment, R_1 is optionally substituted C_1.C_6 alkyl, or C_3-C_7 cycloalkyl groups;

R_2 is an unsubstituted or substituted aryl ring, or an unsubstituted or substituted heterocyclyl ring containing from 1 to 3 heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein when R_2 is substituted, the substituents on the aryl ring or heterocyclyl ring comprises of one, two or three substituents independently selected from the group consisting of oxo, OH, CN, NH_2, halogen, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_4)_2$, $(CH_2)_{1-6}NHC(=O)OR_4$, $(CH_2)_{1-6}NHC(=O)R_4$, $C(=O)OR_4$, $C(=O)R_4$, $(CH_2)_{1-4}C(=O)$ NHR_4, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ Ar_1 Preferred substituents are selected from halogen, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $(CH_2)_{1-6}NHC(=O)OR_4$, $(CH_2)_{1-6}NHC(=O)R_4$.

In a further embodiment, R_1 and R_2 together with the nitrogen atom to which they attach may form a saturated, unsaturated or partly saturated single or fused heterocyclic ring which may optionally be substituted and which may further optionally contain one or more additional heteroatoms selected from nitrogen, oxygen or sulphur or may comprise an -SO- or an -SO_2-group. When the heterocyclic ring formed by R_1 & R_2 as defined above further comprises one or more nitrogen atom, such nitrogen atom may optionally be substituted with optionally substituted groups selected from C_1-C_8 alkyl, C_1-C_8 alkanoyl, optionally substituted aryl or heterocyclic group. When R_1 and R_2 together with the nitrogen atom forms a heterocyclic ring as define above, the heterocyclic ring may further be substituted with one or more optionally substituted aryl or heterocyclic group or the groups selected from haloalkyl, haloalkoxy, C_1-C_8-alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_4)_2$, $(CH_2)_1$.

$_6$NHC(=O)OR$_4$, $(CH_2)_{1-6}$NHC(=O) R_4, C(=O)OR$_4$ or –C(=O)R$_4$, $(CH_2)_{1-4}$C(=O) NHR$_4$, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$ and $(CH_2)_{1-5}OAr_1$, $(CH_2)_{0-4}$ Ar_1.

The term Ar_1 at each iteration, independently represents unsubstituted or substituted aryl or heterocyclyl ring substituted with one, two, three or four substituents independently selected from the group comprising of OH, CN, NH_2, halogen, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, C(O)NHC_1-C_6 alkyl, NHC(O)C_1-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_4)_2$, $(CH_2)_{1-6}$NHC(=O)OR$_4$, $(CH_2)_{1-6}$NHC(=O)R$_4$, C(=O)OR$_4$ or –C(=O)R$_4$, $CH_2(CH_2)_{0-4}$C(=O) NHR$_4$.

R_4 at each occurrence is independently selected from the group comprising of hydrogen, C_1-C_4 alkyl group C_1-C_4 haloalkyl, C_3-C_7 cycloalkyl groups.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1 to 4 hetero atoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur hetero atoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these hetero atoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" or the term "heteroaryl" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

The term heterocycle as used in the specification includes both aromatic and non-aromatic single or fused cyclic system containing at least one heteroatom selected from N, O, S. Examples of heterocycles include, but are not limited to, acridinyl,

azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

Suitable substituents wherever applicable includes, but are not limited to the following radicals, alone or in combination with other radicals, hydroxyl, oxo, halo, thio, nitro, amino, alkyl, alkoxy, haloalkyl or haloalkoxy groups;

In a further embodiment the groups, radicals described above may be selected from:

- the "alkyl" group used either alone or in combination with other radicals, denotes a linear or branched radical containing one to six carbons, selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, and the like;
- The term "alkenyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing two to twelve carbons; such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-

hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branched chains;

- The term "alkynyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing two to twelve carbons, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, and the like. The term "alkynyl" includes di- and tri-ynes;
- The term "alkoxy" used herein, either alone or in combination with other radicals, denotes a radical alkyl, as defined above, attached directly to an oxygen atom, such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like;
- The term "halo" or "halogen" used herein, either alone or in combination with other radicals, such as "haloalkyl", "perhaloalkyl" etc refers to a fluoro, chloro, bromo or iodo group. The term "haloalkyl" denotes an alkyl radical, as defined above, substituted with one or more halogens; such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups. The term "haloalkoxy" denotes a haloalkyl, as defined above, directly attached to an oxygen atom, such as fluoromethoxy, chloromethoxy, fluoroethoxy chloroethoxy groups, and the like.
- The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenyl.
- The term "$(CH_2)_0$" as employed in expressions such as "$(CH_2)_{0-4}$" means a direct covalent bond. Similarly, when an integer defining the presence of certain number of atoms in a group is equal to zero, it means that the atom adjacent thereto is connected directly by a bond.

The present invention can be used alone or in combination with at least one agent for the treatment of cardiovascular disease and related conditions and diseases as listed herein. The combination of present renin inhibitor can be made with following agents selected from the group consisting of HMG-Co-A reductase inhibitor,

angiotension converting enzyme (ACE) inhibitor, calcium channel blocker, aldosterone synthase inhibitor, aldoasterone antagonist, dual angiotension converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor, endothelin antagonist, angiotension II receptor blocker (ARB) and pharmaceutically acceptable salt thereof.

The term combination means that the component can be can be administrated together as a part of pharmaceutical composition or as part of same unitary dosage form.

List of Abbreviation

Boc: *tert*-Butyloxycarbonyl

DMF: Dimethyl formamide

DCM: Dichloromethane

EDAC.HCl : N-(3-Dimethyl aminopropyl)-N'-ethyl carbodiimide hydrochloride,

EDC: 1,2-Dichloroethane

HOBT: 1-Hydroxybenzotriazole

TFA: Trifluoroacetic acid

DCC: Dicyclohexylcarbodiimide

DIPEA: Disopropylethyl amine

EtOAc: Ethyl acetate

h: Hour(s)

min: Minute(s)

t_{ret}: Retention time

HCl : Hydrochloric acid

RT: Room temperature [25-30 ^{0}C]

MABP : Mean arterial blood pressure

ACN : Acetonitrile

Rf : Retention factor

Instrument details

Mass spectrum was recorded on LC-MS 2010-A Shimadzu. HPLC purity was determined by using agilent-1100 instrument.

HPLC condition:

HPLC Column: YMC J sphere C 18(150*4.6 mm) 4u

Mobile phase: 0.05 % TFA: ACN gradient.

Flow rate: 1.0 ml/min.

Wave length: UV at 220 nm.

Polar and Nonpolar isomers will be differentiated from HPLC t_{ret} time and on basis of Rf on Thin layer chromatography. Isomer with higher Rf value is considered nonpolar isomer and lower Rf value is considered as polar isomer.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Particularly useful compounds may be selected from

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-methoxybenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-3-(Cyclopropyl(2,3-dimethylbenzyl)carbamoyl)piperidin-4-yl)-6-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)nicotinamide dihydrochloride [Mixture of isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride. [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dichlorobenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-((4-fluoronaphthalen-1-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-((4-fluoronaphthalen-1-yl)methyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(3,5-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3,4-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3,4-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethoxybenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethoxybenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

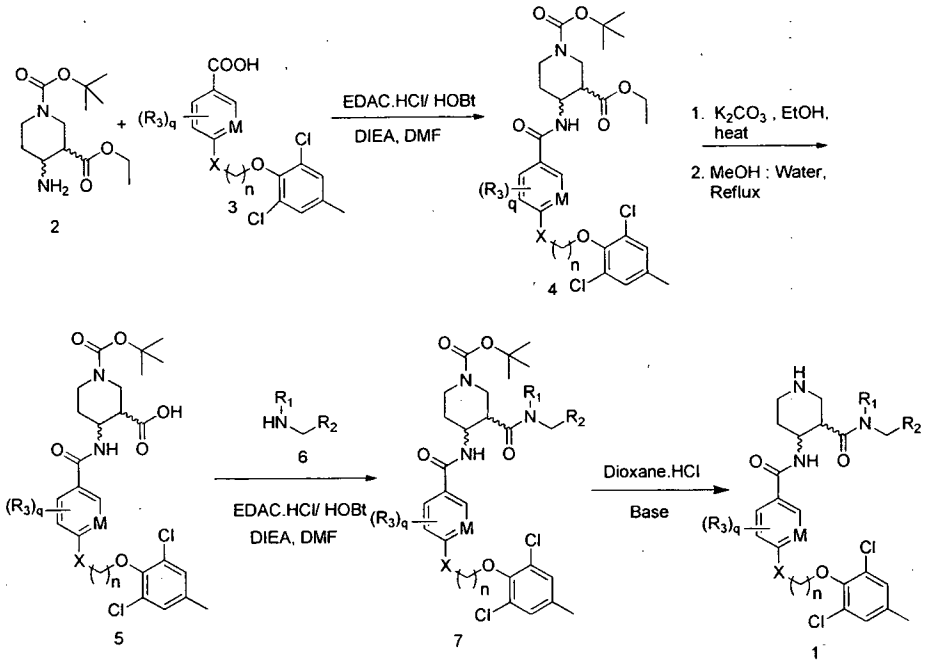
4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride.[Polar isomer];

The compounds of the present invention may be prepared using the methods described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art. Referred methods include, but are not limited to those described below, where all symbols are as defined earlier.

Scheme-I



1-*tert*-Butyl-3-ethyl-4-substituted benzamidopiperidine-1,3-dicarboxylate **(4)** where all symbols are as defined earlier, may be synthesized by reacting 1-*tert*-butyl 3-ethyl 4-aminopiperidine-1,3-dicarboxylate **(2)** with benzoic acid derivative **(3)** where all symbols are as defined earlier, using carboxyl group activating agents such as EDAC.HCl, dicyclohexyl carbodiimide and the like in the presence of an additive HOBT and base like triethyl amine or DIPEA in solvent(s) like DMF or DCM at temperature 0-25 ^{0}C. Epimerisation in **(4)** is carried out by using suitable base like sodium ethoxide, potassium carbonate and like in dry protic solvent(s) like methanol or ethanol at temperature 60-90 ^{0}C followed by hydrolysis of an ester group in **(4)** is carried out by treating with suitable base like lithium hydroxide, sodium hydroxide, potassium carbonate and the like in protic solvent(s) like methanol or ethanol at temperature 25-80 ^{0}C to afford piperidine-3-carboxylic acid derivative **(5)** where all symbols are as defined earlier. Diastereomeric mixture of 3-carboxamido piperidine **(7)** may be synthesized by reacting piperidine-3-carboxylic acid **(5)** with amine derivative **(6)** where all symbols are as described earlier, by using similar procedure described for preparation of compound **(4)**. Polar and non polar isomers were separated by using column chromatography technique. Deprotection of Boc group in piperidine **(7)** by using various Boc deprotecting reagents like TFA, dioxane.HCl, methanolic HCl and

the like at temperature 0-25 ^{0}C give corresponding salt of piperidine derivative **(1)** which upon treatment with base gives further piperidine derivative of formula **(1)**

The amine derivative of formula **[2]**, where all the symbols are as defined earlier can be synthesized by using (S)-1-phenylethanamine as per the general procedure mentioned in

WO2006066747 along with suitable variations as are well known to a skilled person. Similarly other two isomers may be synthesized by using amine derivative of formula **[2]**, by using (R)-1-phenylethanamine as per the general procedure mentioned in WO2006066747 along with suitable variations as are well known to a skilled person

The benzoic acid derivative **[3]**, where all the symbols are as defined earlier can be synthesized by variety of methods known to those skilled in the art following procedure set forth in reference such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, Comprehensive Organic Transformations, 2.nd edition Wiley- VCH, New York 1999; Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; Comprehensive Heterocyclic Chemistry II, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-1 1 ; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1–40, to name some of the known literature processes.

The acid building blocks required for synthesizing the compounds of the present invention are prepared as per the process given below:

Acid	Chemical Name
Acid 1	4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-2-methylbenzoic acid
Acid 2	4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzoic acid
Acid 3	2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzoic acid
Acid 4	4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzoic acid
Acid 5	4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-3-methoxybenzoic acid
Acid 6	6-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)nicotinic acid

Preparation of 4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-2-methylbenzoic acid. [Acid 1]

Step 1 : 2-(2,6-Dichloro-4-methyl-phenoxy)-ethanol.

2,6-Dichloro-4-methyl phenol (1 eq), ethylene carbonate (1.5 eq) and piperidine (0.1 eq) were combined and heated at 140 ^{0}C for 6 h to afford the title compound as brown oil.

Step 2: 2-(2,6-Dichloro-4-methylphenoxy)ethyl methanesulfonate.

2-(2,6-Dichloro-4-methyl-phenoxy)-ethanol (1 eq) obtained from step 1 above, and triethyl amine (3 eq) were taken up in 5 v of DCM. To this, then added methane sulfonyl chloride (1.2 eq) at 0-10 ^{0}C. Mixture was allowed to attain RT and stirred for 4-6 h. Mixture was diluted with water and compound was extracted with DCM. Combined organic layer was washed with brine and dried over sodium sulfate. Filtration and concentration of filtrate *in vacuo* afforded a brown solid compound.

Step 3: 4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-2-methylbenzoate.

2-(2,6-Dichloro-4-methylphenoxy)ethyl methanesulfonate (1 eq) obtained from step 2 above, and 2-methyl-4-hydroxy methyl benzoate (1 eq) were taken up in 5 v of DMF. To this anhydrous potassium carbonate (3 eq) was added and mixture was heated to 80-100 ^{0}C for 4-6 h. Mixture was diluted with water. Solid product obtained was filtered, washed with water, dried under *vacuo* which afforded title compound as off white solid.

Step 4: **Acid 1**

4-(2-(2,6-Dichloro-4-methylphenoxy)ethoxy)-2-methylbenzoate (1 eq) obtained from step 3 above, and lithium hydroxide (3 eq) were taken up in a mixture of THF : Water (5 v, 50 %). Mixture was stirred for 4-6 h at RT. Mixture was diluted with water, acidification with dil. HCl afforded title compound as white solid.

Acid 2:

Prepared similar to the procedure described in **Acid 1** but using 2-fluoro-4-hydroxy ethyl benzoate instead as a starting material.

Acid 3:

Prepared similar to the procedure described in **Acid 1** but using 2-chloro-4-hydroxy ethyl benzoate instead as a starting material.

Acid 4:

Prepared similar to the procedure described in **Acid 1** but using 3-fluoro-4-hydroxy ethyl benzoate instead as a starting material

Acid 5:

Prepared similar to the procedure described in **Acid 1** but using 3-methoxy-4-hydroxy ethyl benzoate instead as a starting material.

Acid 6:

Prepared similar to the procedure described in **Acid 1** but using ethyl 6-hydroxynicotinate instead as a starting material.

The amine building blocks were synthesized by the process described beneath.

Amine	Name
Amine 1	N-(2,3-Dimethylbenzyl)cyclopropanamine
Amine 2	N-(2-Chloro-4-fluorobenzyl)cyclopropanamine
Amine 3	N-(2,3-Dichlorobenzyl)cyclopropanamine
Amine 4	N-((2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)methyl)cyclopropanamine
Amine 5	N-(Naphthalen-1-ylmethyl)cyclopropanamine
Amine 6	N-((4-Fluoronaphthalen-1-yl)methyl)cyclopropanamine
Amine 7	N-(3,5-Dimethylbenzyl)cyclopropanamine
Amine 8	N-(2-Methoxy phenyl)cyclopropanamine
Amine 9	N-(3,4-Dimethylbenzyl)cyclopropanamine
Amine 10	N-(2-(3-Methoxypropoxy)benzyl)cyclopropanamine
Amine 11	N-(3-(3-Methoxypropoxy)benzyl)cyclopropanamine
Amine 12	N-(Naphthalen-2-ylmethyl)cyclopropanamine
Amine 13	N-(2,3-Dimethoxybenzyl)cyclopropanamine

Amine 1: N-(2,3-Dimethylbenzyl)cyclopropanamine.

Step 1. N-Cyclopropyl-2,3-dimethylbenzamide

To a solution of 2,3-dimethyl benzoic acid (1 eq) in DMF (5 v), was added HOBT (1. 5 eq). To this reaction mixture, was added EDAC.HCl (1.2 eq), cyclopropylamine (1.2 eq) and DIEA (1.5 eq) under N_2 at 0-5 ^{0}C. The resulting reaction mixture was stirred at RT for 16 h. Mixture was quenched in water, solid obtained was filtered, dried *in vacuo* to afford title compound as off white solid.

Step 2: **Amine 1**

N-Cyclopropyl-2,3-dimethylbenzamide (1 eq) obtained from step 1 above was dissolved in dry THF and boron dimethyl sulfide was added dropwise at 60 ^{0} C. After completion of reaction organic volatiles were removed *in vacuo*. Mixture was decomposed by adding 50 % HCl solution. Mixture was basified by adding ammonia solution. Compound was extracted with EtOAc (20 V x 2). Combined organic layer was washed with water, brine, dried over sodium sulfate and removed *in vacuo* afforded oily compound. Crude product thus was purified by the way of flash

chromatography (silica gel G; mobile phase Hexane to 50 % ethyl acetate in hexane). Title compound obtained as light yellow liquid.

Amine 2 : N-(2-Chloro-4-fluorobenzyl)cyclopropanamine.

Prepared similar to the procedure described in **Amine 1** but using 2-chloro-4-fluoro benzoic acid instead as a starting material.

Amine 3: N-(2,3-Dichlorobenzyl)cyclopropanamine.

Prepared similar to the procedure described in **Amine 1** but using 2,3-dichloro benzoic acid instead as a starting material.

Amine 4 :. N-((2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)methyl)cyclopropanamine

Prepared similar to the procedure described in **Amine 1** but using 2,3-dihydrobenzo[b][1,4]dioxine-5-carboxylic acid instead as a starting material.

Amine 5 : N-(Naphthalen-1-ylmethyl)cyclopropanamine.

Prepared similar to the procedure described in **Amine 1** but using 1-napthoic acid instead as a starting material.

Amine 6 :. N-((4-Fluoronaphthalen-1-yl)methyl)cyclopropanamine

Prepared similar to the procedure described in **Amine 1** but using 4-fluoro-1-napthoic acid instead as a starting material.

Amine 7 :. N-(3,5-Dimethylbenzyl)cyclopropanamine.

Prepared similar to the procedure described in **Amine 1** but using 3,5-dimethyl benzoic acid instead as a starting material.

Amine 8 :. N-(2-Methoxy phenyl)cyclopropanamine.

Prepared similar to the procedure described in **Amine 1** but using 2-methoxy benzoic acid instead as a starting material.

Amine 9 :. N-(3,4-Dimethylbenzyl)cyclopropanamine.

Prepared similar to the procedure described in **Amine 1** but using 3,4- dimethyl benzoic acid instead as a starting material.

Amine 10 :. N-(2-(3-Methoxypropoxy) benzyl)cyclopropanamine

A mixture of 2-(3-methoxypropoxy)benzaldehyde (1 eq), cyclopropyl amine (1.2 eq) and sodium bicarbonate (1.5 eq) were refluxed in methanol (10 v) for 1 h. The reaction mixture was then cooled in ice and sodium borohydride (1.2 eq) was introduced portion wise. After complete addition, mixture was allowed to warm to RT and stirred for 3 h. The volatiles were then removed *in vacuo* and the resulting residue was partitioned between water and DCM. The organic layer was separated, washed

with water, dried over sodium sulfate and filtered. Concentration of the organic layer *in vacuo* afforded the title compound as light yellow oil.

Purification of crude product thus obtained by the way of chromatography using (Silica, hexane to 40 % EtOAc in hexane) afforded title compound as light yellow oil.

Amine 11 :. N-(3-(3-Methoxypropoxy)benzyl)cyclopropanamine

Prepared similar to the procedure described in **Amine 10** but using 3-(3-methoxypropoxy)benzaldehyde instead as a starting material

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula **(1)** with suitable acids in suitable solvents by processes known in the art.

The invention is further exemplified by the following examples below, which provides some of the several preferred embodiments of the present invention. These examples are provided merely as representative embodiments and should not be construed to limit the scope of the invention in any way.

Example 1

Preparation of N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide. [Polar isomer]

Step 1: Ethyl 4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methyl benzamido) piperidine-3-carboxylate

To a solution of 4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzoic acid [1.3 g, 3.6 mmol] in 60 mL DMF, was added HOBT [0.94 g, 5.49 mmol]. To this reaction mixture, was added EDAC.HCl [0.91 g, 4.75 mmol], 1-*tert*-butyl 3-ethyl-4-amino piperidine-1,3-dicarboxylate [0.99 g, 3.66 mmol] and DIEA [1.41 g, 10.9 mmol] under nitrogen atmosphere at 0-5 ^{0}C. The resulting reaction mixture was stirred at RT for 16 h. Mixture was diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford thick liquid compound as a mixture of diastereomers. Purification of crude product was done by the way of column chromatography (SiO_2, hexane to 30 % EtOAc in hexane) to get oily compound (1.15 g, 52 %). The title compound was characterized by spectral analysis ESI-MS: 509 $(M)^+$; HPLC t_{ret} : 25.04 min.

Step 2: 1-(*Tert*-butoxycarbonyl)-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy) benzamido)piperidine-3-carboxylic acid.

A solution of ethyl 4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methyl benzamido) piperidine-3-carboxylate [1.15 g, 1.8 mmol] in methanol (5 v) and molecular sieves [4A^0] was refluxed for 2 h and anhydrous potassium carbonate [0.78 g, 3.0 mmol] was added and mixture was heated for another 5 h. Mixture was filtered through hyflow, methanol:water (4:1,(v/v)), potassium carbonate [0.78 g, 3.0 mmol] was added and mixture was refluxed for 16 h. Mixture was cooled to room temperature and quenched in water. Acidified the mixture to pH ~4 by using 5 % aq HCl. Solid obtained was filtered, washed with water and dried. The title compound was isolated as a mixture of diastereomers as white solid (0.86 g, 80 %) and characterized by spectral analysis. ESI-MS: 580.9 $(M)^+$; HPLC t_{ret} : 21.69 min.

Step 3: *tert*-Butyl 3-(cyclopropyl(2,3-dimethylbenzyl)carbamoyl)-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)piperidine-1-carboxylate.

To a solution of 1-(*tert*-butoxycarbonyl)-4-(4-(2-(2,6-dichloro-4-methylphenoxy) ethoxy) benzamido)piperidine-3-carboxylic acid [0.86 g, 1.48 mmol] in 15 mL DMF, was added HOBT [0.30 g, 2.2 mmol]. To this reaction mixture, was added EDAC.HCl [0.37 g, 1.9 mmol], N-(2,3-dimethybenzyl)cyclopropanamine [0.31 g, 1.7 mmol] and DIEA [0.48 g, 3.7 mmol] under nitrogen atmosphere at 0-5 ^{0}C. The resulting reaction mixture was stirred at RT for 16 h. Mixture was diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford thick liquid compound as a mixture of diastereomers. Both the diastereomers were separated by the way of column chromatography (SiO_2, hexane to 50 % EtOAc in hexane). Non polar isomer obtained (0.19 g, 18.11 %) as thick liquid and characterized by spectral analysis. ESI-MS: 739.2 $(M)^+$; HPLC t_{ret} : 27.33 min. Polar isomer obtained (0.425 g, 40 %) as a semisolid mass and characterized by spectral analysis ESI-MS : 739.8 $(M)^+$, HPLC t_{ret} 26.05 min.

Step 4: N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methyl benzamido) -N-(2,3-dimethylbenzyl)piperidine-3-carboxamide [Polar isomer]

To a solution of *tert*-butyl 3-(cyclopropyl(2,3-dimethylbenzyl)carbamoyl)-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)piperidine-1-carboxylate (Polar isomer). (0.46 g, 0.62 mmol) in 10 v of DCM was added Dioxane. HCl (4M, 20 eq) and mixture was stirred at RT for 2 h. Removal of organic volatiles afforded the title compound as hydrochloride salt. Treatment of this hydrochloride salt

with methanolic ammonia afforded title compound. The compound was characterized by spectral analysis. ESI-MS: 639.7 $(M+H)^+$; HPLC t_{ret} : 17.912 min.

Example 2 :

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 1** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 643.90 HPLC t_{ret} : 17.70 min.

Example 3 :

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-methoxybenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 5** and **Amine 1** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 654.1; HPLC t_{ret} : 17.23 min.

Example 4 :

N-3-(Cyclopropyl(2,3-dimethylbenzyl)carbamoyl)piperidin-4-yl)-6-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)nicotinamide dihydrochloride [Mixture of isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 6** and **Amine 1** as starting material. The title compound was obtained as sticky solid. ESI-MS: = $(M)^+$:625 HPLC t_{ret} : 17.30 min.

Example 5:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 1** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 638.60; HPLC t_{ret} : 18.26 min.

Example 6:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide [Non polar isomer]

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 1** as starting material. The title compound was obtained as thick oil. ESI-MS: = $(M+H)^+$: 642.2; HPLC t_{ret} : 18.19 min.

Example 7:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 1** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 642.3; HPLC t_{ret} : 17.88 min.

Example 8:

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy) ethoxy)-2-fluorobenzamido)piperidine-3-carboxamide hydrochloride [Non polar isomer]

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 2** as starting material. The title compound was obtained as thick oil. ESI-MS: = $(M+H)^+$: 666.2; HPLC t_{ret} : 18.32 min.

Example 9:

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy) ethoxy)-2-fluorobenzamido)piperidine-3-carboxamide hydrochloride [Polar isomer]

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 2** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 668.3; HPLC t_{ret} : 17.85 min.

Example 10:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride. [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 1** as starting material. The title compound was obtained as sticky solid. ESI-MS: = $(M+H)^+$: 642.3; HPLC t_{ret} : 18.39 min.

Example 11:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dichlorobenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 3** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 684.0; HPLC t_{ret} : 18.44 min.

Example 12:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 4** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 672.3; HPLC t_{ret}: 17.13 min.

Example 13:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 4** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 672.0; HPLC t_{ret}: 17.55 min.

Example 14:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 10** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 702.3; HPLC t_{ret}: 17.46 min.

Example 15:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 10** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+Na)^+$: 720.3; HPLC t_{ret}: 17.84 min.

Example 16:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 11** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$ 702.0; HPLC t_{ret}: 17.36 min.

Example 17:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 11** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 698.1; HPLC t_{ret} : 17.52 min.

Example 18:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 4** and **Amine 11** as starting material. The title compound was obtained as sticky solid. ESI-MS: = $(M)^+$: 702.3; HPLC t_{ret} : 17.87 min.

Example 19:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 11** as starting material. The title compound was obtained as light yellow oil. ESI-MS: = $(M)^+$: 698.2; HPLC t_{ret} : 18.09 min.

Example 20:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 5** as starting material. The title compound was obtained as low melting solid. ESI-MS: = $(M)^+$: 660.1; HPLC t_{ret} : 18.69 min.

Example 21:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 5** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 660.0; HPLC t_{ret} : 18.31 min.

Example 22:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 5** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 664.1; HPLC t_{ret} : 17.81 min.

Example 23 :

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy) ethoxy)-2-methylbenzamido)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 2** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 664.1; HPLC t_{ret} : 18.01 min.

Example 24:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-((4-fluoronaphthalen-1-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 6** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 682.1; HPLC t_{ret} : 17.77 min.

Example 25:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-((4-fluoronaphthalen-1-yl)methyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 6** as starting material. The title compound was obtained as low melting solid. ESI-MS: = $(M+H)^+$: 682.0; HPLC t_{ret} : 18.35 min.

Example 26:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 1** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 658.1; HPLC t_{ret} : 17.78 min.

Example 27:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 1** as starting material. The title compound was obtained as low melting solid. ESI-MS: = $(M+H)^+$: 660.2; HPLC t_{ret} : 18.19 min.

Example 28:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 5** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 682.1; HPLC t_{ret} : 17.98 min.

Example 29:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 5** as starting material. The title compound was obtained as sticky solid. ESI-MS: = $(M+H)^+$: 682.4; HPLC t_{ret} : 18.23 min.

Example 30:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 10** as starting material. The title compound was obtained as thick oil. ESI-MS: = $(M+H)^+$: 702.3; HPLC t_{ret} : 17.89 min.

Example 31:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 10** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 702.2; HPLC t_{ret} : 17.38 min.

Example 32:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(3,5-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 2** and **Amine 7** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 642.1; HPLC t_{ret} : 17.83 min.

Example 33:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3,4-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 9** as starting material. The title compound was obtained as sticky solid. ESI-MS: = $(M)^+$: 638.2; HPLC t_{ret} : 18.32 min.

Example 34:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3,4-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 9** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 638.1; HPLC t_{ret} : 17.90 min.

Example 35:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 8** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 640.1; HPLC t_{ret} : 17.26 min.

Example 36:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 8** as starting material. The title compound was obtained as oil. ESI-MS: = $(M)^+$: 640.3; HPLC t_{ret} : 17.61 min.

Example 37:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer]

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 12** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 660.3; HPLC t_{ret} : 18.44 min.

Example 38:

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 1** and **Amine 12** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 660.3; HPLC t_{ret} : 17.94 min.

Example 39:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethoxybenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 13** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 692.1; HPLC t_{ret} : 17.52 min.

Example 40:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethoxybenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 13** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 692.1; HPLC t_{ret} : 17.06 min.

Example 41:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 12** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 682.2; HPLC t_{ret} : 17.91 min.

Example 42:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 12** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M)^+$: 680.1; HPLC t_{ret} : 18.26 min.

Example 43:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 4** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 690.2; HPLC t_{ret} : 17.21 min.

Example 44:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 4** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 690.0; HPLC t_{ret} : 17.36 min.

Example 45:

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride.[Polar isomer].

Prepared similar to the procedure described in Example 1 but using instead **Acid 3** and **Amine 8** as starting material. The title compound was obtained as off white solid. ESI-MS: = $(M+H)^+$: 660.1; HPLC t_{ret} : 17.38 min

Biological Data:

In-vitro protocol for the Inhibition of human recombinant renin by the compound of invention

Procedure: The enzymatic *in vitro* assay was performed in 96 well polypropylene plate (Nunc), using a modified renin inhibitor screening assay protocol (Cayman, cat no:10006270). The reaction system comprised assay buffer containing 50 mM Tris-HCL, pH=8.0 & 100 mM sodium chloride, human recombinant rennin (1:20 diluted with fixed activity), synthetic renin substrates (Cayman, cat no:10006906) (14.4 µM) and different concentrations of renin inhibitors in DMSO in a total reaction system of 100µl. The entire reaction mixture were incubated at 37^0C for 30 mins and the fluorescence was read at excitation wavelengths of 320-360 nm and emission wavelengths of 490-520 nm. Test compounds efficacy was determined by the percent inhibition of renin activity using Aliskiren (Tekturna) as a reference standard.

The following table shows the percentage renin inhibition of selected compounds at 0.1 μM and 0.01 μM concentration.

Compounds	0.1μM	0.01μM
Example 4	76	31
Example 9	67	8.5
Example 14	90	31
Example 15	82	29
Example 41	69.6	46
Example 42	100	65.5

Following table represents measured IC_{50} values of the selected compounds for its inhibition of human recombinant renin.

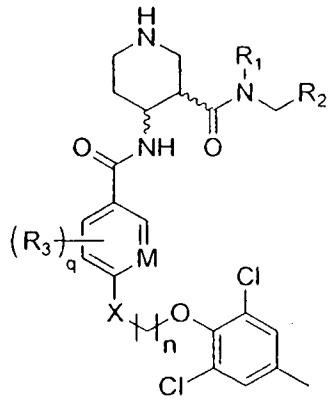
Compounds	IC_{50} nM
Example 11	12.7
Example 12	15.4
Example 21	13.9
Example 26	10.8
Example 28	6
Example 31	9.9
Example 35	31.6
Example 40	20.3

Anaesthetized Guinea pig model.

Experimental procedure: Guinea pigs were treated with furosemide in drinking water (5 mg/Kg/day) for four days and intramuscular injection (10 mg/Kg) at 18 and 3 h before experiment. There after they were anaesthetized by using intramuscular injection of xylazine and ketamine (7:70 mg/Kg mixture). The left or right jugular vein was exposed and cannulated for intraperitonial [i.p.] administration of the NCEs. The left or right carotid artery was exposed and cannulated for recording blood pressure using Biopac system. 0 (vehicle control), 30 mg/kg of NCEs were administered and change in blood pressure from pretreatment was measured.

We Claim

1. Compound represented by the formula **(1)**, including their stereoisomers, tautomers,



(I)

& solvates

wherein 'X' is independently selected from the group comprising of $-CH_2-$, O, and $S(O)_p$; p in each instance when it occurs is independently selected from the integers 0,1,2; 'n' is an integer selected from 1,2. 'M' is nitrogen or carbon atom; R_3 at each occurrence is independently selected from the group comprising of OH, CN, halogen, N_3, NO_2, COOH, OCF_2H, CF_3, $C_{(1-6)}$ alkyl, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkoxy, $C(O)C_1$-C_6 alkyl, $C(O)OC_1$-C_6 alkyl, $S(O)_p$ $C_{(1-6)}$ alkyl or $(CH_2)_{1-2}O$-alkyl groups; 'q' represents an integer from 1-4 & 'p' is as defined earlier; R_1 is optionally substituted C_1.C_6 alkyl, or C_3-C_7 cycloalkyl groups; R_2 is an unsubstituted or substituted aryl ring, or an unsubstituted or substituted heterocyclyl ring containing from 1 to 3 heteroatoms independently selected from oxygen, sulfur and nitrogen or in an alternate embodiment, R_1 and R_2 together with the nitrogen atom to which they attach forms an optionally substituted saturated, unsaturated or partly saturated single or fused heterocyclic ring which is optionally substituted and further optionally contains one or more additional heteroatoms selected from nitrogen, oxygen or sulphur or comprises an -SO- or an $-SO_2$-group wherein further one or more of such nitrogen atoms is optionally substituted with optionally substituted groups selected from C_1-C_8 alkyl, C_1-C_8 alkanoyl or an optionally substituted aryl or heterocyclic group.

2. The compounds as claimed in claim 1 wherein the substituents on R_2 are independently selected from oxo, OH, CN, NH_2, halogen, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_4)_2$, $(CH_2)_{1-6}NHC(=O)OR_4$, $(CH_2)_{1-6}NHC(=O)R_4$, $C(=O)OR_4$, $C(=O)R_4$, $(CH_2)_{1-4}C(=O)$ NHR_4, $(CH_2)_0$-

Compd. Id.	MABP (mm/Hg) reduction at 30 mg/Kg dose
Example 1	17
Example 2	13
Example 3	16
Example 22	13
Example 24	18

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula **(1)** according to this invention.

The quantity of active component, that is, the compounds of formula **(1)** according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration.

This class of compounds showed nano molar potency in *invitro* fluorogenic substrate assay with an excellent PK profile which is translated in to the *in vivo efficacy*. The representative example 7 showed IC_{50}=9.2 nM and Cmax : 498 ng, AUC(0-t) : 2.5 µg, %F : 22 [Pk performed at 30 mg/Kg oral dose in C57 mice]. In anaesthetized Guinea pig model it showed 21 mm reduction in blood pressure at 30 mg/kg dose.

$_4O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ Ar_1, wherein the group representing Ar_1 at each iteration, independently represents unsubstituted or substituted aryl or heterocyclyl ring and the group R_4 at each occurrence is independently selected from the group comprising of hydrogen, C_1-C_4 alkyl group, C_1-C_4 haloalkyl, C_3-C_7 cycloalkyl groups..

3. The compounds as claimed in claim 1 wherein when R_1 and R_2 together with the nitrogen atom forms a heterocyclic ring, the heterocyclic ring further is substituted with one or more optionally substituted aryl or heterocyclic group or the groups selected from haloalkyl, haloalkoxy, C_1-C_8-alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_4)_2$, $(CH_2)_{1-6}NHC(=O)OR_4$, $(CH_2)_{1-6}NHC(=O)$ R_4, $C(=O)OR_4$ or $-C(=O)R_4$, $(CH_2)_{1-4}C(=O)$ NHR_4, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$ and $(CH_2)_{1-5}OAr_1$, $(CH_2)_{0-4}$ Ar_1, wherein Ar_1 & R_4 is as defined above.

4.. The compounds as claimed in preceding claims wherein the substitutions on Ar_1 are selected from OH, CN, NH_2, halogen, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_4)_2$, $(CH_2)_{1-6}NHC(=O)OR_4$, $(CH_2)_{1-6}NHC(=O)R_4$, $C(=O)OR_4$ or $-C(=O)R_4$, $CH_2(CH_2)_{0-4}C(=O)$ NHR_4, R_4 is as defined above

5. The compounds as claimed in claim 1 wherein the R_3 groups are selected from halogen, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy groups.

6. The compounds as claimed in any preceding claims wherein the substituents on R_2 are selected from halogen, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $(CH_2)_{1-6}NHC(=O)OR_4$, $(CH_2)_{1-6}NHC(=O)R_4$.

7. The compounds of any preceding claims selected from

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-methoxybenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-3-(Cyclopropyl(2,3-dimethylbenzyl)carbamoyl)piperidin-4-yl)-6-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)nicotinamide dihydrochloride [Mixture of isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy) ethoxy)-2-fluorobenzamido)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride. [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2,3-dichlorobenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-3-fluorobenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-(2-Chloro-4-fluorobenzyl)-N-cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-((4-fluoronaphthalen-1-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-((4-fluoronaphthalen-1-yl)methyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-1-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(2-(3-methoxypropoxy)benzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-fluorobenzamido)-N-(3,5-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3,4-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(3,4-dimethylbenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

N-Cyclopropyl-4-(4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)-2-methylbenzamido)-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethoxybenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2,3-dimethoxybenzyl)piperidine-3-carboxamide hydrochloride [Non polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(naphthalen-2-ylmethyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

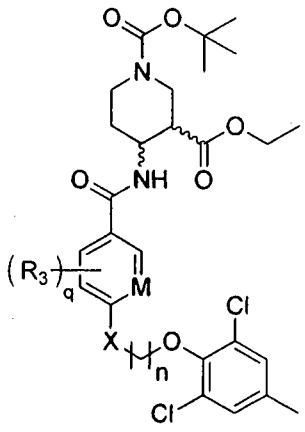
4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)piperidine-3-carboxamide hydrochloride [Non Polar isomer];

4-(2-Chloro-4-(2-(2,6-dichloro-4-methylphenoxy)ethoxy)benzamido)-N-cyclopropyl-N-(2-methoxybenzyl)piperidine-3-carboxamide hydrochloride.[Polar isomer].

8. The compounds of any of the preceding claims suitably formulated into a suitable pharmaceutical composition. 9. The compounds of the preceding claims suitable as renin inhibitors.

10. The use of compounds of formula **(1)** for preparing pharmaceutical compositions suitable for treatment of diseases wherein the renin enzyme has a patho physiological function.
11. The pharmaceutical composition containing renin inhibitors of the present invention.
12. The pharmaceutical composition containing the compounds of the present invention for the treatment of hypertension.
13. A method of treating hypertension and associated disease conditions by treatment with the compounds of the present invention to a person in need thereof.
14. The compounds of the present invention include all the stereoisomer and mixture thereof.
15. A pharmaceutical composition comprising compounds of formula (I) in combination with one or more pharmaceutically active agent selected from group consisting of HMG-Co-A reductase inhibitor, angiotension converting enzyme (ACE) inhibitor, calcium channel blocker, aldosterone synthase inhibitor, aldoasterone antagonist, dual angiotension converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor, endothelin antagonist, angiotension II receptor blocker (ARB) and pharmaceutically acceptable salts thereof.
16. The use of the pharmaceutical composition as claimed in claim 15for the treatment of cardiovascular and other allied disorders.
17. An intermediate of formula **4** and their isomers



(4)

wherein the symbols R_3, X, M, n, q, are as defined in claim 1.