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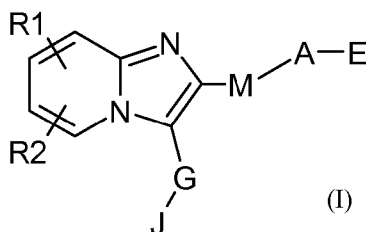
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(57) Abstract: Disclosed are small molecule inhibitors which are useful in treating various diseases and conditions involving chymase.

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Chymase Inhibitors

Application Data

This application claims benefit to US provisional application serial no. 60/828,441 filed
5 October 6, 2006.

Field of the Invention

The invention relates to small molecule inhibitors which are useful in treating various
diseases and conditions involving Chymase.

10

Background of the Invention

In cardiac tissue of cardiomyopathic patients, transforming growth factor- β (TGF- β),
which has been demonstrated to stimulate cardiac fibrosis in animal models (Kuwahara,
et al. Circulation, 2002, 106, 130), is increased (Li et al., Circulation, 1997, 96, 874). In
15 the myocardial fibrotic area, it is known that mast cells are increased in number and may
contribute to the development of fibroblast proliferation in cardiac tissues of patients with
cardiomyopathy (Patella et al., Circulation, 1998, 97, 971). Chymase is a chymotrypsin-
like serine protease contained in the secretory granules of mast cells. Although the
precise physiological roles of Chymase have not been completely revealed, Chymase is
20 known to transform angiotensin I to angiotensin II and may contribute to activation of
TGF- β , matrix proteases, and cytokines (Taipale et al., J. Biol. Chem., 1995, 270, 4689;
Takai et al., Life Sci., 1996, 58, 591; Takai et al., Circulation, 1999, 100, 654).

A potent and selective Chymase inhibitor may have potential use as a treatment of chronic heart failure, atherosclerosis, restenosis, and myocardial infarction by inhibiting local production of angiotensin II in the heart and release of TGF- β , two independent
5 mediators of cardiac remodeling. An inhibitor may also have potential use for treatment of mast cell mediated diseases such as dermatitis, asthma, chronic obstructive pulmonary disease (COPD), and pulmonary inflammation, since Chymase is implicated in microvascular leakage, neutrophil accumulation, the stimulation of mucus secretion, and the modulation of cytokines (He et al., Eur. J. Pharmacol., 1998, 352, 91).

10

Several small molecule Chymase inhibitors have been reported to be efficacious in the cardiomyopathic hamster model of heart failure (Takai et al. J. Pharmacol. Exp. Ther. 2003, 305, 17), in carotid artery injury by a balloon catheter in dogs (Takai et al. J. Pharmacol. Exp. Ther, 2003, 304, 841), and in the hamster left anterior descending
15 coronary artery ligation model of heart failure (WO 03/018061). Additionally, a Chymase inhibitor has been demonstrated to be efficacious in a sheep asthma model (WO 2005/073214). However, there is no example of commercialization of a Chymase inhibitor as a medicament.

20 SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a small molecule a Chymase inhibitor as defined herein, and pharmaceutical compositions thereof.

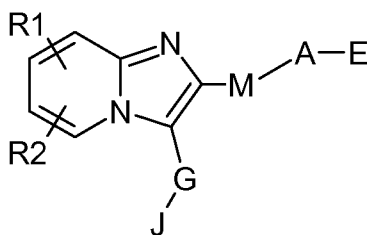
25 It is also an object of the invention to provide methods of using said Chymase inhibitors to treat various diseases and conditions related thereto.

It is a further object of the invention to provide processes of preparing said Chymase inhibitors.

30

DETAILED DESCRIPTION OF THE INVENTION

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



5

(I)

R1 and **R2** are independently hydrogen, halogen, trihaloalkyl, trihaloalkoxy, cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CORd, -COORd, -CON(Rc)Rd, -N(Rc)Rd, -N(Rc)CORd wherein each Rd is independently a hydrogen, C₁₋₆ linear or branched alkyl or cycloalkyl, C₁₋₆ linear or branched alkenyl or heterocyclyl or where R1 and R2 together represent -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-, wherein each group is optionally independently substituted with one to three substituents chosen from C₁₋₄ acyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, dialkylamino, cyano, carboxy, carboxamido, halogen, hydroxyl and phenyl optionally substituted with halogens;

15

A is C₁₋₇ linear, branched or cyclic alkyl group optionally interrupted by one or more -O-, -S-, -SO-, -SO₂- and -NRa- optionally substituted with one to three substituents chosen from halogen, C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkoxy, C₁₋₆ linear or branched alkylthio, C₁₋₆ linear or branched alkylsulfonyl, phenyl and oxo;

20

E is -COORe, -SO₃Re, -CONHRe, -SO₂NHRe, -NHCO₂Re, -CONHCO₂Re, -SO₂NHCO(Rf), heteroaryl, heterocyclyl, wherein each Re is independently hydrogen, C₁₋₄ alkyl or aryl, and Rf is C₁₋₄ alkyl or aryl;

25

G is C₁₋₆ linear or branched alkyl optionally interrupted by one or more of -O-, -S-, -SO₂ or -NRa-, wherein the alkyl group is optionally substituted with hydroxyl, cyano, C₁₋₆ linear or branched alkyl or C₁₋₆ linear or branched alkoxy;

M is a methylene group, oxygen, -N(Rb)-, or -S(O)_m-, where m is an integer of 0-2; and, wherein the said methylene group is optionally substituted by one to two substituents chosen from hydroxyl, cyano, C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkoxy, trihalomethyl, trihalomethoxy, phenyl and oxo;

5

J is an optionally mono- or poly-substituted aromatic carbocycle or a heteroaromatic group having 4-10 carbon atoms containing one or more hetero atoms chosen from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom in its ring(s); each substituent on said aromatic or heteroaromatic groups is chosen from halogen, hydroxyl, cyano, C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkoxy, C₁₋₆ linear or branched alkylthio, C₁₋₆ linear or branched alkylsulfonyl, phenylsulfonyl, C₁₋₆ linear or branched acyl, C₁₋₆ linear or branched acylamino, trihalomethyl, trihalomethoxy, phenyl, oxo, -COORa, -CON(Rc)Ra, SO₂N(Rc)Ra, -N(Rc)Ra and phenoxy optionally substituted by one or more halogens;

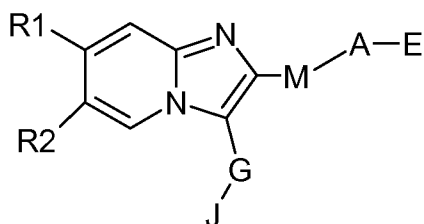
15

Ra, Rb and Rc are each independently C1-3 alkyl or hydrogen;

or the pharmaceutically acceptable salts thereof.

20 In another embodiment there is provided a compound according to the embodiment immediately above and wherein:

R1 and **R2** are attached as follows:



25

and are independently hydrogen, Cl, Br, F, I, trihaloalkyl, trihaloalkoxy cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CORd, -COORd, -CON(Rc)Rd, -N(Rc)Rd, -N(Rc)CORd wherein each Rd is independently a hydrogen, C₁₋₆ linear or branched alkyl or cycloalkyl,

C₁₋₆ linear or branched alkenyl or heterocyclyl chosen from pyrrole, pyrrolidinyl, pyrazole, imidazole, furan, tetrahydrofuran, oxazole, thiophene, tetrahydrothiophene and thiazole wherein for each ring possessing a sulfur heteroatom the sulfur is -S-, -S(O)- or -S(O)₂-, or where R1 and R2 together represent -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-,

wherein each group is optionally independently substituted with one to three substituents chosen from C₁₋₄ acyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, dialkylamino, cyano, carboxy, carboxamido, Cl, Br, F, I, hydroxyl and phenyl optionally substituted with one to three Cl, Br, F, I;

A is C₁₋₇ linear, branched optionally independently substituted with one to three substituents chosen from amino, cyano, carboxy, carboxamido, halogen, hydroxyl, nitro, phenyl, C₁₋₆ linear or branched alkyl and C₁₋₆ linear or branched alkoxy;

E is -COOR_e, -SO₃R_e, -CONHR_e, -CONHSO₂R_e, -SO₂NH-CO(R_f), tetrazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 5-oxo-1,2,4-thiadiazol-3-yl, 5-thioxo-1,2,4-oxadiazol-3-yl, 5-thioxo-1,2,4-thiadiazol-3-yl, 3-oxo-1,2,4-oxadiazol-5-yl, N3,5-dioxo-5-oxadiazolidino, 2-oxo-1,3,4-oxadiazol-2-yl, 3-oxo-1,2,4-triazol-5-yl or 2,dioxo-benzothiadiazin-6-yl, wherein each R_e is independently hydrogen, C₁₋₄ alkyl or phenyl, and R_f is C₁₋₄ alkyl or aryl;

G is C₁₋₄ linear or branched alkyl optionally substituted with a substituent chosen from hydroxyl, a cyano, C₁₋₆ linear or branched alkyl and C₁₋₆ linear or branched alkoxy ;

M is a methylene group, oxygen, -N(R_b)-, or -S(O)_m-, where m is an integer of 0-2;

J is an optionally mono- or di-substituted phenyl, naphthyl, benzothienyl, benzopyrrolyl, benzimidazolyl, indolyl; each substituent on said aromatic or heteroaromatic groups is chosen from halogen, hydroxyl, cyano, C₁₋₄ linear or branched alkyl, C₁₋₄ linear or branched alkoxy, C₁₋₆ linear or branched alkylthio, C₁₋₆ linear or branched alkylsulfonyl, phenylsulfonyl, C₁₋₆ linear or branched acyl, C₁₋₆ linear or branched acylamino,

trihalomethyl, trihalomethoxy, phenyl, oxo, -COORa, -CON(Rc)Ra, -SO₂N(Rc)Ra, N(Rc)Ra and phenoxy optionally substituted by one or more halogens.

In another embodiment there is provided a compound according to the embodiment
5 immediately above and wherein:

R1 and **R2** are independently hydrogen, Cl, F, trihalomethyl, trihalomethoxy, cyano, hydroxyl, C₁₋₂ alkyl, C₁₋₄ alkoxy, -CORd, -CON(Rc)Rd, -N(Rc)Rd, -N(Rc)CORd
10 wherein each Rd is independently a hydrogen or C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkenyl, furan, tetrahydrofuran, thiophene and tetrahydrothiophene wherein for each ring possessing a sulfur heteroatom the sulfur is -S-, -S(O)- or -S(O)₂- or where R1 and R2 together represent -O-CH₂-CH₂-O-, wherein each group is optionally independently substituted with one to three substituents chosen from C₁₋₄ alkyl, C₁₋₄ alkoxy amino, cyano, carboxy, carboxamido, Cl, Br, F, I, and
15 hydroxyl;

A is a -(CH₂)₃-group, optionally substituted with one substituent chosen from phenyl and C₁₋₃ alkyl;

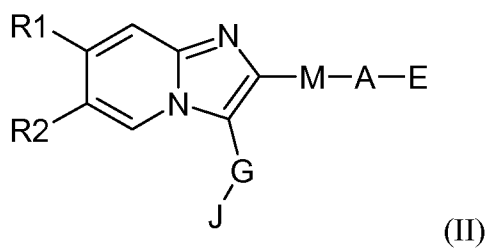
20 **E** is -COORE wherein Re is hydrogen or methyl;

G is C₁₋₂ alkyl;

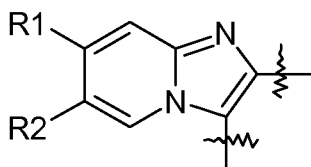
M is a methylene group, oxygen, -NH-, -N(CH₃)- or sulfur;

25 **J** is naphthyl, benzothienyl, benzopyrrolyl, benzimidazolyl, indolyl each optionally substituted with one to three groups chosen from halogen, hydroxyl, cyano and C₁₋₆ linear or branched alkyl.

In another generic aspect of the invention, there is provided a compound of the formula
30 (II):



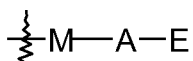
wherein for the Formula (II), the component



5

is chosen from A1 – A8 in the table I below; in combination with any

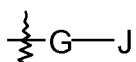
10 component



chosen from B1 – B19 in the table I below;

15

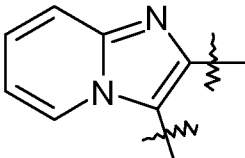
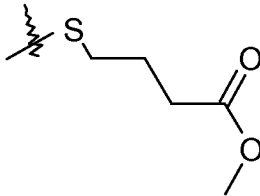
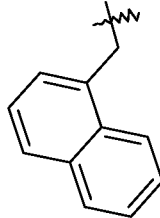
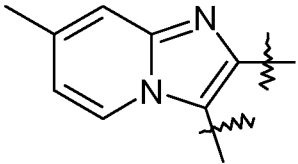
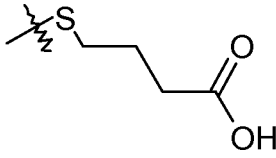
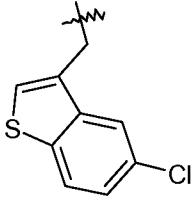
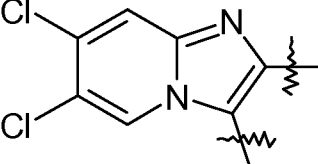
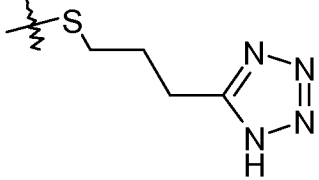
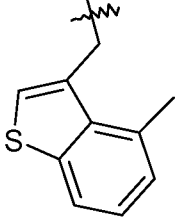
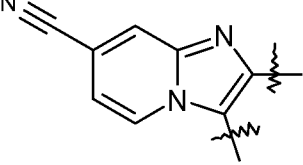
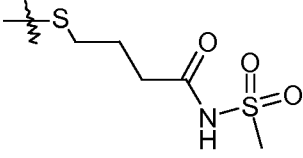
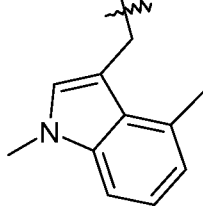
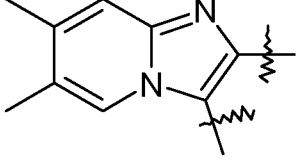
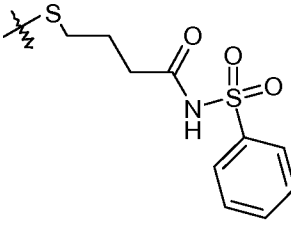
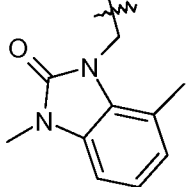
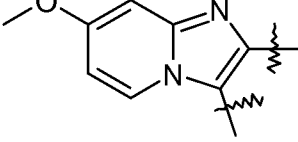
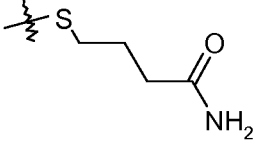
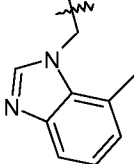
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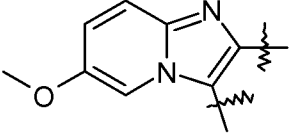
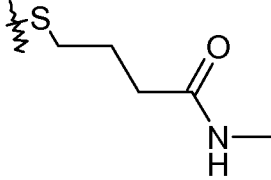
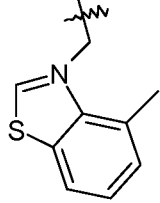
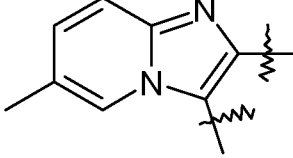
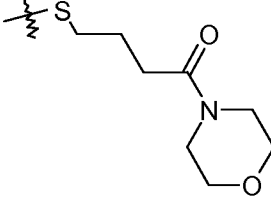
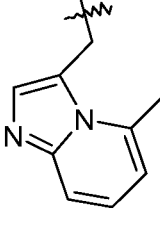
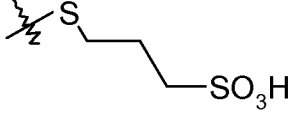
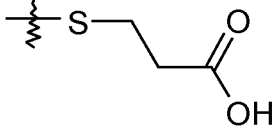
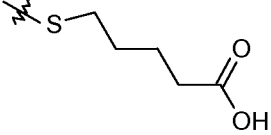
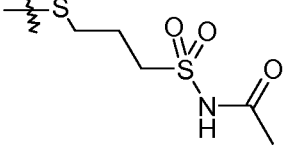
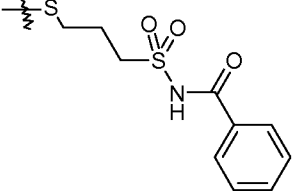


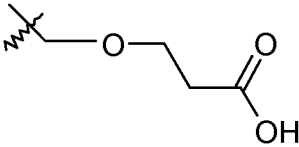
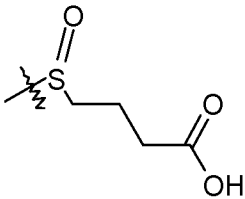
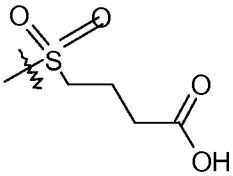
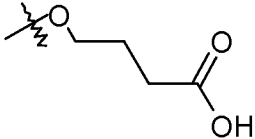
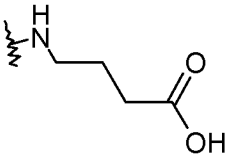
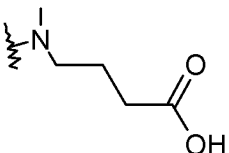
20 chosen from C1 – C8 in the table I below;

Table I

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A1		B1		C1	
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	
A5		B5		C5	
A6		B6		C6	

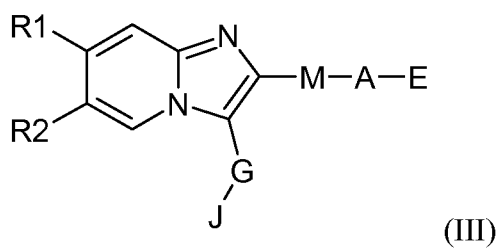
A7		B7		C7	
A8		B8		C8	
		B9			
		B10			
		B11			
		B12			
		B13			

		B14			
		B15			
		B16			
		B17			
		B18			
		B19			

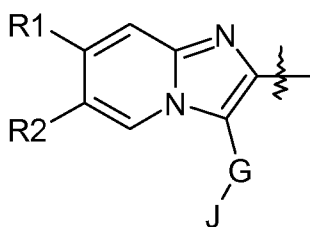
or the pharmaceutically acceptable salts thereof.

In another generic aspect of the invention, there is provided a compound of the formula

5 (III):



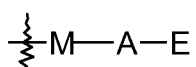
wherein for the Formula (III), the component



5

is chosen from A1 – A15 in the table I below; in combination with any

10 component

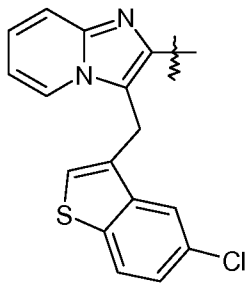
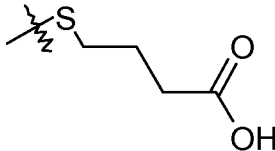
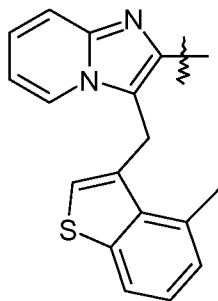
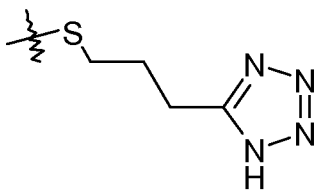
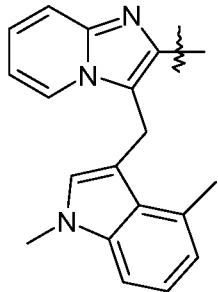
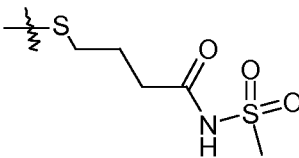
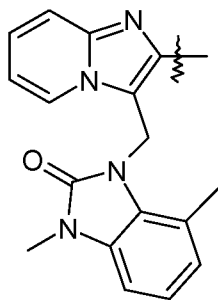
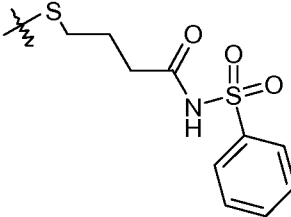


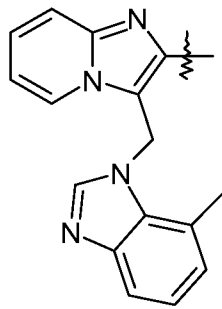
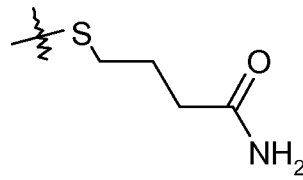
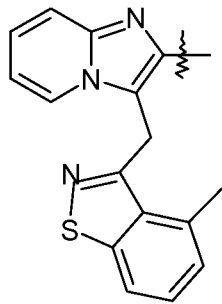
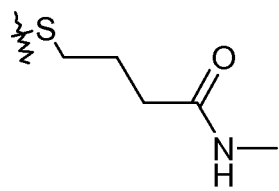
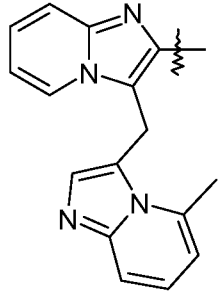
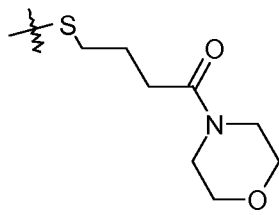
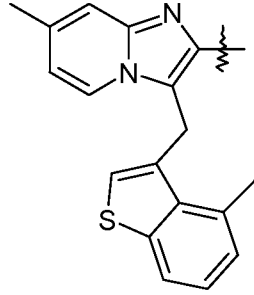
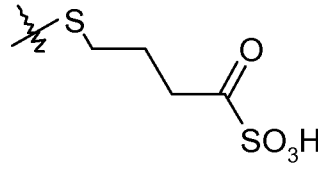
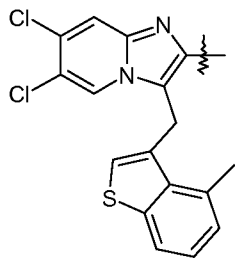
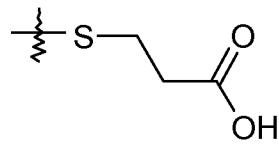
chosen from B1 – B19 in the table II below;

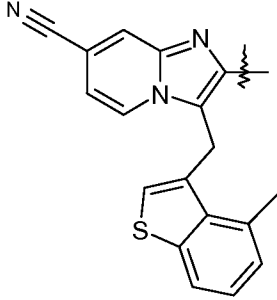
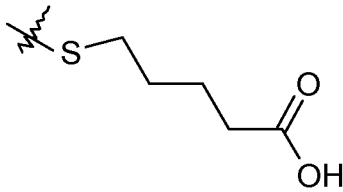
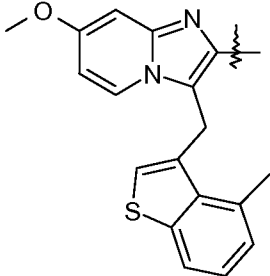
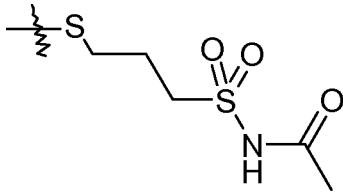
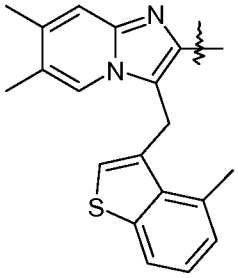
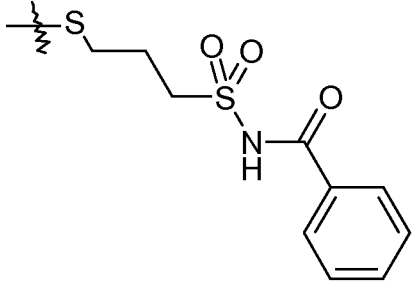
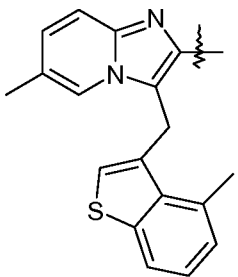
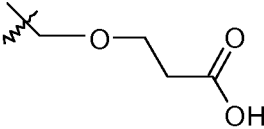
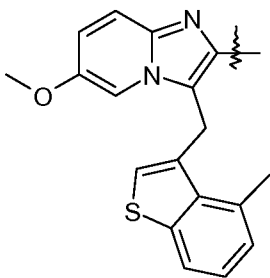
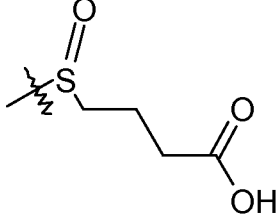
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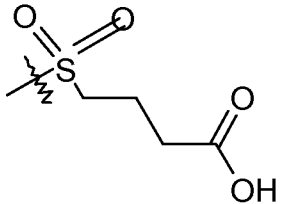
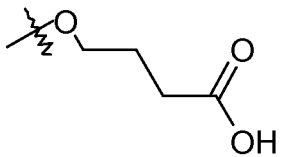
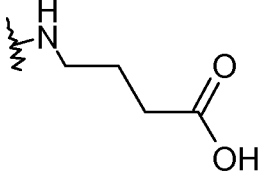
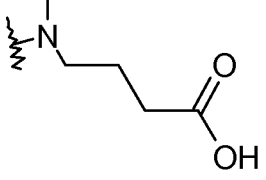
Table II

A1		B1	

<p>A2</p>		<p>B2</p>	
<p>A3</p>		<p>B3</p>	
<p>A4</p>		<p>B4</p>	
<p>A5</p>		<p>B5</p>	

<p>A6</p>		<p>B6</p>	
<p>A7</p>		<p>B7</p>	
<p>A8</p>		<p>B8</p>	
<p>A9</p>		<p>B9</p>	
<p>A10</p>		<p>B10</p>	

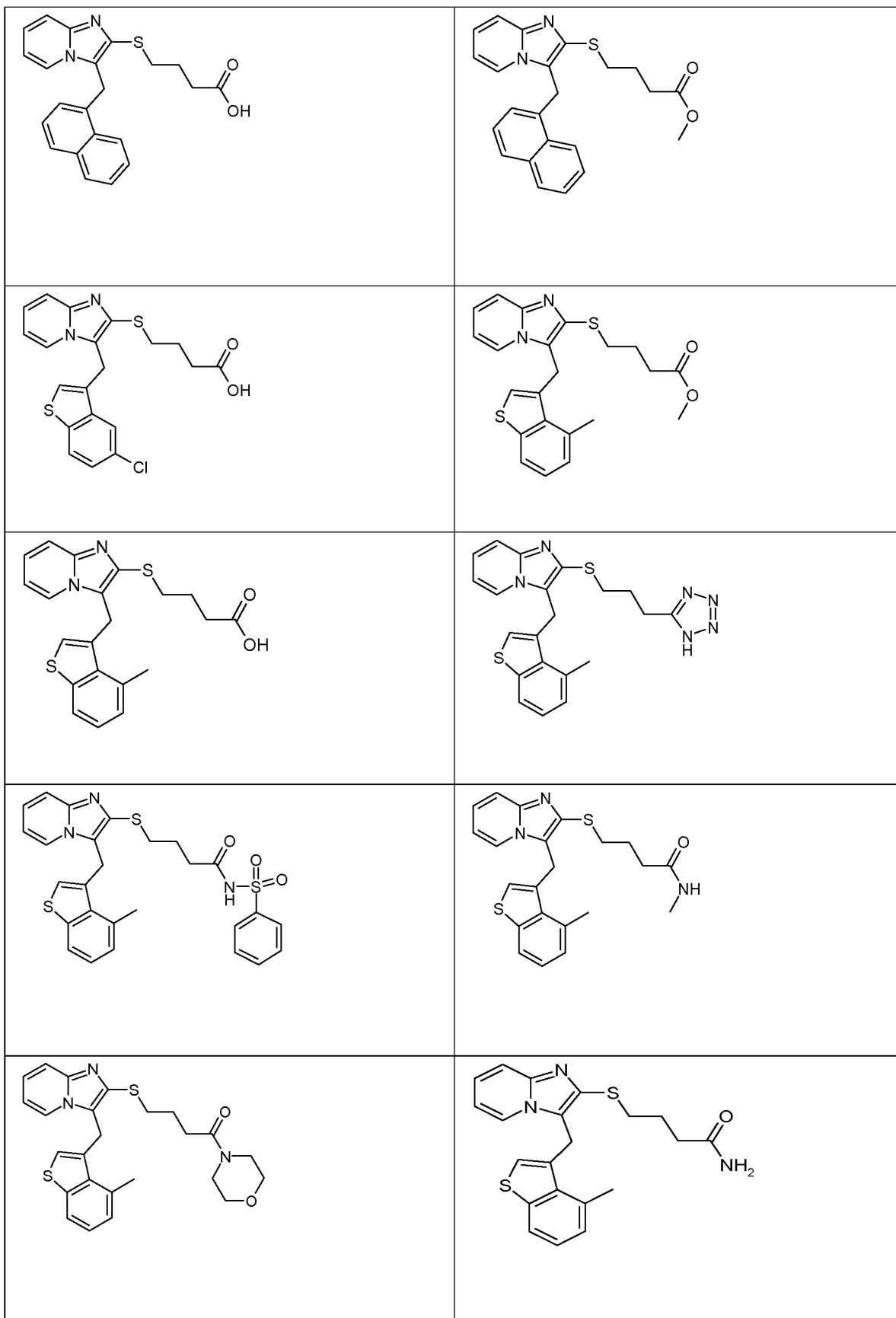
A11		B11	
A12		B12	
A13		B13	
A14		B14	
A15		B15	

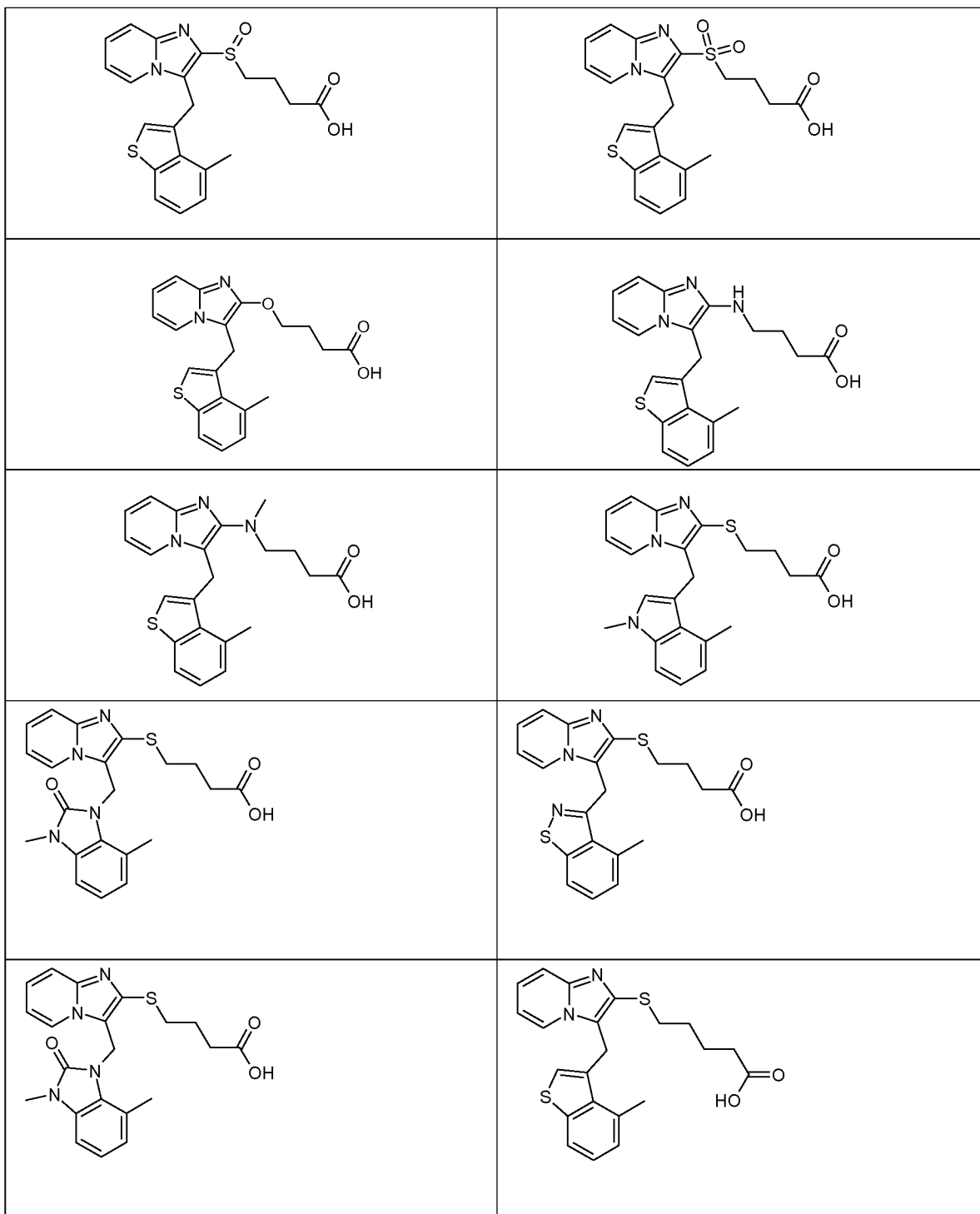
		B16	
		B17	
		B18	
		B19	

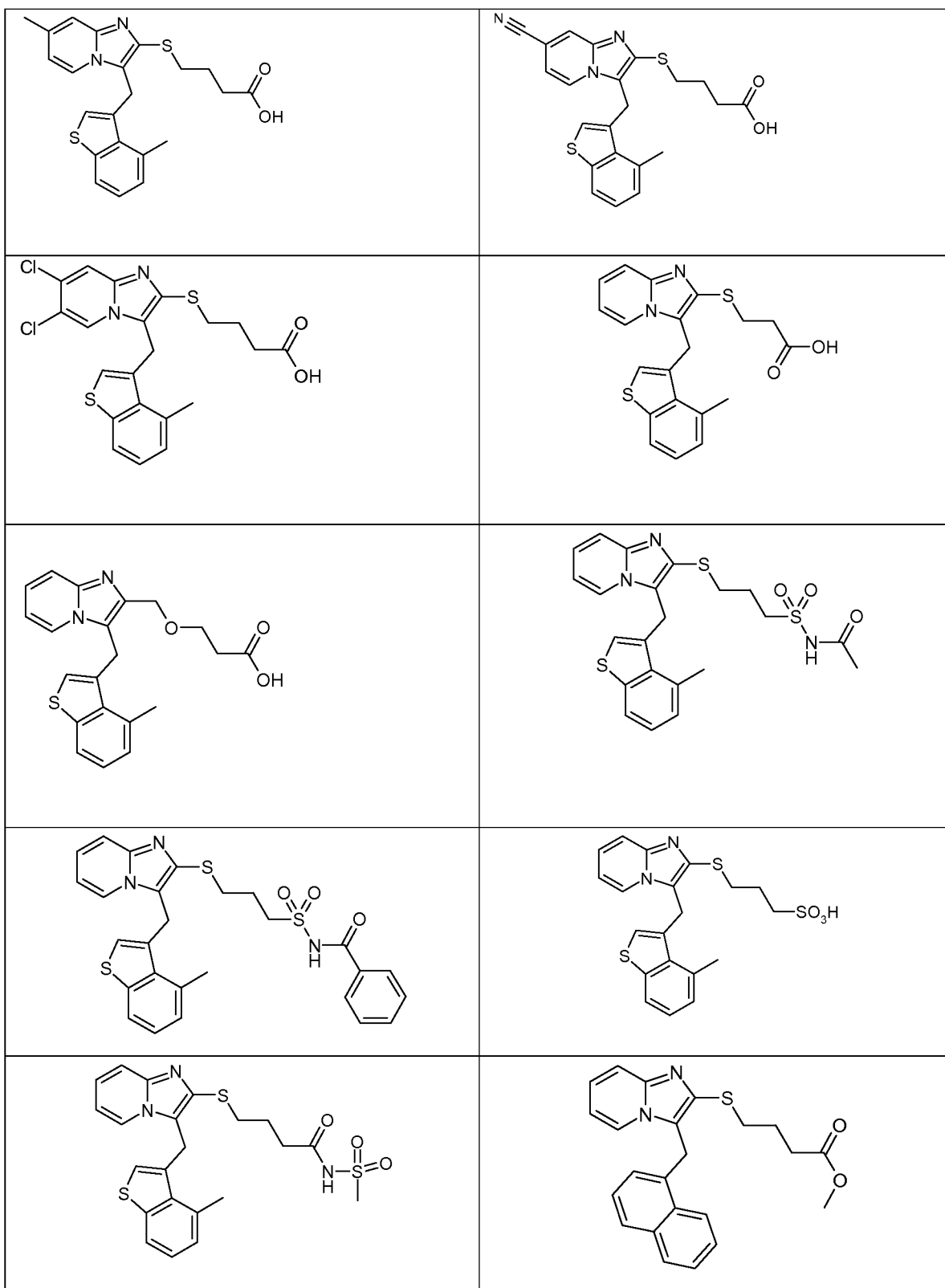
or the pharmaceutically acceptable salts thereof.

In another embodiment of the invention there is provided the following compounds, in
5 table III , which can be made according to the general synthetic procedures and examples
which follow:

Table III





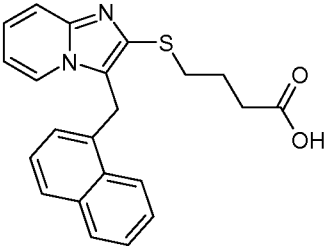
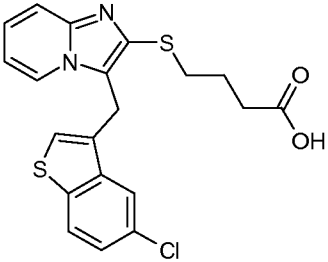
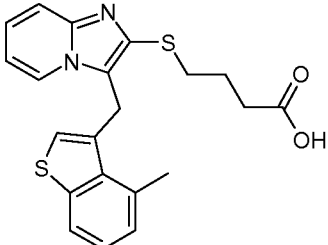
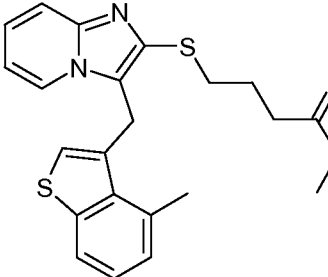


or the pharmaceutically acceptable salts thereof.

In another embodiment of the invention there is provided the following preferred compounds, in table IV, which can be made according to the general synthetic procedures and examples which follow:

5

Table IV

 <p>Chymase IC₅₀=195 nM</p>	 <p>Chymase IC₅₀= 425 nM</p>
 <p>Chymase IC₅₀= 32 nM</p>	 <p>Chymase IC₅₀= 945 nM</p>

10 or the pharmaceutically acceptable salts thereof.

In all the compounds disclosed hereinabove in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

15

The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each

stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of formula (I), (II) or (III) can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, C₁₋₄alkoxy includes the organic radical C₁₋₄alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, butoxy.

All organic radicals: alkyl, alkenyl and alkynyl groups, or such groups which are incorporated in other radicals such as acyl and alkoxy, shall be understood as being branched or unbranched where structurally possible and unless otherwise specified, and may be partially or fully halogenated.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A cyclic group shall be understood to mean carbocycle, heterocycle or heteroaryl, each may be partially or fully halogenated.

An acyl group is a radical defined as -C(O)-R, where R is an organic radical or a cyclic group. Acyl represents, for example, carbocyclic or heterocyclic aroyl, cycloalkylcarbonyl, (oxa or thia)-cycloalkylcarbonyl, lower alkanoyl, (lower alkoxy, hydroxy or acyloxy)-lower alkanoyl, (mono- or di- carbocyclic or heterocyclic)-(lower alkanoyl or lower alkoxy-, hydroxy- or acyloxy- substituted lower alkanoyl), or biaroyl.

Carbocycles include hydrocarbon rings containing from three to fourteen carbon atoms. These carbocycles may be either aromatic either aromatic or non-aromatic ring systems.

The non-aromatic ring systems may be mono- or polyunsaturated, monocyclic, bicyclic or tricyclic and may be bridged. Preferred carbocycles include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, benzyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl, benzocycloheptanyl, adamantyl, norbornyl, fluorene, and benzocycloheptenyl. Certain terms for cycloalkyl such as cyclobutanyl and cyclobutyl shall be used interchangeably.

The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or non-aromatic 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Unless otherwise stated, heterocycles include but are not limited to, for example pyrrolidinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, dioxalanyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone.

The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms such as N,O and S. Unless otherwise stated, such heteroaryls include aziridinyl, thienyl, furanyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, quinoxalanyl, indolyl, benzimidazolyl, benzoxazolyl, benzopyrrolyl, benzothiazolyl, benzothienyl, quinolinyl, quinazolinyl, naphthyridinyl, indazolyl, triazolyl, pyrazolo[3,4-*b*]pyrimidinyl, purinyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, tubercidinyl, oxazo[4,5-*b*]pyridinyl, tetrazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 5-oxo-1,2,4-thiadiazol-3-yl, 5-thioxo-1,2,4-oxadiazol-3-yl, 5-thioxo-1,2,4-thiadiazol-3-yl, 3-oxo-1,2,4-oxadiazol-5-yl, N3,5-dioxo-5-oxadiazolidino, 2-

oxo1,3,4-oxadiazol-2-yl, 3-oxo1,2,4-triazol-5-yl, 2,dioxo-benzothiadiazin-6-yl, 1,2-dioxo-3-hydroxy-3-cyclobuten-4-yl, and imidazo[4,5-*b*]pyridinyl.

5 The term “heteroatom” as used herein shall be understood to mean atoms other than carbon such as oxygen, nitrogen, sulfur and phosphorous.

As used herein, “nitrogen” and “sulfur” include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen. All heteroatoms in open chain or cyclic radicals include all oxidized forms.

10

In all alkyl groups or carbon chains one or more carbon atoms can be optionally replaced by heteroatoms: O, S or N, it shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can
15 be substituted as herein above described by groups such as oxo to result in definitions such as but not limited to: alkoxy-carbonyl, acyl, amido and thioxo.

The term “aryl” as used herein shall be understood to mean aromatic carbocycle or heteroaryl as defined herein. Each aryl or heteroaryl unless otherwise specified includes
20 it’s partially or fully hydrogenated derivative and/or is partially or fully halogenated. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include its hydrogenated derivatives such as tetrahydronaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

25

The term “halogen” as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine, preferably fluorine. The definitions “partially or fully halogenated”; partially or fully fluorinated; “substituted by one or more halogen atoms”, includes for example, mono, di or tri halo derivatives on one or more carbon
30 atoms. For alkyl, a nonlimiting example would be -CH₂CHF₂, -CF₃ etc.

The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the inventive methods disclosed herein.

5

The invention includes pharmaceutically acceptable derivatives of compounds of formula (I), (II) or (III). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the formula (I), (II) or (III).

15

Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(C₁-C₄ alkyl)₄⁺ salts.

25

In addition, within the scope of the invention is use of prodrugs of compounds of the formula (I). Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a

30

prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

The compounds described herein are either commercially available or can be made by methods and any necessary intermediates well known in the art .

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

10

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials used in the scheme below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

15

GENERAL SYNTHETIC METHODS

The invention also provides processes for making compounds of Formula (I), (II) and (III). In all schemes, unless specified otherwise, R1, R2, A, E, G, M and J in the formulas below shall have the meaning of R1, R2, A, E, G, M and J in Formula (I), (II) and (III) of the invention described herein above.

Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC), if desired, and intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.

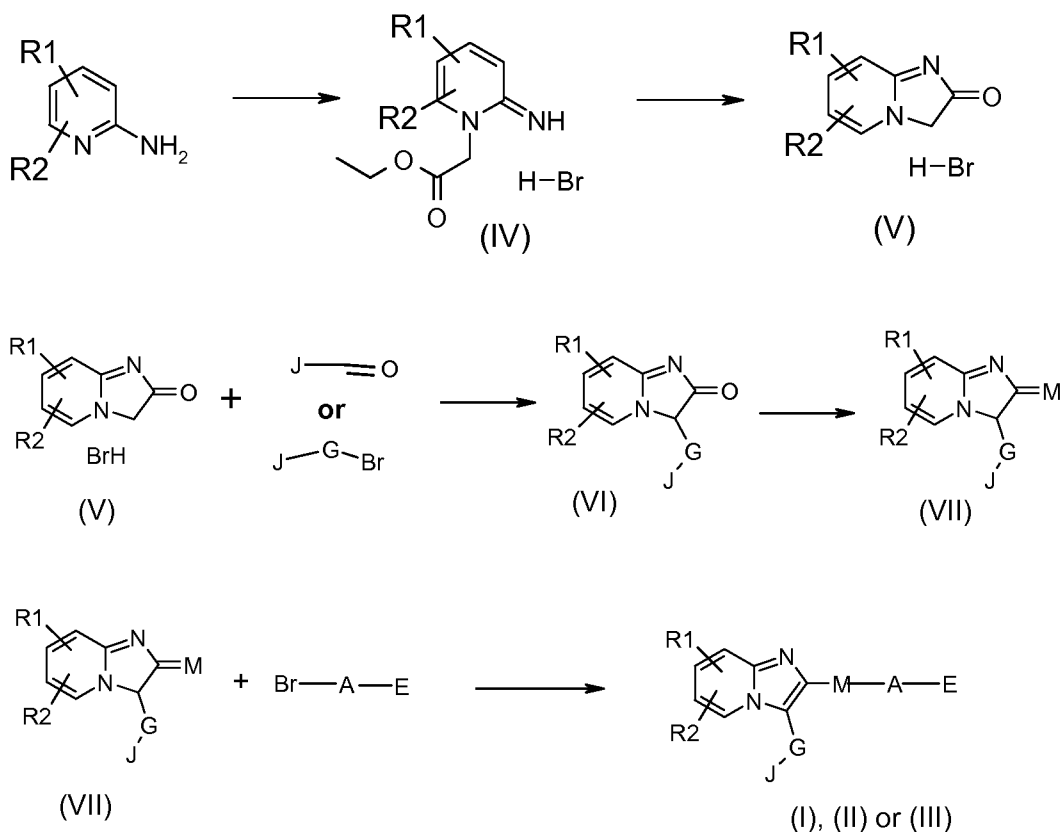
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The appropriately substituted starting materials and intermediates used in the preparation of compounds of the invention are either commercially available or readily prepared by methods

known in the literature to those skilled in the art, and are illustrated in the synthetic examples below.

Compounds of Formula (I), (II) and (III) may be synthesized by the method illustrated in

5 Scheme 1



10

Scheme 1

Reaction of an optionally substituted 2-amino pyridine with ethylbromoacetate in a suitable solvent provides an imino pyridinyl compound of formula (IV). Cyclization of the imino pyridinyl compound, by heating in a suitable solvent, provides an intermediate imidazo pyridinone of formula (V). Reacting the intermediate of formula (V) with an aldehyde J-CHO, followed by reduction using a suitable reducing agent, provides an alkylated intermediate of formula (VI) wherein G = CH₂. Alternatively, alkylation of the intermediate (V) with a suitable alkylating agent J-G-Br provides the intermediate of formula (VI).

15
20
Reacting the intermediate of formula (VI) with a suitable reagent, such as Lawesson's reagent, in a suitable solvent, provides a thione of formula (VII). Reaction of the intermediate

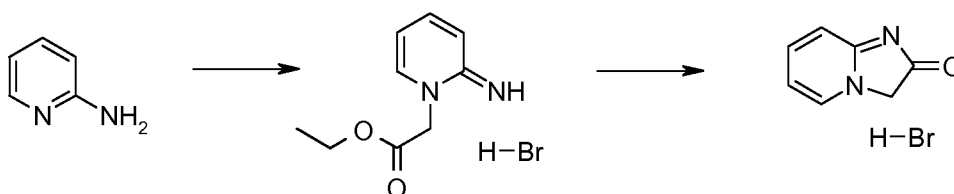
thione of formula (VII) with Br-A-E, in a suitable solvent, provides compounds of formula (I), (II) or (III).

Further modification of the initial product of formula (I) or (II) by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of this invention.

Example 1: Synthesis of 4-(3-Naphthalen-1-ylmethyl-2,3-dihydro-imidazo[1,2-a]pyridin-2-ylsulfanyl)-butyric acid

Synthesis of imidazo[1,2-a]pyridin-2-one hydrobromide salt

10



(2-Imino-2H-pyridin-1-yl)-acetic acid ethyl ester hydrobromide salt

To 39 mL (0.35 mol) of ethyl bromoacetate is added 9.4 g (0.1 mol) of 2-aminopyridine portionwise at 0°C. The resulting mixture is allowed to warm to room temperature and stirred at this temperature for 30 minutes. The precipitate is collected and washed with hexane to give the desired compound as light tan solid.

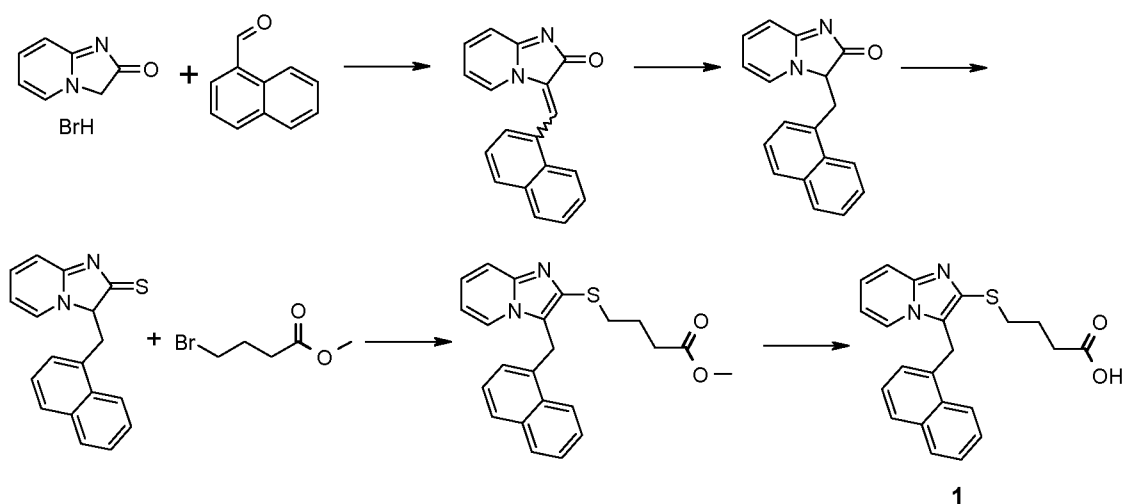
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Imidazo[1,2-a]pyridin-2-one hydrobromide salt

A solution of 9g (34.4 mmol) of (2-imino-2H-pyridin-1-yl)-acetic acid ethyl ester

20

hydrobromide salt in 200 mL of ethanol is heated at reflux for 18h. The reaction mixture is then cooled to room temperature and the precipitate is collected. The isolated solid is washed with ethanol to give the desired compound.



3-[1-Naphthalen-1-yl-meth-ylidene]-imidazo[1,2-a]pyridin-2-one

A mixture of 1g (4.7 mmol) of imidazo[1,2-a]pyridin-2-one hydrobromide salt and 726 mg (4.7 mmol) of 1-naphthaldehyde in 20 mL of ethanol is heated at reflux for 1h and then cooled to room temperature. The precipitate is collected. The isolated solid is suspended in 40 mL of 2M potassium carbonate solution and the resulting mixture is stirred for 48 h at room temperature. The precipitated solid is collected and washed with water to give the desired compound.

10

3-Naphthalen-1-ylmethyl-imidazo[1,2-a]pyridin-2-one

To a suspension of 137 mg (3.7 mmol) of sodium borohydride in 15 mL of ethanol is added a solution of 500mg (1.8 mmol) of 3-[1-naphthalen-1-yl-methylidene]-imidazo[1,2-a]pyridin-2-one in 50 mL of methanol, dropwise at -78°C . After stirring for 10 min at -78°C , the reaction mixture is quenched with saturated aqueous ammonium chloride solution at -78°C . The product is extracted with dichloromethane. The organic layer is dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the desired compound.

15

3-Naphthalen-1-ylmethyl-imidazo[1,2-a]pyridine-2-thione

A suspension of 200 mg (0.73 mmol) of 3-naphthalen-1-ylmethyl-imidazo[1,2-a]pyridin-2-one and 250 mg (0.62 mmol) of 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) in 20 mL of toluene is heated at 160°C for 1h under microwave condition. The resulting mixture is dissolved in methanol and absorbed on silica gel. The slurry is dried under reduced pressure and is purified by flash chromatography on

20

silica gel. The compound is eluted 5~10 % methanol in dichloromethane solution to give the desired compound.

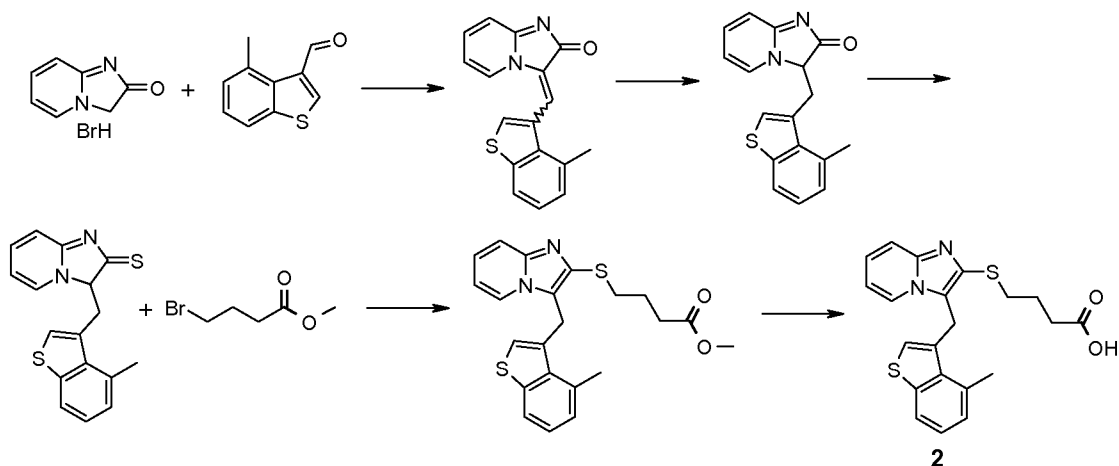
4-(3-Naphthalen-1-ylmethyl-2,3-dihydro-imidazo[1,2-a]pyridin-2-ylsulfanyl)-butyric acid
5 methyl ester

A mixture of 75 mg (0.26 mmol) of 3-naphthalen-1-ylmethyl-imidazo[1,2-a]pyridine-2-thione and 70 mg (0.39 mmol) of methyl 4-bromobutyrate and 72 mg (0.52 mmol) of potassium carbonate in 3 mL of 50% acetone in dichloromethane is stirred at room temperature for 18 h. The mixture is concentrated *in vacuo* and the residue is purified by
10 flash chromatography on silica gel eluting with 50~75% ethyl acetate in hexanes to give the desired compound.

4-(3-Naphthalen-1-ylmethyl-2,3-dihydro-imidazo[1,2-a]pyridin-2-ylsulfanyl)-butyric acid

A solution of 50 mg (0.13 mmol) of 4-(3-naphthalen-1-ylmethyl-2,3-dihydro-imidazo[1,2-
15 a]pyridin-2-ylsulfanyl)-butyric acid methyl ester in 2mL of THF is treated with a solution of 11 mg (0.26 mmol) of lithium hydroxide monohydrate in 1mL of water at room temperature. The resulting mixture is heated to 40⁰C, and stirred at this temperature for 3 h. Then the reaction mixture is cooled to room temperature and concentrated *in vacuo*. The residue is diluted with water and neutralized with 1N HCl solution. The product is extracted with ethyl
20 acetate, and the organic layer is separated. The organic layer is washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography eluting with 3~10 % methanol in dichloromethane solution to give the title compound. LCMS (ESMS): m/z 377 (M+H⁺)

25 **Example 2: Synthesis of 4-[3-(4-Methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid**



3-(4-Methyl-benzo[b]thiophen-3-ylmethylene)-imidazo[1,2-a]pyridin-2-one

A mixture of 1.6 g (7.4 mmol) of imidazo[1,2-a]pyridin-2-one hydrobromide salt and 1.2 g
 5 (6.7 mmol) of 4-methyl-benzo[b]thiophene-3-carbaldehyde in 40 mL of ethanol is heated at reflux for 1h and then cooled to room temperature. The precipitate is collected. The isolated solid is suspended in 40 mL of 2M potassium carbonate solution and the resulting mixture is stirred for 48h at room temperature. The solid is collected and washed with water to give the desired compound.

10

3-(4-Methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-one

To a suspension of 121 mg (3.2 mmol) of sodium borohydride in 50 mL of ethanol is added a
 solution of 624 mg (2.1 mmol) of 3-(4-methyl-benzo[b]thiophen-3-ylmethylene)-
 imidazo[1,2-a]pyridin-2-one in 50 mL of methanol dropwise at -78°C . After stirring for 15
 15 minutes at -78°C , the reaction mixture is quenched with saturated aqueous ammonium
 chloride solution at -78°C . The product is extracted with dichloromethane. The organic layer
 is dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the desired
 compound.

3-(4-Methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridine-2-thione

A suspension of 475 mg (1.6 mmol) of 3-(4-methyl-benzo[b]thiophen-3-ylmethyl)-
 imidazo[1,2-a]pyridin-2-one and 525 mg (1.3 mmol) of 2,4-bis-(4-methoxyphenyl)-1,3-
 dithia-2,4-diphosphetane 2,4-disulfide in 20 mL of toluene is heated at 170°C for 90 minutes

under microwave condition. The precipitated solid is collected to give the desired compound.

4-[3-(4-Methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid methyl ester

5

A mixture of 472 mg (1.5 mmol) of 3-(4-methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridine-2-thione and 407 mg (2.3 mmol) of methyl 4-bromobutyrate and 415 mg (3.0 mmol) of potassium carbonate in 5 mL of DMF is stirred at room temperature for 18 h. The mixture is diluted with water and the product is extracted with ethyl acetate. The organic layer is washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel eluted with 1~5% methanol in dichloromethane to give the desired compound.

10

4-[3-(4-Methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid

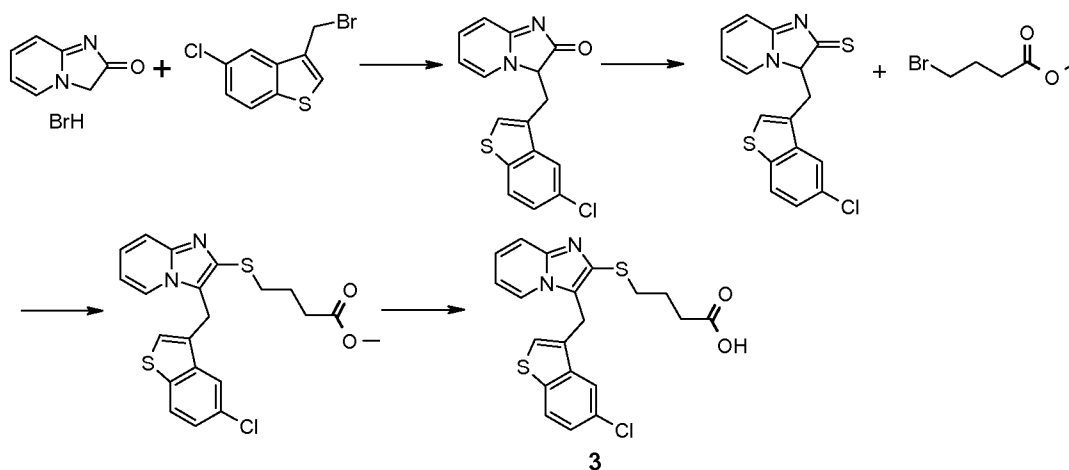
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A solution of 100 mg (0.24 mmol) of 4-[3-(4-methyl-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid methyl ester in 2mL of THF is treated with a solution of 20 mg (0.48 mmol) of lithium hydroxide monohydrate in 1mL of water at room temperature. The resulting mixture is heated to 40⁰C, and stirred at this temperature for 3 h. The reaction mixture is then cooled to room temperature and concentrated *in vacuo*. The residue is diluted with water and neutralized with 1N HCl solution. The product is extracted with ethyl acetate, and the organic layer is separated. The organic layer is washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography eluting with 3~10 % methanol in dichloromethane solution to give the title compound. LCMS (ESMS): m/z 397 (M+H⁺)

20

25

Example 3: Synthesis of 4-[3-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid



3-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-one

A mixture of 100 mg (0.47 mmol) of imidazo[1,2-a]pyridin-2-one hydrobromide salt and 122 mg (0.47 mmol) 3-bromomethyl-5-chloro-benzo[b]thiophene in 5 mL of THF is treated with 1 mL (1.0 mmol) of 1M lithium bis(trimethylsilyl)amide THF solution at -78°C . The resulting mixture is stirred this temperature for 1 h and the mixture is quenched with saturated ammonium chloride solution. The product is extracted with ethyl acetate. The organic layer is washed with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to give the desired compound.

3-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridine-2-thione

A suspension of 172 mg (0.55 mmol) of 3-(5-chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-one and 110 mg (0.27 mmol) of 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide in 20 mL of toluene is heated at 160°C for 90 min under microwave condition. The resulting mixture is concentrated *in vacuo* and the residue is purified by flash chromatography to give the desired compound.

4-[3-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid methyl ester

A mixture of 60 mg (0.18 mmol) of 3-(5-chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridine-2-thione and 38 mg (0.21 mmol) of methyl 4-bromobutyrate and 58 mg (0.42 mmol) of potassium carbonate in 2 mL of DMF is stirred at room temperature for 18 h. The

mixture is diluted with water and the product is extracted with ethyl acetate. The organic layer is washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel eluted with 1~5% methanol in dichloromethane to give the desired compound.

5

4-[3-(5-Chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid

A solution of 15 mg (0.04 mmol) of 4-[3-(5-chloro-benzo[b]thiophen-3-ylmethyl)-imidazo[1,2-a]pyridin-2-ylsulfanyl]-butyric acid methyl ester in 2mL of THF is treated with a
10 solution of 10 mg (0.24 mmol) of lithium hydroxide monohydrate in 1mL of water at room temperature. The resulting mixture is heated to 50°C, and stirred at this temperature for 2 h. The reaction mixture is then cooled to room temperature and concentrated *in vacuo*. The residue is purified by preparative TLC on silica gel to give the title compound. LCMS (ESMS): m/z 417 (M+H⁺).

15

METHODS OF USE

In accordance with the invention, there are provided methods of using the compounds as
20 described herein and their pharmaceutically acceptable derivatives. The compounds used in the invention inhibit Chymase. Since Chymase is known to transform angiotensin I to angiotensin II and may contribute to activation of TGF-β, matrix proteases and cytokines, the inhibition of Chymase is an attractive means for preventing and treating a variety of diseases or conditions. Examples include heart failure including chronic heart failure
25 (non-ischemic), post-myocardial infarction heart failure (ischemic), acute myocardial infarction, reperfusion injury, left ventricular dysfunction, cardiac fibrosis, diastolic heart failure and hypertrophic cardiomyopathy, hypertension including pulmonary
hypertension, systolic hypertension and resistant hypertension, including coronary artery disease, peripheral arterial occlusive disease, aneurism, stable/unstable angina, restenosis,
30 diabetic nephropathy, atrial fibrillation/ventricular arrhythmias, valvular heart disease, pericardial diseases, renal insufficiency (chronic kidney disease, end stage renal disease),

stroke. The compounds of the invention may also be useful for the following procedures: coronary artery bypass grafting, percutaneous coronary intervention and stenting.

Other diseases within the scope of the invention include allergic rhinitis, dermatitis,
5 asthma, chronic obstructive pulmonary disease (COPD), and pulmonary inflammation,
asthma, osteoarthritis, bone resorption diseases, multiple sclerosis, Guillain-Barre
syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease,
systemic lupus erythematosus, rheumatoid arthritis, toxic shock syndrome, Alzheimer's
disease, inflammatory bowel diseases, acute and chronic pain as well as symptoms of
10 inflammation, thermal injury, adult respiratory distress syndrome (ARDS), multiple
organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute
inflammatory components, acute purulent meningitis or other central nervous system
disorders, syndromes associated with hemodialysis, leukopherisis, granulocyte
transfusion associated syndromes, and necrotizing enterocolitis, traumatic arthritis, and
15 sepsis. Reference in this regard may be made to U.S. 5,948,785 ; U.S. 6,271,238; U.S.
5,691,335; U.S. 5,814,631; U.S. 6,300,337; EP 1,099,690; U.S. 6,323,219; US 2005-
0245536 A1; Fukami, et al., *Current Pharmaceutical Design* **1998**, vol. 4, pp. 439-453.

20 As disclosed in the Background of the Invention, the compounds of the invention may
contribute to activation of cytokines, they will therefore be useful for treating oncological
diseases. Reference in this regard may be made to US 2005-0245536 A1. These diseases
include but are not limited to solid tumors, such as cancers of the breast, respiratory tract,
brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck,
25 thyroid, parathyroid and their distant metastases. Those disorders also include
lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma,
invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma and mesothelioma .

5 Examples of brain cancers include, but are not limited to brain stem, optic and hypophthalmic glioma, cerebella and cerebral astrocytoma, medulloblastoma, ependymoma, as well as pituitary,neuroectodermal and pineal tumor.

Examples of peripheral nervous system tumors include, but are not limited to neuroblastoma, ganglioneuroblastoma, and peripheral nerve sheath tumors.

10 Examples of tumors of the endocrine and exocrine system include, but are not limited to thyroid carcinoma, adrenocortical carcinoma, pheochromocytoma, and carcinoid tumors.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal.

15

These disorders have been well characterized in man, but also exist with a similar etiology in other mammals, and can be treated by pharmaceutical compositions of the present invention.

20 For therapeutic use, the compounds may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

25

The compounds described herein may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or

dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Combinations with other therapeutics include but are not limited to: angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, CETP inhibitors/apoA1 mimetics, adenosine diphosphate (P2Y12) inhibitors, direct thrombin inhibitors, aldosterone antagonists, factor Xa inhibitors, natriuretic peptides (ANP/BNP), renin inhibitors, anti-arrhythmics, Chymase inhibitors, HMG-CoA Reductase inhibitors (Statins), Rho kinase inhibitors, beta-blockers, Lipoprotein-associated phospholipase A2 inhibitors, cardiac glycosides, calcium channel blockers, diuretics, fibrates, Endothelin Receptor Antagonists, GPIIb/IIIa inhibitors, histone deacetylase inhibitors, heparins, nicotinic acid derivatives, vasopeptidase inhibitors, nitrites and nitrates, fatty acid oxidation inhibitors, oral anticoagulants, acyl-CoA:cholesterol acyltransferase inhibitors, thrombolytics, microsomal triglyceride transfer protein inhibitors, thiazolidinediones, adenosine receptor modulators, cholesterol absorption inhibitors, Advanced Glycation End products/receptor (AGE/RAGE) interaction modulators/blockers, acetyl salicylic acid, dipyridamole, gene therapy and cell therapy.

Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 5%, but more preferably at least about 20%, of a compound (w/w) or a combination thereof. The optimum percentage (w/w) of a compound of the invention may vary and is within the

purview of those skilled in the art. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

5 As mentioned above, dosage forms of the above-described compounds include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet,
10 liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill
15 in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance,
20 specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

The term "patient" includes both human and non-human mammals.

25

The term "effective amount" means an amount of a compound according to the invention which, in the context of which it is administered or used, is sufficient to achieve the desired effect or result. Depending on the context, the term effective amount may include or be synonymous with a pharmaceutically effective amount or a diagnostically effective
30 amount.

The terms “pharmaceutically effective amount” or “therapeutically effective amount” means an amount of a compound according to the invention which, when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to
5 elicit the biological or medical response of a tissue, system, or patient that is sought by a researcher or clinician. The amount of a compound of according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the
10 duration of treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex, and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

15

The term “diagnostically effective amount” means an amount of a compound according to the invention which, when used in a diagnostic method, apparatus, or assay, is sufficient to achieve the desired diagnostic effect or the desired biological activity necessary for the diagnostic method, apparatus, or assay. Such an amount would be
20 sufficient to elicit the biological or medical response in a diagnostic method, apparatus, or assay, which may include a biological or medical response in a patient or in a *in vitro* or *in vivo* tissue or system, that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a diagnostically effective amount will vary depending on such factors as the compound and its biological activity, the
25 diagnostic method, apparatus, or assay used, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of administration, drugs and other compounds used in combination with or coincidentally with the compounds of the invention, and, if a patient is the subject of the diagnostic administration, the age, body weight, general health, sex, and diet of the
30 patient. Such a diagnostically effective amount can be determined routinely by one of

ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

The terms “treating” or “treatment” mean the treatment of a disease-state in a patient, and
5 include:

(i) preventing the disease-state from occurring in a patient, in particular, when such patient is genetically or otherwise predisposed to the disease-state but has not yet been diagnosed as having it;

(ii) inhibiting or ameliorating the disease-state in a patient, i.e., arresting or slowing
10 its development; or

(iii) relieving the disease-state in a patient, i.e., causing regression or cure of the disease-state.

In vitro assay for inhibition of Chymase

15

Chymase assays were performed in a total volume of 15 μ L in Corning black opaque 384-well microtiter plates with a non-binding surface (Corning, NY). The assay buffer was comprised of 20 mM Tris HCl pH 8.0, 50 mM NaCl, 0.01% CHAPS. The test compounds were serially diluted 3-fold with neat DMSO in a 96-well polypropylene
20 plate from a 10mM DMSO stock to give the 10 point dose response curve. 3 μ L of the resulting DMSO solution were transferred to a 384-well polypropylene plate in duplicate, and 37 μ L of assay buffer was added. Chymase was added to the assay plate in 3 uL of assay buffer followed by 2 uL of the appropriate compound dilution using a PlateMate Plus (Matrix Technologies Corp., Hudson, NH). The reaction was initiated by the
25 addition of 10 uL rhodamine 110, bis-(succinoyl-L-alanyl-L-alanyl-L-prolyl-L-phenylalanylamide) (American Peptides, Sunnyvale, CA) in assay buffer containing 150 μ M tris(2-carboxyethyl)phosphine (TCEP, Pierce Chemical, Rockford, IL) using a

Multidrop (Thermo Electron Corp., Waltham, MA). Final assay concentrations were 500 pM chymase, 100 nM substrate, 100 μ M TCEP, and 1% DMSO. The plates were incubated at 28° C and 80% humidity for 1 hour, at which time the fluorescence was read on a Viewlux 1430 Microplate Imager (Perkin Elmer Life Sciences, Boston, MA) with 5 485 nm excitation, 530 nm emission, and a fluorescein dichroic mirror. The percentage of control values were calculated relative to assay blanks containing complete reaction minus chymase and a 100% control containing assay buffer with 1% DMSO in place of compound. IC50 values were obtained by fitting the data using XLFit4 (IDBS Software). Preferred compounds of the invention have an activity of 1 microMolar or less.

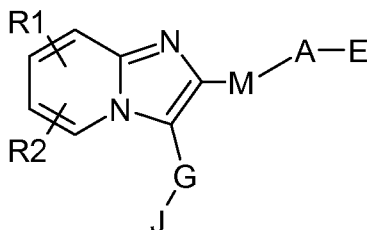
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All patent and literature references cited in this application are incorporated herein by reference in their entirety.

What is Claimed:

1. A compound of the formula (I):

5



(I)

R1 and **R2** are independently hydrogen, halogen, trihaloalkyl, trihaloalkoxy, cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CORd, -COORd, -CON(Rc)Rd, -N(Rc)Rd, -N(Rc)CORd wherein each Rd is independently a hydrogen, C₁₋₆ linear or branched alkyl or cycloalkyl, C₁₋₆ linear or branched alkenyl or heterocyclyl or where R1 and R2 together represent -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-, wherein each group is optionally independently substituted with one to three substituents chosen from C₁₋₄ acyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, dialkylamino, cyano, carboxy, carboxamido, halogen, hydroxyl and phenyl optionally substituted with halogens;

A is C₁₋₇ linear, branched or cyclic alkyl group optionally interrupted by one or more -O-, -S-, -SO-, -SO₂- and -NRa- optionally substituted with one to three substituents chosen from halogen, C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkoxy, C₁₋₆ linear or branched alkylthio, C₁₋₆ linear or branched alkylsulfonyl, phenyl and oxo;

E is -COORe, -SO₃Re, -CONHRe, -SO₂NHRe, -NHSO₂Re, -CONHSO₂Re, -SO₂NH-CO(Rf), heteroaryl, heterocyclyl, wherein each Re is independently hydrogen, C₁₋₄ alkyl or aryl, and Rf is C₁₋₄ alkyl or aryl;

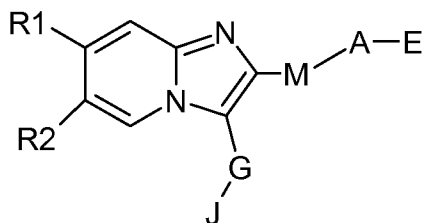
G is C₁₋₆ linear or branched alkyl optionally interrupted by one or more of -O-, -S-, -SO₂ or -NRa-, wherein the alkyl group is optionally substituted with hydroxyl, cyano, C₁₋₆ linear or branched alkyl or C₁₋₆ linear or branched alkoxy;

- 5 **M** is a methylene group, oxygen, -N(Rb)-, or -S(O)_m-, where m is an integer of 0-2; and, wherein the said methylene group is optionally substituted by one to two substituents chosen from hydroxyl, cyano, C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkoxy, trihalomethyl, trihalomethoxy, phenyl and oxo;
- 10 **J** is an optionally mono- or poly-substituted aromatic carbocycle or a heteroaromatic group having 4-10 carbon atoms containing one or more hetero atoms chosen from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom in its ring(s); each substituent on said aromatic or heteroaromatic groups is chosen from halogen, hydroxyl, cyano, C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkoxy, C₁₋₆ linear or branched alkylthio, C₁₋₆ linear or branched alkylsulfonyl, phenylsulfonyl, C₁₋₆ linear or branched acyl, C₁₋₆ linear or branched acylamino, trihalomethyl, trihalomethoxy, phenyl, oxo, -COORa, -CON(Rc)Ra, SO₂N(Rc)Ra, -N(Rc)Ra and phenoxy optionally substituted by one or more halogens;
- 15
- 20 Ra, Rb and Rc are each independently C1-3 alkyl or hydrogen;

or the pharmaceutically acceptable salts thereof.

- 25 2. The compound according to claim 1 and wherein:

R1 and **R2** are attached as follows:



and are independently hydrogen, Cl, Br, F, I, trihaloalkyl, trihaloalkoxy cyano, hydroxyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CORd, -COORd, -CON(Rc)Rd, -N(Rc)Rd, -N(Rc)CORd wherein each Rd is independently a hydrogen, C₁₋₆ linear or branched alkyl or cycloalkyl, 5 C₁₋₆ linear or branched alkenyl or heterocyclyl chosen from pyrrole, pyrrolidinyl, pyrazole, imidazole, furan, tetrahydrofuran, oxazole, thiophene, tetrahydrothiophene and thiazole wherein for each ring possessing a sulfur heteroatom the sulfur is -S-, -S(O)- or -S(O)₂-, or where R1 and R2 together represent -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-CH₂-,

10 wherein each group is optionally independently substituted with one to three substituents chosen from C₁₋₄ acyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, dialkylamino, cyano, carboxy, carboxamido, Cl, Br, F, I, hydroxyl and phenyl optionally substituted with one to three Cl, Br, F, I,;

15 **A** is C₁-C₇ linear, branched optionally independently substituted with one to three substituents chosen from amino, cyano, carboxy, carboxamido, halogen, hydroxyl, nitro, phenyl, C₁₋₆ linear or branched alkyl and C₁₋₆ linear or branched alkoxy;

E is -COORe, -SO₃Re, -CONHRe, -CONHSO₂Re, -SO₂NH-CO(Rf), tetrazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 5-oxo-1,2,4-thiadiazol-3-yl, 5-thioxo-1,2,4-oxadiazol-3-yl, 5-20 thioxo-1,2,4-thiadiazol-3-yl, 3-oxo-1,2,4-oxadiazol-5-yl, N3,5-dioxo-5-oxadiazolidino, 2-oxo1,3,4-oxadiazol-2-yl, 3-oxo1,2,4-triazol-5-yl or 2,dioxo-benzothiadiazin-6-yl, wherein each Re is independently hydrogen, C₁₋₄ alkyl or phenyl, and Rf is C₁₋₄ alkyl or aryl;

25

G is C₁₋₄ linear or branched alkyl optionally substituted with a substituent chosen from hydroxyl, a cyano, C₁₋₆ linear or branched alkyl and C₁₋₆ linear or branched alkoxy ;

M is a methylene group, oxygen, -N(Rb)-, or -S(O)_m-, where m is an integer of 0-2;

30

J is an optionally mono- or di-substituted phenyl, naphthyl, benzothienyl, benzopyrrolyl, benzimidazolyl, indolyl; each substituent on said aromatic or heteroaromatic groups is chosen from halogen, hydroxyl, cyano, C₁₋₄ linear or branched alkyl, C₁₋₄ linear or branched alkoxy, C₁₋₆ linear or branched alkylthio, C₁₋₆ linear or branched alkylsulfonyl, phenylsulfonyl, C₁₋₆ linear or branched acyl, C₁₋₆ linear or branched acylamino, trihalomethyl, trihalomethoxy, phenyl, oxo, -COORa, -CON(Rc)Ra, -SO₂N(Rc)Ra, N(Rc)Ra and phenoxy optionally substituted by one or more halogens.

3. The compound according to claim 2 and wherein:

R1 and **R2** are independently hydrogen, Cl, F, trihalomethyl, trihalomethoxy, cyano, hydroxyl, C₁₋₂ alkyl, C₁₋₄ alkoxy, -CORd, -CON(Rc)Rd, -N(Rc)Rd, -N(Rc)CORd wherein each Rd is independently a hydrogen or C₁₋₆ linear or branched alkyl, C₁₋₆ linear or branched alkenyl, furan, tetrahydrofuran, thiophene and tetrahydrothiophene wherein for each ring possessing a sulfur heteroatom the sulfur is -S-, -S(O)- or -S(O)₂- or where R1 and R2 together represent -O-CH₂-CH₂-O-, wherein each group is optionally independently substituted with one to three substituents chosen from C₁₋₄ alkyl, C₁₋₄ alkoxy amino, cyano, carboxy, carboxamido, Cl, Br, F, I, and hydroxyl;

A is a -(CH₂)₃-group, optionally substituted with one substituent chosen from phenyl and C₁₋₃ alkyl;

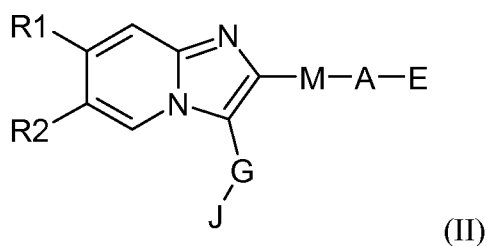
E is -COORe wherein Re is hydrogen or methyl;

G is C₁₋₂ alkyl;

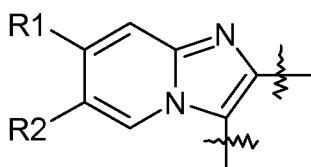
M is a methylene group, oxygen, -NH-, -N(CH₃)- or sulfur;

J is naphthyl, benzothieryl, benzopyrrolyl, benzimidazolyl, indolyl each optionally substituted with one to three groups chosen from halogen, hydroxyl, cyano and C₁₋₆ linear or branched alkyl.

5 4. A compound of the formula (II):



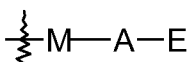
wherein for the formula (II), the component



10

is chosen from A1 – A8 in the table I below; in combination with any

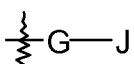
15 component



chosen from B1 – B19 in the table I below;

20

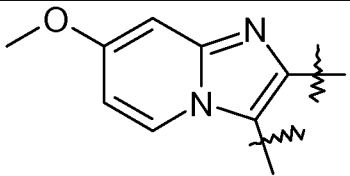
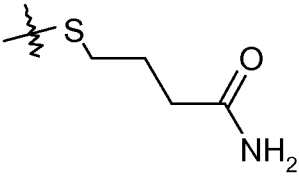
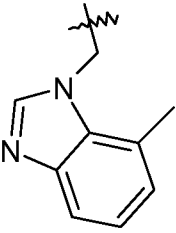
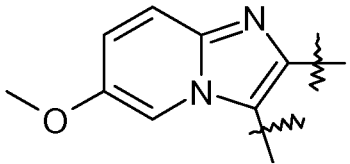
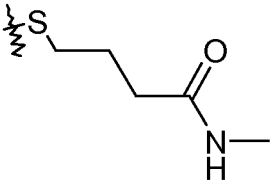
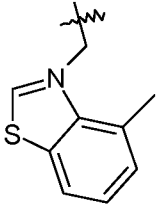
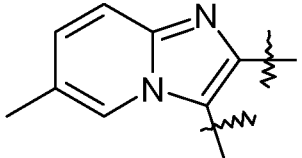
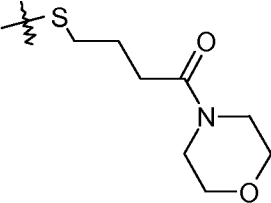
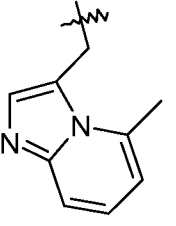
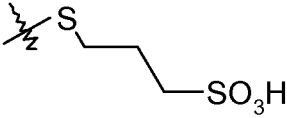
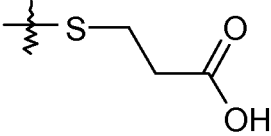
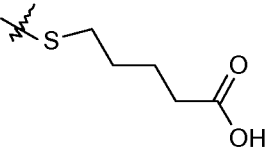
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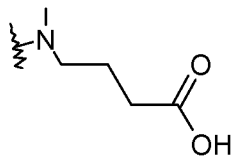
25 chosen from C1 – C8 in Table I below;

Table I

A1		B1		C1	
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	
A5		B5		C5	

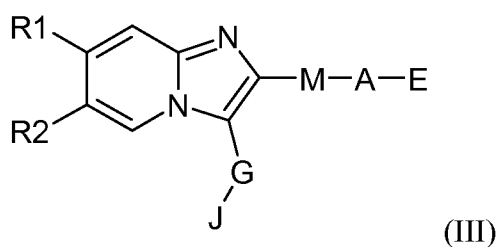
A6		B6		C6	
A7		B7		C7	
A8		B8		C8	
		B9			
		B10			
		B11			

		B12			
		B13			
		B14			
		B15			
		B16			
		B17			
		B18			

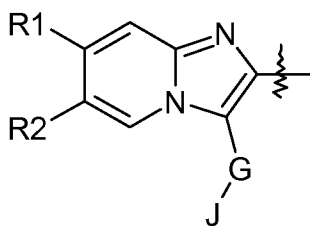
		B19			
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or the pharmaceutically acceptable salts thereof.

5 5. A compound of the formula (III):



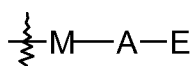
wherein for the Formula (III), the component



10

is chosen from A1 – A15 in the table I below; in combination with any

15 component



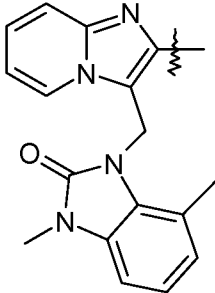
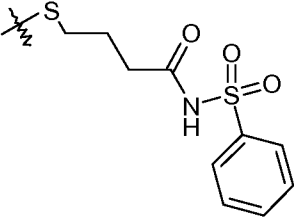
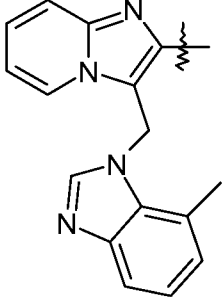
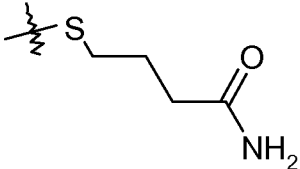
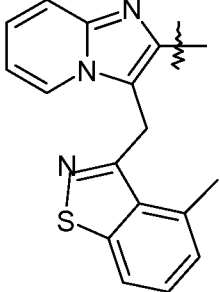
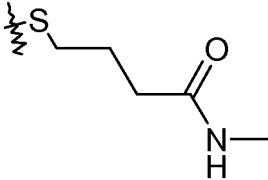
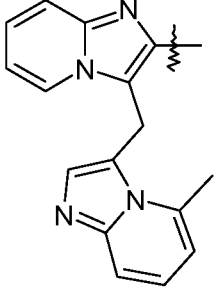
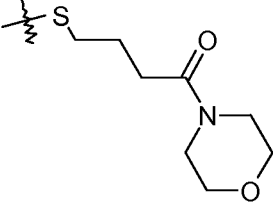
chosen from B1 – B19 in the table II below;

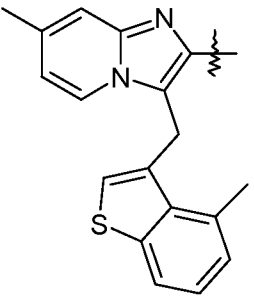
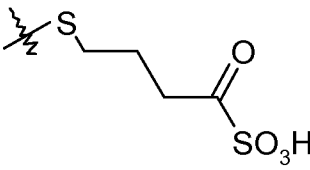
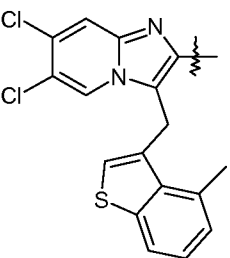
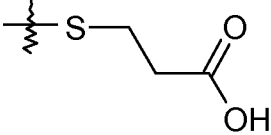
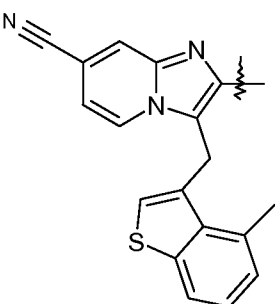
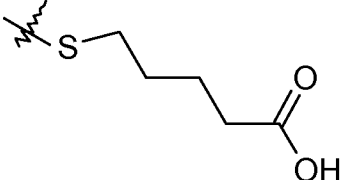
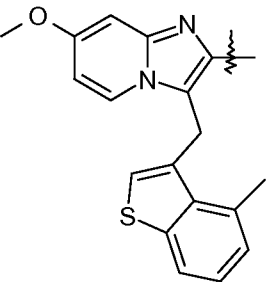
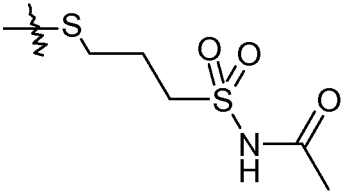
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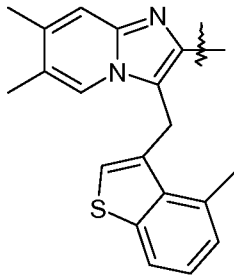
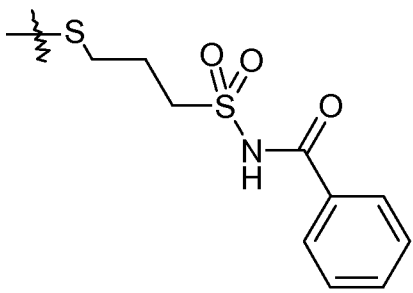
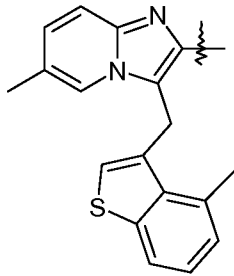
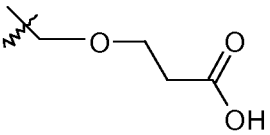
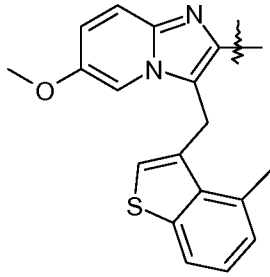
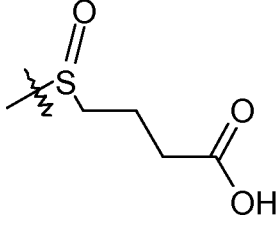
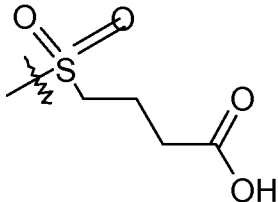
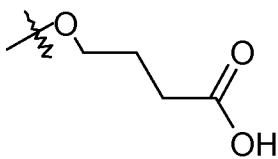
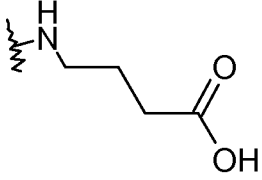
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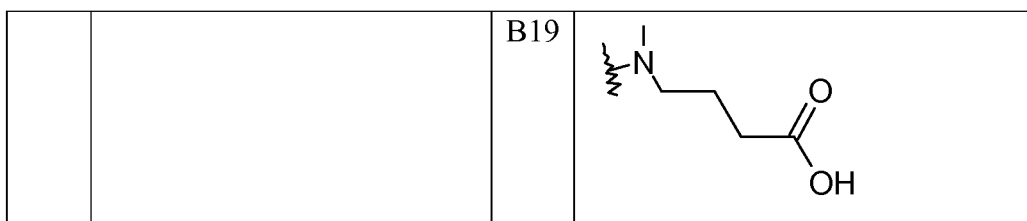
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	<p>A pyridine-imidazole ring system. The pyridine ring has substituents R1 and R2. The imidazole ring has a wavy line at the 2-position and a substituent G at the 4-position, which is further connected to a wavy line labeled J.</p>		<p>A linker structure consisting of a wavy line connected to M, which is connected to A, which is connected to E.</p>
A1	<p>A pyridine-imidazole ring system with a wavy line at the 2-position, connected via a methylene group to a naphthalene ring.</p>	B1	<p>A linker structure: a wavy line connected to a sulfur atom (S), which is connected to a propyl chain, which is connected to a carbonyl group (C=O), which is connected to an oxygen atom (O) bonded to a methyl group.</p>
A2	<p>A pyridine-imidazole ring system with a wavy line at the 2-position, connected via a methylene group to a thiophene ring. The thiophene ring has a chlorine atom (Cl) at the 5-position.</p>	B2	<p>A linker structure: a wavy line connected to a sulfur atom (S), which is connected to a propyl chain, which is connected to a carbonyl group (C=O), which is connected to a hydroxyl group (OH).</p>
A3	<p>A pyridine-imidazole ring system with a wavy line at the 2-position, connected via a methylene group to a thiophene ring. The thiophene ring has a methyl group (CH3) at the 2-position.</p>	B3	<p>A linker structure: a wavy line connected to a sulfur atom (S), which is connected to a propyl chain, which is connected to a tetrazole ring.</p>
A4	<p>A pyridine-imidazole ring system with a wavy line at the 2-position, connected via a methylene group to an imidazole ring. The imidazole ring has a methyl group (CH3) at the 2-position.</p>	B4	<p>A linker structure: a wavy line connected to a sulfur atom (S), which is connected to a propyl chain, which is connected to a carbonyl group (C=O), which is connected to a nitrogen atom (NH) bonded to a sulfur atom (S) double-bonded to two oxygen atoms (O2) and bonded to a methyl group.</p>

<p>A5</p>		<p>B5</p>	
<p>A6</p>		<p>B6</p>	
<p>A7</p>		<p>B7</p>	
<p>A8</p>		<p>B8</p>	

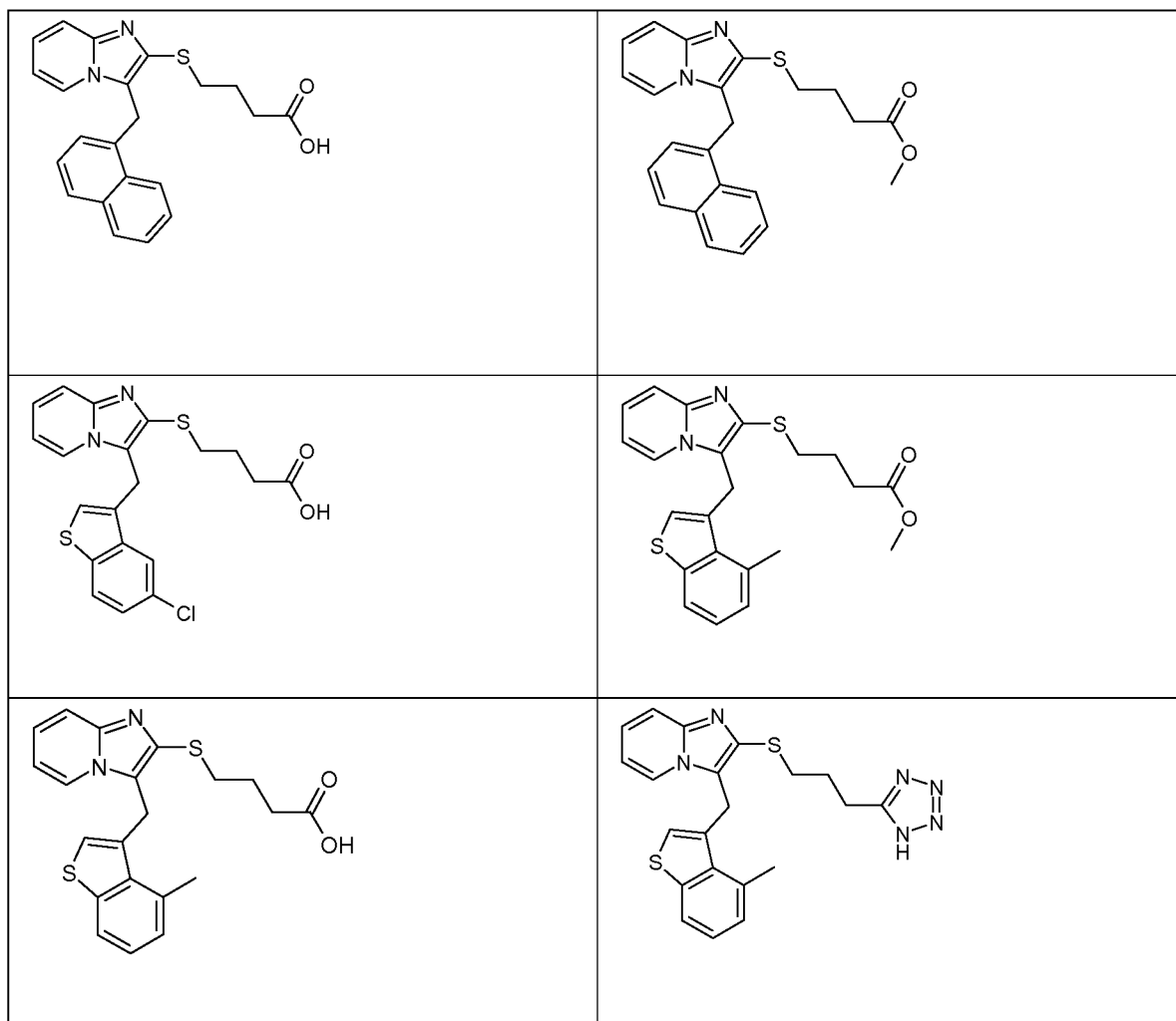
A9		B9	
A10		B10	
A11		B11	
A12		B12	
A13		B13	

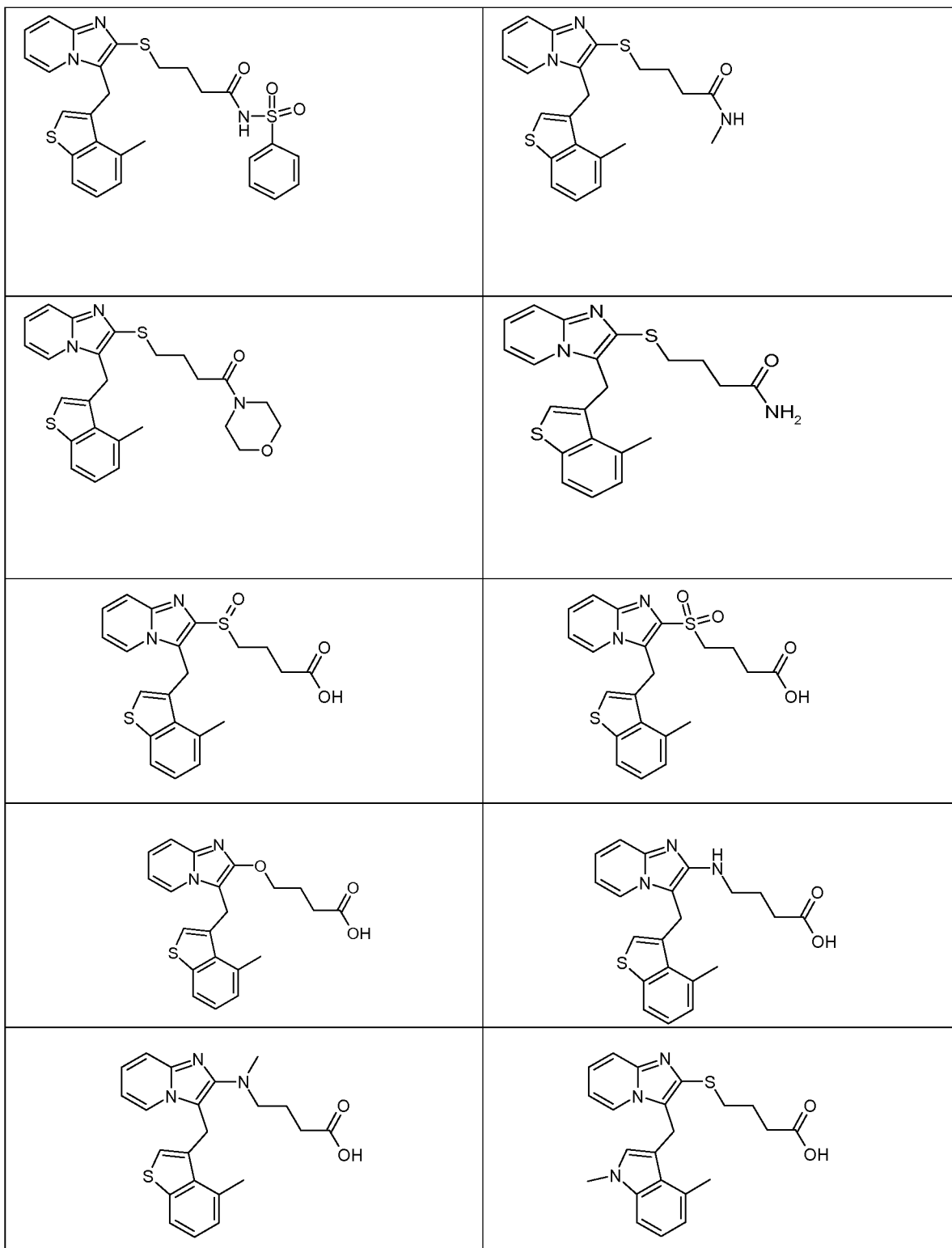
			
A14		B14	
A15		B15	
		B16	
		B17	
		B18	

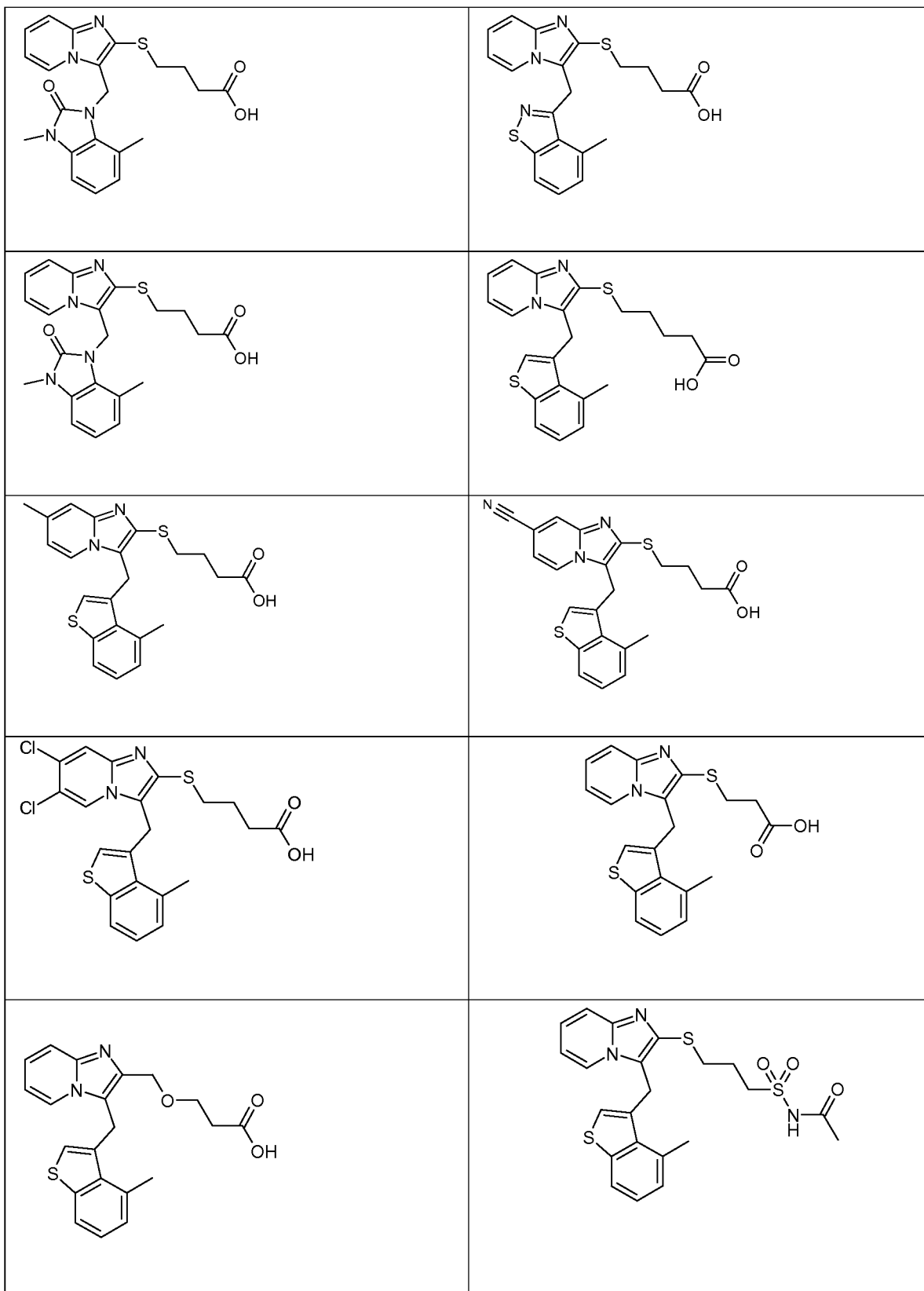


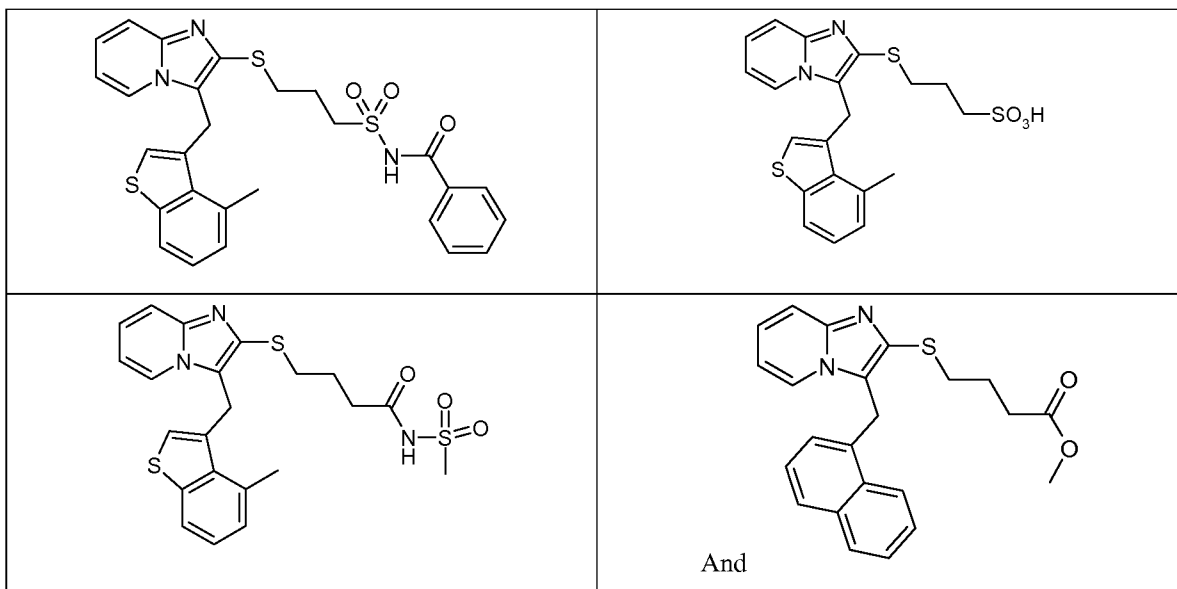
or the pharmaceutically acceptable salts thereof.

5 6. A compound chosen from





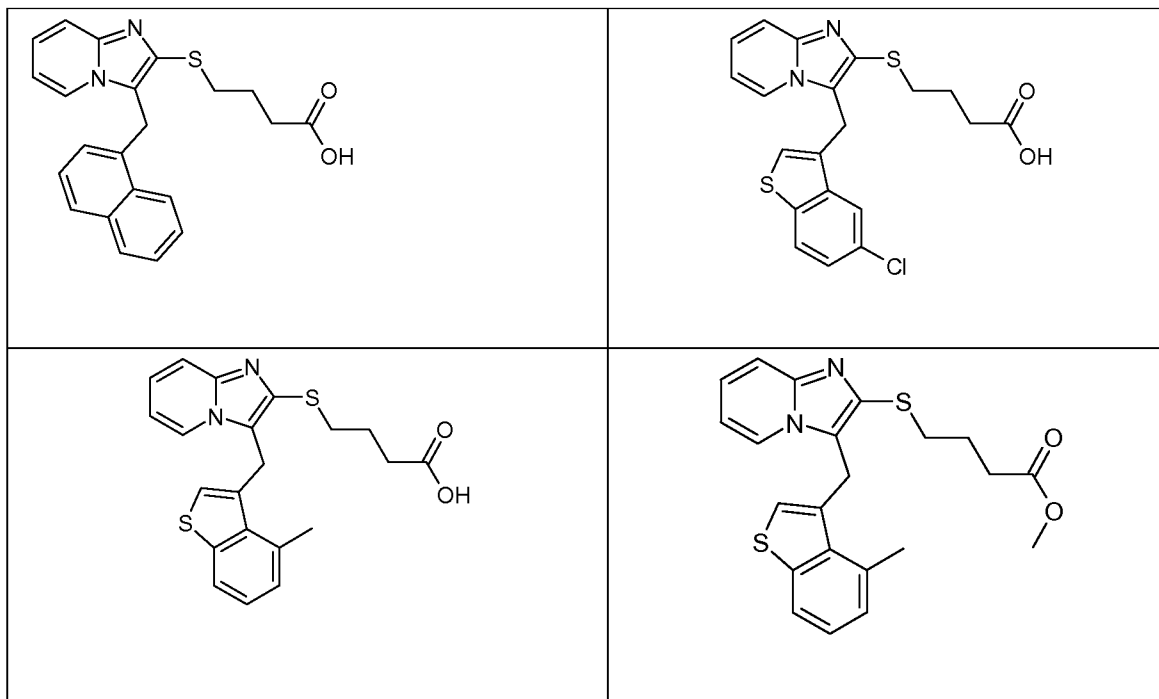




or the pharmaceutically acceptable salts thereof.

7. A compound chosen from

5



or the pharmaceutically acceptable salts thereof.

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1.

9. A method of treating a disease or condition chosen from chronic heart failure (non-
5 ischemic), post-myocardial infarction heart failure (ischemic), acute myocardial
infarction, reperfusion injury, left ventricular dysfunction, cardiac fibrosis, diastolic heart
failure, hypertrophic cardiomyopathy, pulmonary hypertension, systolic hypertension,
resistant hypertension, coronary artery disease, peripheral arterial occlusive disease,
aneurism, stable/unstable angina, restenosis, diabetic nephropathy, atrial
10 fibrillation/ventricular arrhythmias, valvular heart disease, pericardial diseases, chronic
kidney disease, end stage renal disease and stroke comprising administering to a patient a
pharmaceutically effective amount of a compound according to claim 1.

10. A method of treating a disease or condition requiring a medical procedure chosen
15 from coronary artery bypass grafting, percutaneous coronary intervention and stenting,
said method comprising further administering to a patient a pharmaceutically effective
amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/079660

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P9/00

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

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 practical, 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.
A	WO 2006/096444 A (SMITHKLINE BEECHAM CORP [US]; GUDMUNDSSON KRISTJAN [US]; CATALANO JOHN) 14 September 2006 (2006-09-14) claims 45,49,53; examples 15,58,59 -----	1
A	WO 01/53298 A (NEUROGEN CORP [US]; PETERSON JOHN M [US]; HUTCHISON ALAN [US]; SHAW KE) 26 July 2001 (2001-07-26) claims 28-30; examples 2-5 -----	1
A	JP 2006 131559 A (TAKEDA CHEMICAL INDUSTRIES LTD) 25 May 2006 (2006-05-25) abstract; paragraphs [0340], [0344] -----	1
-/--		

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
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 February 2008

Date of mailing of the international search report

22/02/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Beyss-Kahana, Ellen

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/079660

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/073214 A (JANSSEN PHARMACEUTICA NV [BE]; HAWKINS MICHAEL J [US]; GRECO MICHAEL N) 11 August 2005 (2005-08-11) cited in the application claim 50 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/079660

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9,10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/079660

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