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(54) Title: NOVEL COMPOUNDS, THEIR PREPARATION AND THEIR USES

(57) Abstract: Novel compounds and their synthesis are described. Methods for using these compounds in the prevention or treatment of cancer, a bacterial infection or a viral infection in a subject are also described.

# NOVEL COMPOUNDS, THEIR PREPARATION AND THEIR USES

## CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to and the benefit of U.S. Provisional Application Serial No. 61/709,704 filed on October 4, 2012, the entire content of which is incorporated herein by reference.

## STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOMENT

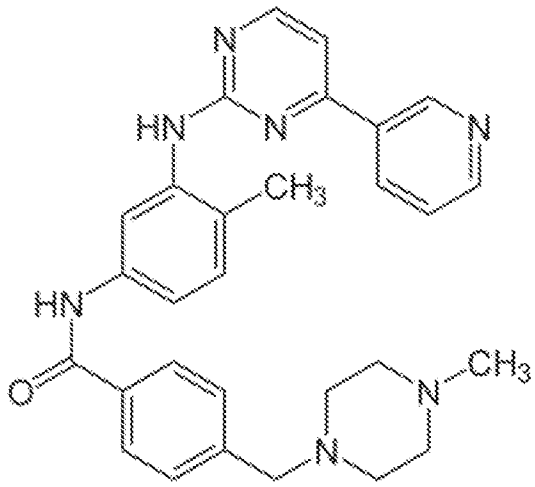
This invention was made in part with Government support under Contract No. 1R43NS069213-01 / 343NS069213-01S1, awarded by the United States' National Institutes of Health. The Government has certain rights in this invention.

## FIELD OF INVENTION

The present invention relates to novel compounds with improved pharmacokinetic and pharmacodynamic properties and a process for the synthesis of these compounds.

## BACKGROUND OF INVENTION

Imatinib is the first of a new class of drugs that acts by specifically inhibiting a certain enzyme that is characteristic of a particular cancer cell, rather than non-specifically inhibiting and killing all rapidly dividing cells. Imatinib was a model for other targeted therapies that inhibited the class of enzymes, tyrosine kinases. Imatinib, present as its mesylate salt, multi-targets several pathways and is found to inhibit c-kit, PDGF-R and c-ABL. It is also known for its inhibition of T-cell proliferation stimulated by DCs and PHA. Imatinib Mesylate binds preferentially to ATP–binding sites of the c-kit proto-oncogene product, platelet-derived growth factor receptor (PDGF-R), and Abelson kinase (c-ABL) impeding the ensuing signal transduction. Imatinib, a reversible tyrosine kinase inhibitor, is effective in treatment of chronic myelogenous leukemia (CML), gastrointestinal stromal tumors, eosinophilic disorders, and systemic mast cell disease.



**1001**

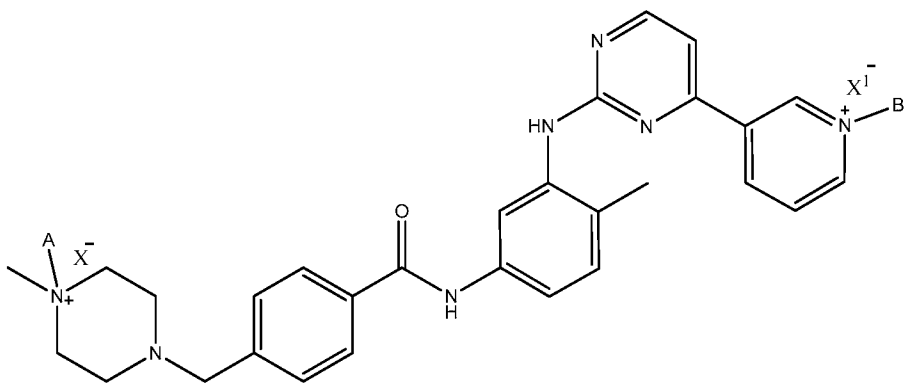
**4-[(4-methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide**

However, it is desirable to improve pharmacokinetic and if possible the pharmacodynamic parameters of imatinib, to favorably alter the dose and the dosing regimen of imatinib and to reduce the side effects.

## SUMMARY OF INVENTION

The present invention comprises novel compounds that, when administered to a patient, provide an active form of imatinib.

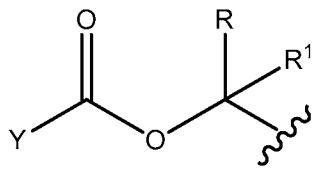
The present application provides novel compounds of formula (I) or their pharmaceutically acceptable salts:



**(I)**

wherein:

A and B are independently selected from absent, H or a moiety of Formula **(II)**, with the proviso that at least one of A and B is a moiety of Formula (**II**);




**(II)**

wherein:

R and $R^1$ are each independently selected from H, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl and heteroaryl substituents; or R and $R^1$ taken together with the atom to which they are attached form a 3- to 7-membered ring, wherein the 3- to 7-membered ring optionally contains up to two heteroatom groups selected from O, N $R^4$, S, SO and $SO_2$, and is optionally substituted with 1 to 4 alkoxy, F or Cl substituents;

Y is selected from $R^2$, $OR^2$, $NH_2$, $NHR^2$, and $NR^2R^3$;

$R^2$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl substituents;

$R^3$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and

$C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl; or

$R^2$ and $R^3$ may be taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered ring, wherein the 3- to 7-membered ring optionally contains up to three heteroatom groups selected from O, $NR^4$, S, SO and $SO_2$, and is optionally substituted with alkoxy, F or Cl;

$R^4$ is, independently for each occurrence, selected from H or $C_1$-$C_8$ alkyl; and

X and $X^1$ are each independently an anion or absent, provided that X is absent only when A is absent, and $X^1$ is absent only when B is absent.

The present application also provides a method for the preparation of novel compounds.

The present application also provides compositions comprising novel compounds.

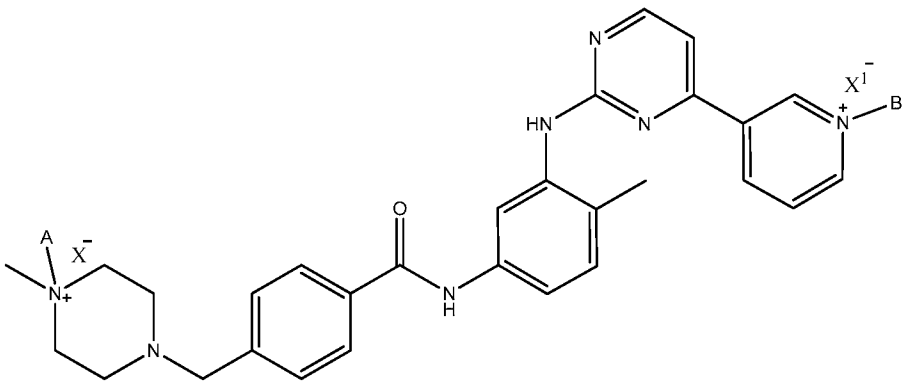
The present application also provides for the use of the compounds for c-ABL, PDGFR and SCFR (c-Kit) inhibition.

## DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present application provides novel compounds of formula (I) or their pharmaceutically acceptable salts and process for producing these compounds.

## COMPOUNDS OF THE PRESENT INVENTION

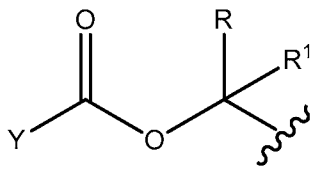
The present application provides novel compounds of formula (I) or their pharmaceutically acceptable salts:



**(I)**

wherein:

A and B are independently selected from absent, H or a moiety of Formula **(II)**, with the proviso that at least one of A and B is a moiety of Formula (**II**);




**(II)**

wherein:

R and $R^1$ are each independently selected from H, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl and heteroaryl substituents; or R and $R^1$ taken together with the atom to which they are attached form a 3- to 7-membered ring, wherein the 3- to 7-membered ring optionally contains up to two heteroatom groups selected from O, N $R^4$, S, SO and $SO_2$, and is optionally substituted with 1 to 4 alkoxy, F or Cl substituents;

Y is selected from $R^2$, $OR^2$, $NH_2$, $NHR^2$, and $NR^2R^3$;

$R^2$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl substituents;

$R^3$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and

$C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl; or

$R^2$ and $R^3$ may be taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered ring, wherein the 3- to 7-membered ring optionally contains up to three heteroatom groups selected from O, $NR^4$, S, SO and $SO_2$, and is optionally substituted with alkoxy, F or Cl;

$R^4$ is, independently for each occurrence, selected from H or $C_1$-$C_8$ alkyl; and

X and $X^1$ are each independently an anion or absent, provided that X is absent only when A is absent, and $X^1$ is absent only when B is absent.

In some embodiments, R and $R^1$ are each independently selected from H and $C_1$-$C_8$ alkyl, such as H or methyl. Preferably both R and $R^1$ are H.

In some embodiments, $R^2$ and $R^3$ are independently selected from $C_1$-$C_8$ alkyl and aralkyl. In some such embodiments, $R^2$ and $R^3$ are independently selected from methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, *sec*-butyl, 3-methylbut-2-yl, 1-phenylethyl, benzyl or cyclobutyl.

In some embodiments, $R^4$, independently for each occurrence, is selected from H and $C_1$-$C_8$ alkyl.

In some embodiments, X and $X^1$ are each independently halide or sulfonate, such as mesylate and iodide.

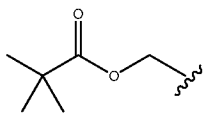
Because anions are not covalently attached to the molecule, it should be understood that X and $X^1$ are not necessarily located proximal to the atom bearing A or B, and should be viewed as interchangeable within any given molecule when both are present.

In some embodiments, A is H and B is a moiety of Formula **(II)**.

In some embodiments, A is a moiety of Formula **(II)** and B is H.

In other embodiments, A is a moiety of Formula **(II)** and B is absent.

In yet other embodiments, A is absent and B is a moiety of Formula **(II)**.

In certain embodiments, neither A nor B is  .

**Definitions**

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, and branched-chain alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (*e.g.*, $C_1$-$C_{30}$ for straight chains, $C_3$-$C_{30}$ for branched chains), and more preferably 20 or fewer. In certain embodiments, alkyl groups are lower alkyl groups, *e.g.* methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl and *n*-pentyl.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (*e.g.*, $C_1$-$C_{30}$ for straight chains, $C_3$-$C_{30}$ for branched chains). In preferred embodiments, the chain has ten or fewer carbon ($C_1$-$C_{10}$) atoms in its backbone. In other embodiments, the chain has six or fewer carbon ($C_1$-$C_6$) atoms in its backbone.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated. In preferred embodiments, a straight chain or branched chain alkenyl has 1-12 carbons in its backbone, preferably 1-8 carbons in its backbone, and more preferably 1-6 carbons in its backbone. Examplary alkenyl groups include allyl, propenyl, butenyl, 2-methyl-2-butenyl, and the like.

The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except

where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated. In preferred embodiments, an alkynyl has 1-12 carbons in its backbone, preferably 1-8 carbons in its backbone, and more preferably 1-6 carbons in its backbone. Exemplary alkynyl groups include propynyl, butynyl, 3-methylpent-1-ynyl, and the like.

The term alkoxy refers to an alkyl group singly bonded to oxygen.

The term “aralkyl”, as used herein, refers to an alkyl group substituted with one or more aryl groups.

The term “aryl”, as used herein, include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. Aryl groups include phenyl, phenol, aniline, naphthyl, biphenyl, anthracenyl and the like.

The term “cycloalkyl”, as used herein, refers to the radical of a saturated aliphatic ring. In preferred embodiments, cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably from 5-7 carbon atoms in the ring structure. Suitable cycloalkyls include cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl.

The terms "cycloalkyl" and "cycloalkenyl" refer to cyclic hydrocarbon groups of 3 to 12 carbon atoms.

The terms "halogen", “halide” and "halo", as used herein, mean halogen and include fluoro, chloro, bromo and iodo.

The term "unsaturated ring" includes partially unsaturated and aromatic rings.

The terms “heterocyclyl”, “heterocycle”, “heterocyclo” and “heterocyclic” refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-

oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, triazolyl, triazinyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo [2,3-c] pyridinyl, furo [3,2-b] pyridinyl] or furo [2,3-b] pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of carbon atoms including at least one heteroatom (e.g., O, S, or $NR^4$, such as where $R^4$ is H or lower alkyl).

The term “heteroaryl” includes substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom (*e.g.*, O, N, or S), preferably one to four or one to 3 heteroatoms, more preferably one or two heteroatoms. When two or more heteroatoms are present in a heteroaryl ring, they may be the same or different. The term “heteroaryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Preferred polycyclic ring systems have two cyclic rings in which both of the rings are aromatic. Exemplary heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furyl, thienyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, quinolinyl, pyridazinyl, triazolyl, triazinyl, and the like.

The term "alkylene" in this text include both linear and branched, saturated and unsaturated (i.e. containing one double bond) divalent alkylene groups and monovalent alkyl groups, respectively.

The term "alkanol" in this text likewise includes linear and branched, saturated and unsaturated alkyl components of the alkanol groups, in which the hydroxyl groups may be situated at any position on the alkyl moiety. The term "cycloalkanol" includes unsubstituted or substituted (e.g. methyl or ethyl) cyclic alcohols.

The term " alkoxy" is intended to mean a alkyl radical, as defined herein, attached directly to an oxygen atom. Some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, 5- isobutoxy, sec-butoxy, and the like.

The term “heteroatom”, as used herein, means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of the invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

As used herein, the term “tumoral disease” refers to a hyperproliferative disease, such as cancer.

As used herein, the term “conjoint administration” means administration of two or more agents to a subject of interest as part of a single therapeutic regimen. The administration(s) can be either simultaneous or sequential, i.e., administering one agent followed by administering of a second (and/or a third one, etc.) at a later time, as long as the agents administered co-exist in the subject being treated, or at least one agent will have the

opportunity to act upon the same target tissues of other agents while said target tissues are still under the influence of said other agents. In a certain embodiment, agents to be administered can be included in a single pharmaceutical composition and administered together. In a certain embodiment, the agents are administered simultaneously, including through separate routes. In a certain embodiment, one or more agents are administered continuously, while other agents are administered only at predetermined intervals (such as a single large dosage, or twice a week at smaller dosages, etc.).

The present invention includes within its scope the salts and isomers. Compounds of the present invention may in some cases form salts which are also within the scope of this invention. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds may be formed, for example, by reacting a compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxy ethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

Exemplary basic salts (formed, for example, wherein the substituent comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium,

lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Solvates of the compounds of the invention are also contemplated herein. Solvates of the compounds of formula I are preferably hydrates or other pharmaceutically acceptable solvates.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound, including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration.

As used herein, the term “treating” or “treatment” includes reversing, reducing, or arresting the symptoms, clinical signs, and underlying pathology of a condition in manner to improve or stabilize a subject's condition. As used herein, and as well understood in the art, “treatment” is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

The present application also envisages within its scope the effect of selection of suitable counter ions. The counter ion of the compounds of the present invention may be chosen by selecting the dissociation constant for the drug capable of ionization within the

said pH range. By estimating the ionized and un-ionized drug concentration of any compound (using well established equations such a Henderson-Hasselbach equation), the solubility and consequently the absorption of the drug may be altered.

The compounds of formula II may be divided in three classes i.e. Type I, where Y = $OR^2$; Type II, where Y = $R^2$ and Type III, where Y = $NR^2R^3$.

wherein $R^2$ and $R^3$ are as defined above

Non limiting Lists of Type I, Type II and type III reagents are presented below:

**Type I Reagents**

i. chloromethyl isopropyl carbonate
ii. benzyl chloromethyl carbonate
iii. chloromethyl morpholinomethyl carbonate
iv. chloromethyl isobutyl carbonate
v. chloromethylmethyl carbonate
vi. (S)-sec-butyl chloromethyl carbonate
vii. (R)-sec-butyl chloromethyl carbonate
viii. chloromethyl ((3S,5R)-3,5-dimethylmorpholino)methyl carbonate
ix. chloromethyl 2-methylcyclopropyl carbonate
x. chloromethyl2-methoxyethyl carbonate
xi. chloromethyl propyl carbonate
xii. chloromethyl cyclobutyl carbonate
xiii. chloromethyl cyclopropyl carbonate
xiv. chloromethyl 2,2-dimethylcyclobutyl carbonate
xv. chloromethyl cyclopentyl carbonate
xvi. chloromethyl oxetan-3-yl carbonate
xvii. (S)-chloromethyl tetrahydrofuran-3-yl carbonate
xviii. chloromethyl cyclohexylmethyl carbonate
xix. chloromethyl 3-methoxycyclohexyl carbonate
xx. (R)-chloromethyl tetrahydrofuran-3-yl carbonate
xxi. chloromethyl ethoxymethyl carbonate
xxii. chloromethyl oxepan-4-yl carbonate
xxiii. (1R,2S,4S)-bicyclo[2.2.1]heptan-2-yl chloromethyl carbonate
xxiv. chloromethyl 2,3-dihydro-1H-inden-1-yl carbonate

xxv. benzyl chloromethyl carbonate
xxvi. (S)-chloromethyl 1-phenylethyl carbonate
xxvii. chloromethyl cyclohexyl carbonate
xxviii. chloromethyl isobutyl carbonate
xxix. chloromethyl 4-methylcyclohexyl carbonate
xxx. chloromethyl 2-(methylthio)ethyl carbonate
xxxi. chloromethyl 3-methylcyclohexyl carbonate
xxxii. chloromethylpentan-2-yl carbonate
xxxiii. chloromethyl neopentyl carbonate
xxxiv. methyl 1-((chloromethoxy)carbonyloxy)cyclopropanecarboxylate
xxxv. chloromethyl cyclopropylmethyl carbonate
xxxvi. chloromethyl 2,2-diethoxyethyl carbonate
xxxvii. chloromethyl cyclopentylmethyl carbonate
xxxviii. methyl 2-((chloromethoxy)carbonyloxy)propanoate
xxxix. (S)-chloromethyl 2,2,4-trimethylcyclopent-3-enyl carbonate
xl. chloromethyl 1,3-dioxolan-2-yl carbonate
xli. chloromethyl (2,6-dimethylcyclohexyl)methyl carbonate
xlii. chloromethyl 2-(tetrahydro-2H-pyran-2-yl)ethyl carbonate
xliii. chloromethyl(tetrahydro-2H-pyran-4-yl)methyl carbonate
xliv. chloromethyl tetrahydro-2H-pyran-4-yl carbonate
xlv. chloromethyl 1-methylcyclopentyl carbonate
xlvi. chloromethyl 1-cyclopentylethyl carbonate
xlvii. chloromethyl 3-methylcyclopentyl carbonate
xlviii. chloromethyl 3,3-dimethylcyclohexyl carbonate
xlix. chloromethyl 2,5-dimethylcyclohexyl carbonate
l. chloromethyl 1-(4-methylcyclohexyl)ethyl carbonate
li. chloromethyl (3-methyloxetan-3-yl)methyl carbonate
lii. chloromethyl (3-methyloxetan-3-yl)methyl carbonate
liii. chloromethyl 2-isopropoxyethyl carbonate
liv. (chloromethyl carbonic) 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoic anhydride
lv. 4-((chloromethoxy)carbonyloxy)-2-hydroxy-4-oxobutanoic acid
lvi. chloromethyl 4-formyl-2-methoxyphenyl carbonate
lvii. chloromethyl 3-oxobutan-2-yl carbonate

lviii. methyl 4-((chloromethoxy)carbonyloxy)benzoate
lix. (R)-2-amino-3-((chloromethoxy)carbonyloxy)propanoic acid
lx. 3-tert-butyl-4-methoxyphenyl chloromethyl carbonate
lxi. (R)-2-amino-3-(4-((chloromethoxy)carbonyloxy)phenyl)propanoic acid
lxii. (R)-2-amino-4-((chloromethoxy)carbonyloxy)-4-oxobutanoic acid
lxiii. (E)-chloromethyl 3,7-dimethylocta-2,6-dienyl carbonate
lxiv. methyl 4-((chloromethoxy)carbonyloxy)benzoate
lxv. chloromethyl 2-(4-methylcyclohex-3-enyl)propan-2-yl carbonate
lxvi. chloromethyl 3,7-dimethylocta-1,6-dien-3-yl carbonate
lxvii. 4-allyl-2-methoxyphenyl chloromethyl carbonate
lxviii. chloromethyl (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl carbonate
lxix. propyl 4-((chloromethoxy)carbonyloxy)benzoate
lxx. (E)-chloromethyl 3,7-dimethylocta-2,6-dienyl carbonate

**Type II Reagents**

i. chloromethyl cyclohexanecarboxylate
ii. chloromethyl 2-cyclohexylacetate
iii. chloromethyl 4-methylcyclohexanecarboxylate
iv. chloromethyl 1-methylcyclohexanecarboxylate
v. chloromethyl cyclopentanecarboxylate
vi. chloromethyl 1-(trifluoromethyl)cyclopentanecarboxylate
vii. chloromethyl cyclobutanecarboxylate
viii. chloromethyl 2-ethylhexanoate
ix. chloromethyl 3-cyclopentylpropanoate
x. chloromethyl cyclopropanecarboxylate
xi. chloromethyl pentanoate
xii. chloromethyl 2-methylpentanoate
xiii. chloromethyl 3,5,5-trimethylhexanoate
xiv. chloromethyl 2,2-dimethylbutanoate
xv. chloromethyl 2-methylbutanoate
xvi. chloromethyl hexanoate
xvii. chloromethyl 2-ethylbutanoate
xviii. chloromethyl butyrate
xix. chloromethyl 3-phenylpropanoate

xx. chloromethyl 2-phenylpropanoate
xxi. (R)-chloromethyl 2-phenylpropanoate
xxii. (S)-chloromethyl 2-phenylpropanoate
xxiii. (1r,4r)-chloromethyl 4-methylcyclohexanecarboxylate
xxiv. chloromethyl 4-methoxycyclohexanecarboxylate
xxv. chloromethyl 4,4-difluorocyclohexanecarboxylate
xxvi. chloromethyl 3-methoxycyclohexanecarboxylate
xxvii. (2R)-chloromethyl 2-methylcyclopentanecarboxylate
xxviii. (R)-chloromethyl 2-methylbutanoate
xxix. (S)-chloromethyl 2-methylbutanoate
xxx. (S)-chloromethyl 2-methoxy-2-phenylacetate
xxxi. (S)-chloromethyl 2-phenylpropanoate
xxxii. (S)-chloromethyl 2-phenylbutanoate
xxxiii. (S)-chloromethyl 3-phenylbutanoate
xxxiv. bis(chloromethyl) 2,2-dimethylmalonate
xxxv. bis(chloromethyl) oxalate
xxxvi. chloromethyl 2-cyclopropylacetate
xxxvii. chloromethyl 2-cyclobutylacetate
xxxviii. chloromethyl 2-cyclopentylacetate
xxxix. chloromethyl 2-(tetrahydrofuran-3-yl)acetate
xl. chloromethyl 2-(tetrahydro-2H-pyran-4-yl)acetate
xli. chloromethyl 2-methylcyclopropanecarboxylate
xlii. chloromethyl 2-(1-methylcyclobutyl)acetate
xliii. chloromethyl 2-(1-methylcyclopropyl)'acetate
xliv. chloromethyl propionate
xlv. chloromethyl acetate
xlvi. chloromethyl isobutyrate
xlvii. chloromethyl 2-isopropyl-3-methylbutanoate
xlviii. chloromethyl 3,5-dimethylcyclohexanecarboxylate
xlix. chloromethyl 2-propylpentanoate
l. chloromethyl 4-methoxybenzoate
li. chloromethyl 4-methylbenzoate
lii. chloromethyl 3-methylbenzoate
liii. chloromethyl 2,2,2-trifluoroacetate

liv. chloromethyl 5,5-dimethyl-3-oxohexanoate
lv. bis(chloromethyl) cyclopropane-1,1-dicarboxylate
lvi. chloromethyl 1,2-dihydrocyclobutabenzene-1-carboxylate
lvii. chloromethyl 2-cyclopentenylacetate
lviii. chloromethyl 2-phenylbutanoate
lix. chloromethyl 2,2-difluoroacetate
lx. chloromethyl 4-fluorobenzoate
lxi. chloromethyl 3-cyclohexylpropanoate
lxii. chloromethyl 2-cyclohexylacetate
lxiii. chloromethyl 3-(tetrahydro-2H-pyran-4-yl)propanoate
lxiv. chloromethyl 2-(tetrahydro-2H-pyran-3-yl)acetate
lxv. chloromethyl 3-(tetrahydro-2H-pyran-3-yl)propanoate
lxvi. chloromethyl nicotinate

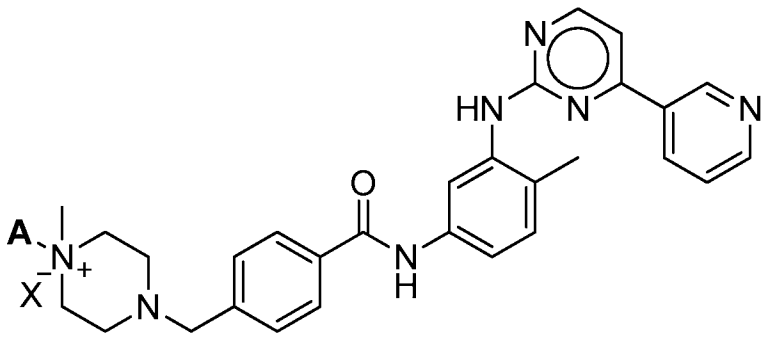
**Type III Reagents**

i. chloromethyl isopropylcarbamate
ii. chloromethyl diisopropylcarbamate
iii. chloromethyl dimethylcarbamate
iv. chloromethyl isobutylcarbamate
v. chloromethyl methylcarbamate
vi. chloromethyl ethyl(isopropyl)carbamate
vii. chloromethylisobutyl(methyl)carbamate
viii. (S)-chloromethyl sec-butylcarbamate
ix. chloromethyl methylcarbamate
x. chloromethyl isopropyl(methyl)carbamate
xi. chloromethyl propylcarbamate
xii. chloromethyl 2-methoxyethylcarbamate
xiii. chloromethyl methyl(propyl)carbamate
xiv. chloromethyl diisobutylcarbamate
xv. chloromethyl tert-butyl(isopropyl)carbamate
xvi. chloromethyl di-sec-butylcarbamate
xvii. chloromethyl aziridine-1-carboxylate
xviii. chloromethyl 2-methylcyclopropylcarbamate
xix. chloromethyl cyclopropylcarbamate

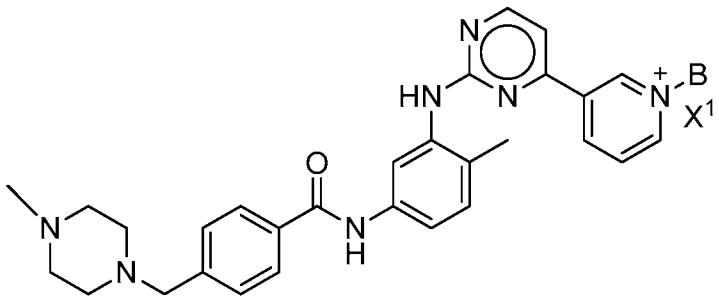
xx. chloromethyl cyclopropylmethyl(propyl)carbamate
xxi. chloromethyl cyclopropyl(methyl)carbamate
xxii. chloromethyl azetidine-1-carboxylate
xxiii. chloromethyl cyclobutylcarbamate
xxiv. chloromethyl 2,2-dimethylcyclobutylcarbamate
xxv. chloromethyl 3-methoxyazetidine-1-carboxylate
xxvi. chloromethyl cyclobutyl(methyl)carbamate
xxvii. chloromethyl oxetan-3-ylcarbamate
xxviii. (S)-chloromethyl 2-methylpyrrolidine-1-carboxylate
xxix. chloromethyl cyclopentylcarbamate
xxx. chloromethl cyclopentyl(methyl)carbamate
xxxi. chloromethyl tetrahydrofuran-3-ylcarbamate
xxxii. chloromethyl piperidine-1-carboxylate
xxxiii. (2R,6S)-chloromethyl 2,6-dimethylpiperidine-1-carboxylate
xxxiv. (R)-chloromethyl 2-methylpiperidine-1-carboxylate
xxxv. chloromethyl piperidine-1-carboxylate
xxxvi. chloromethyl 3-methoxycyclohexylcarbamate
xxxvii. chloromethyl cyclohexylmethylcarbamate
xxxviii. chloromethyl cyclohexylmethyl(methyl)carbamate
xxxix. chloromethyl morpholine-4-carboxylate
xl. (3S,5R)-chloromethyl 3,5-dimethylmorpholine-4-carboxylate
xli. (3R,5S)-chloromethyl 3,5-dimethylmorpholine-4-carboxylate
xlii. (2S,6R)-chloromethyl 2,6-dimethylmorpholine-4-carboxylate
xliii. chloromethyl 4-methylpiperazine-1-carboxylate
xliv. chloromethylazepane-1-carboxylate
xlv. chloromethylcycloheptylcarbamate
xlvi. chloromethyl oxepan-4-ylcarbamate
xlvii. chloromethyl (1R,2S,4S)-bicyclo[2.2.1]heptan-2-ylcarbamate
xlviii. chloromethyl 2,3-dihydro-1H-inden-1-ylcarbamate
xlix. chloromethyl benzylcarbamate
l. (S)-chloromethyl 1-phenylethylcarbamate
li. ethyl 2-((chloromethoxy)carbonylamino)-3-methylbutanoate
lii. ethyl 2-((chloromethoxy)carbonylamino)-3-phenylpropanoate
liii. (S)-diethyl 2-((chloromethoxy)carbonylamino)pentanedioate

liv. ethyl((chloromethoxy)carbonylamino)propanoate
lv. ethyl 2-amino-6-((chloromethoxy)carbonylamino)hexanoate
lvi. ethyl 2-((chloromethoxy)carbonylamino)-4-methylpentanoate
lvii. ethyl 2-((chloromethoxy)carbonylamino)-3-methylpentanoate
lviii. (S)-dimethyl 2-((chloromethoxy)carbonylamino)succinate
lix. (S)-ethyl 2-((chloromethoxy)carbonylamino)-5-guanidinopentanoate
lx. (S)-ethyl 4-amino-2-((chloromethoxy)carbonylamino)-4-oxobutanoate
lxi. (S)-ethyl 2-amino-5-((chloromethoxy)carbonylamino)pentanoate
lxii. (S)-ethyl 5-amino-2-((chloromethoxy)carbonylamino)-5-oxopentanoate
lxiii. ethyl 2-((chloromethoxy)carbonylamino)-4-(methylthio)butanoate
lxiv. 1-chloromethyl 3-methyl 2-methyl-5,6-dihydropyridine-1,3(2H)-dicarboxylate
lxv. (S)-chloromethyl (1-methylpyrrolidin-2-yl)methyl carbonate
lxvi. (R)-chloromethyl (1-methylpyrrolidin-2-yl)methyl carbonate
lxvii. (S)-(1-benzylpyrrolidin-2-yl)methyl chloromethyl carbonate
lxviii. chloromethyl 1H-pyrrole-1-carboxylate
lxix. chloromethyl 2-nicotinoylhydrazinecarboxylate
lxx. (6S)-3-chloro-7-((chloromethoxy)carbonylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
lxxi. (6S)-7-((chloromethoxy)carbonylamino)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
lxxii. (6S)-7-((chloromethoxy)carbonylamino)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
lxxiii. (6R,7R)-7-((chloromethoxy)carbonylamino)-3-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
lxxiv. chloromethyl 3-(4-chlorophenyl)-1H-pyrazole-1-carboxylate
lxxv. chloromethyl 3-(4-fluorophenyl)-1H-pyrazole-1-carboxylate
lxxvi. chloromethyl 3-phenyl-1H-pyrazole-1-carboxylate
lxxvii. chloromethyl 3-(4bromophenyl)-1H-pyrazole-1-carboxylate
lxxviii. chloromethyl 2-cyano-1H-pyrrole-1-carboxylate
lxxix. chloromethyl 4-oxopiperidine-1-carboxylate
lxxx. 1-chloromethyl 3-ethyl 2-oxopiperidine-1,3-dicarboxylate
lxxxi. chloromethyl 2,2,6,6-tetramethyl-4-oxopiperidine-1-carboxylate
lxxxii. chloromethyl 2-oxopiperidine-1-carboxylate

The novel compounds of the present application include compounds of Formula **(III)** and Formula **(IV)**:




Formula **(III)**




Formula **(IV)**

Where A or B =

| | | | |
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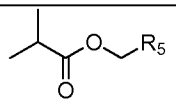
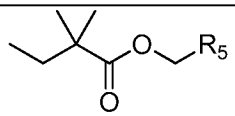
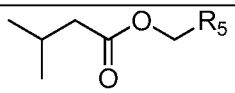
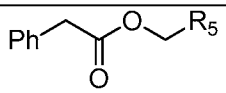
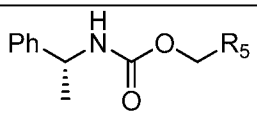
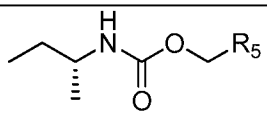
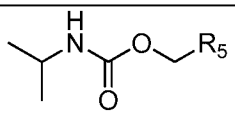
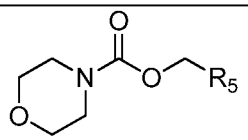
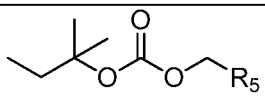
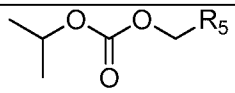
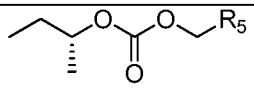
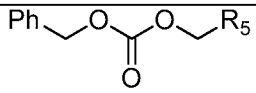
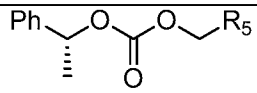
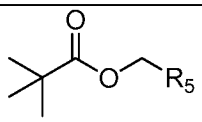
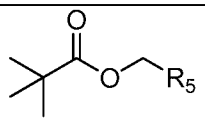
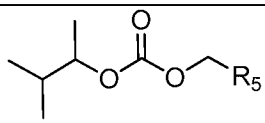
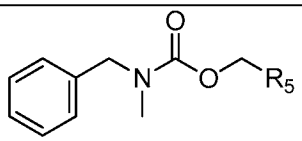
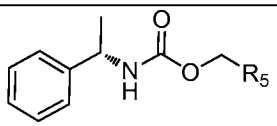
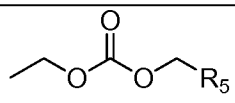
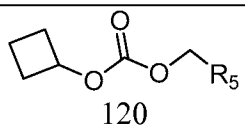
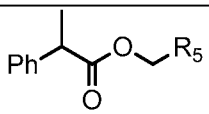
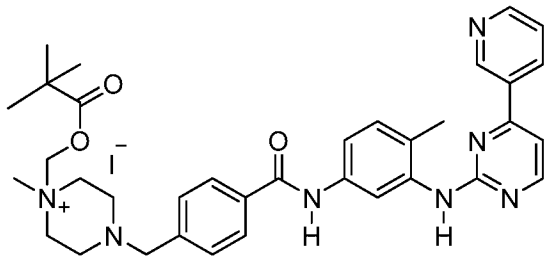
|  101 |  102 |  103 |  104 |
|  105 |  106 |  107 |  108 |
|  109 |  110 |  111 |  112 |
|  113 |  114 |  115 |  116 |
|  117 |  118 |  119 |  120 |
|  121 | | | |

where $R^5$ represents a nitrogen atom of the imatinib moiety linked to A or B, and

X may be iodide, chloride, bromide, mesylate, tosylate, or any other pharmaceutically acceptable anion to provide a pharmaceutically acceptable salt.

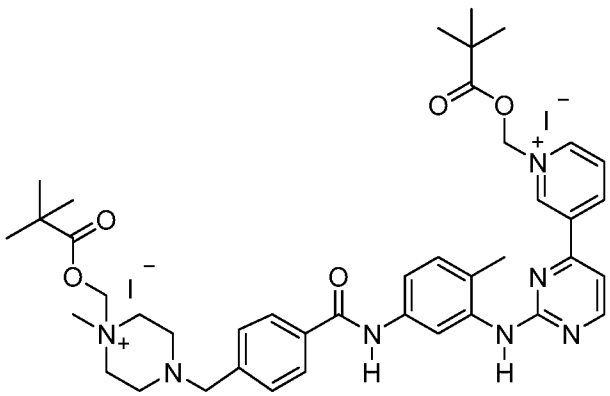
The compounds generated may be present as a single stereoisomer (e.g., enriched to at least 95% purity relative to the total amount of all stereoisomers present), a racemate, or a mixture of enantiomers or diastereomers in any ratio.

The novel compounds herein may be any of the compounds as below:



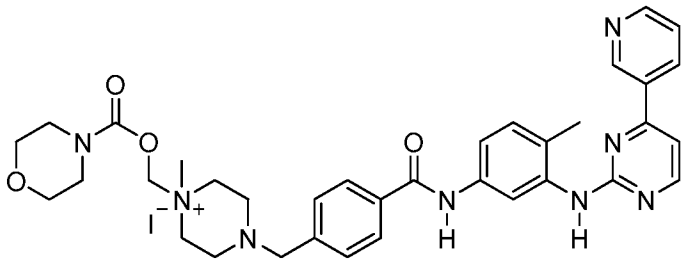
**1002**

1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((pivaloyloxy)methyl)piperazin-1-ium iodide,



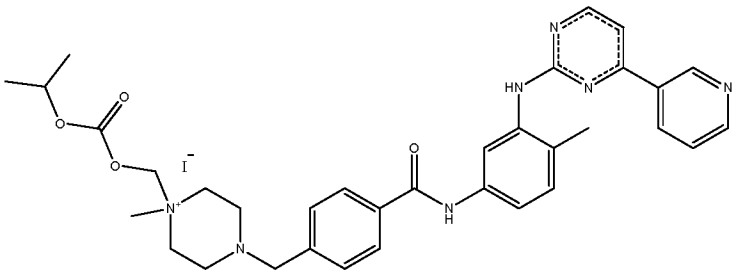
**1003**

1-methyl-4-(4-((4-methyl-3-((4-(1-((pivaloyloxy)methyl)pyridin-1-ium-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((pivaloyloxy)methyl)piperazin-1-ium diiodide



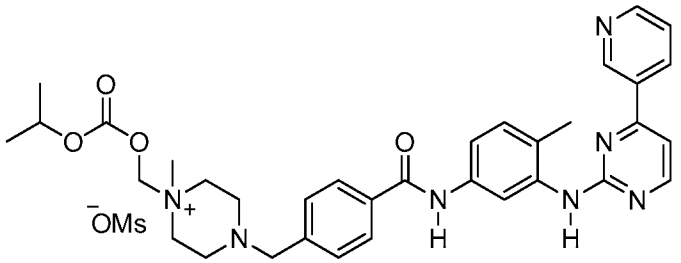
1004

1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((morpholine-4-carbonyl)oxy)methyl)piperazin-1-ium iodide



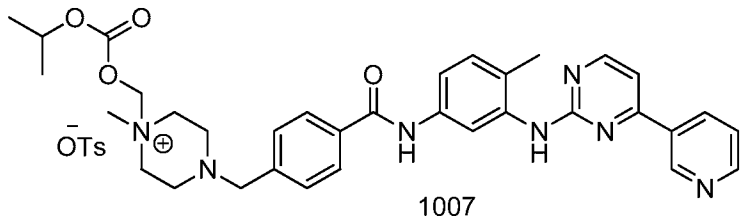
1005

1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide



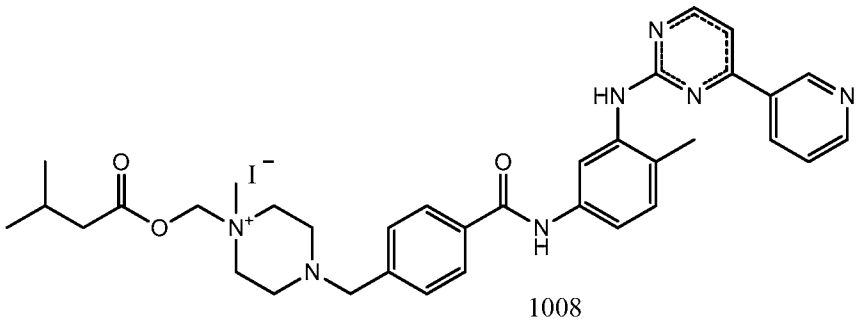
1006

1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methane sulfonate



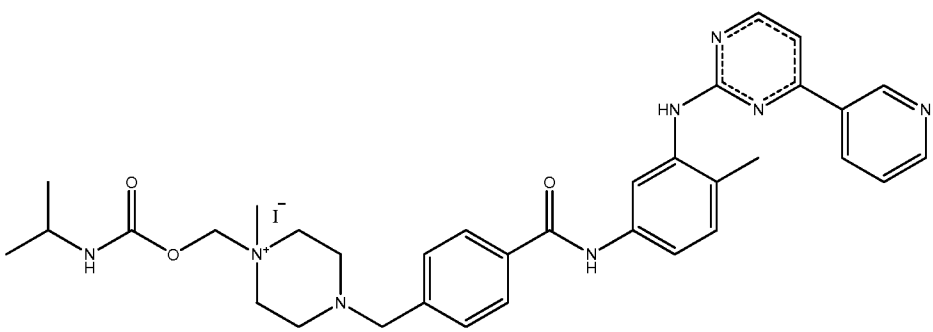
1007

1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium p-tolyl sulfonate



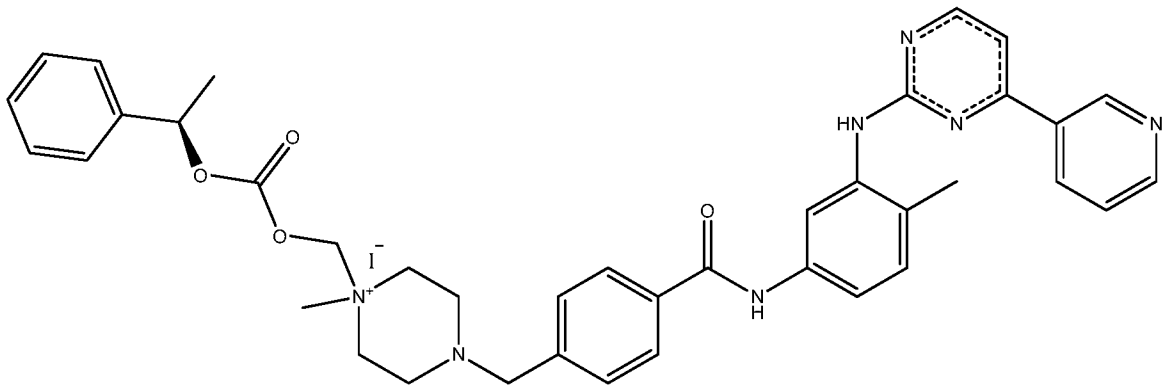
1008

1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((3-methylbutanoyloxy)methyl)piperazin-1-ium iodide



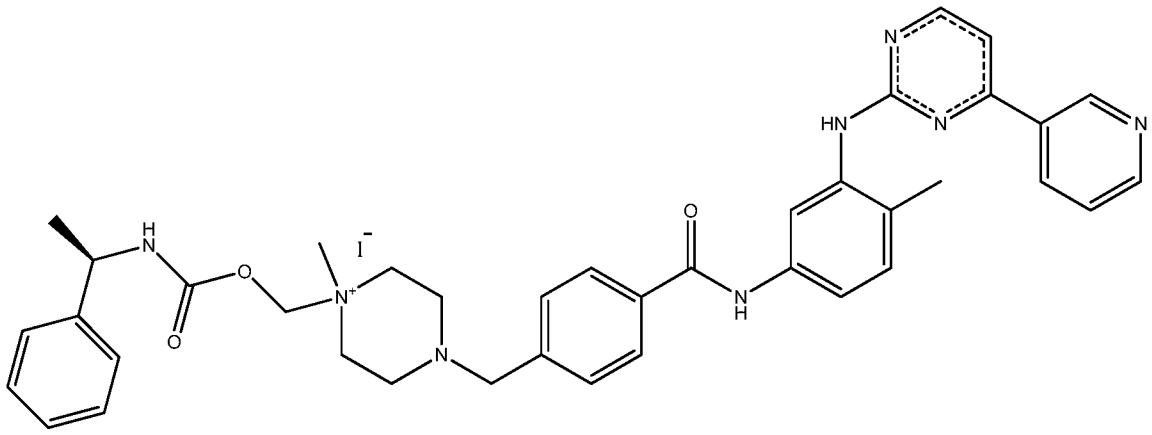
**1009**

1-((isopropylcarbamoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



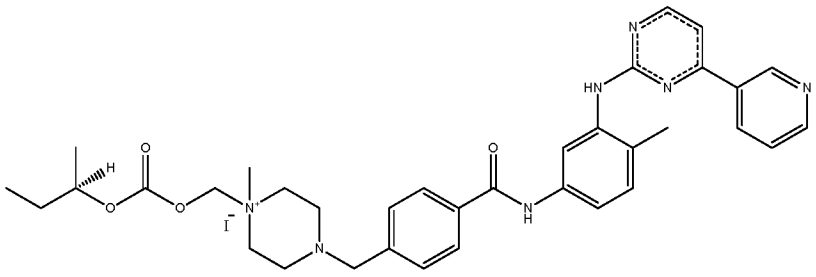
**1010**

(R)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-(((1-phenylethoxy)carbonyloxy)methyl)piperazin-1-ium iodide



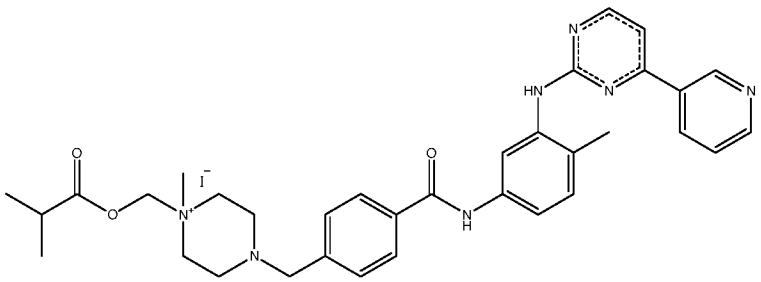
**1011**

(R)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((1-phenylethylcarbamoyloxy)methyl)piperazin-1-ium iodide



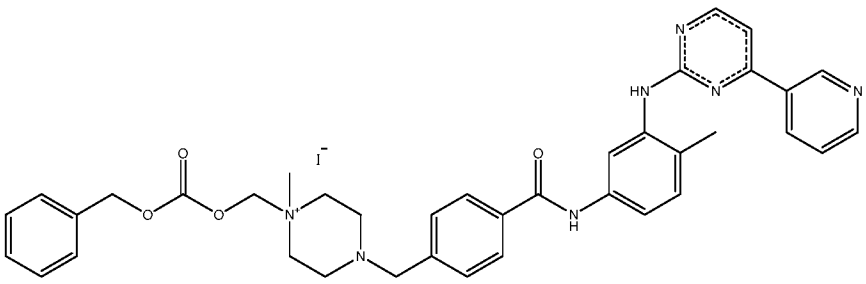
**1012**

(R)-1-((sec-butoxycarbonyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



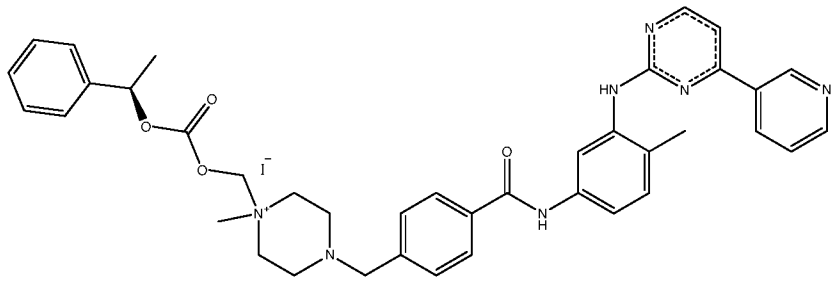
**1013**

1-(isobutyryloxymethyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



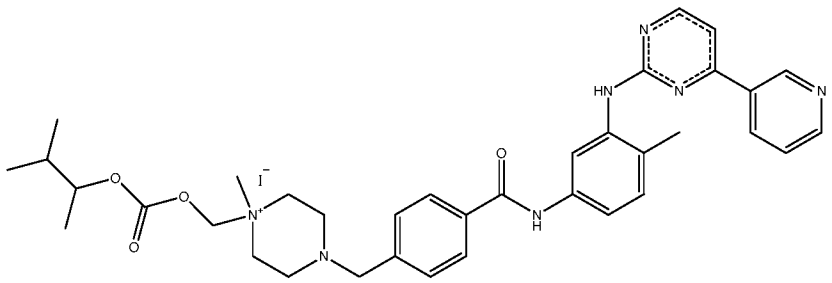
**1014**

1-((benzyloxycarbonyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



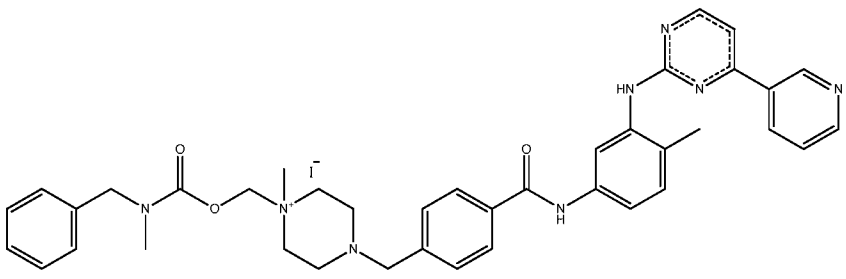
**1015**

(R)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-(((1-phenylethoxy)carbonyloxy)methyl)piperazin-1-ium iodide



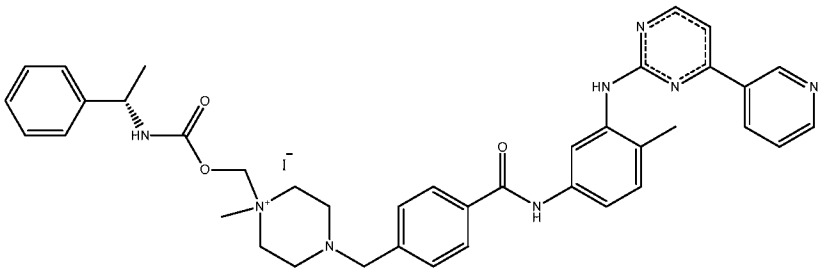
**1016**

1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-(((3-methylbutan-2-yloxy)carbonyloxy)methyl)piperazin-1-ium iodide



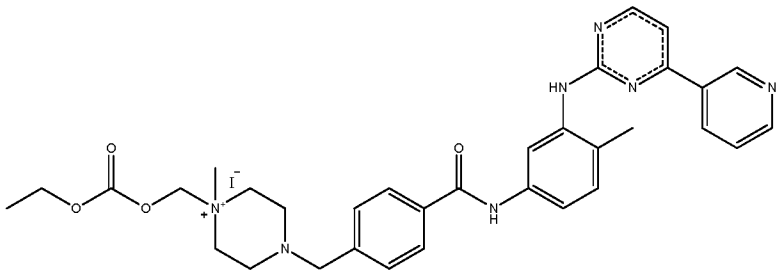
**1017**

1-((benzyl(methyl)carbamoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



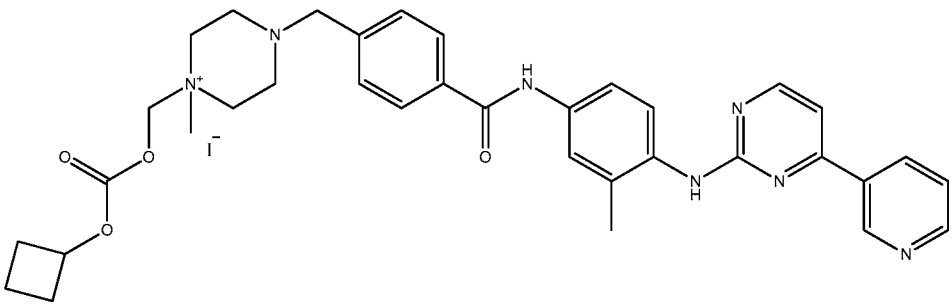
**1018**

(S)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((1-phenylethylcarbamoyloxy)methyl)piperazin-1-ium iodide



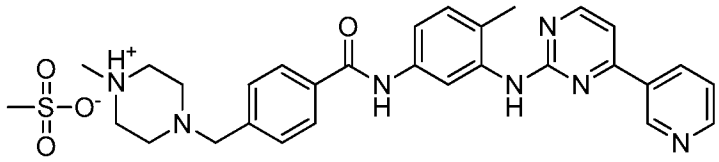
**1019**

1-((ethoxycarbonyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



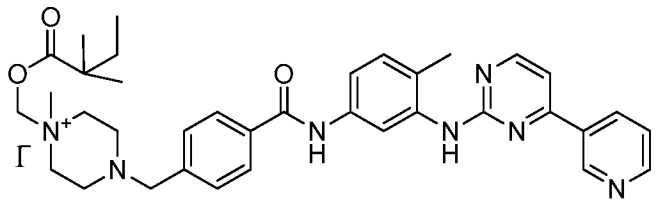
**1020**

1-((cyclobutoxycarbonyloxy)methyl)-1-methyl-4-(4-(3-methyl-4-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



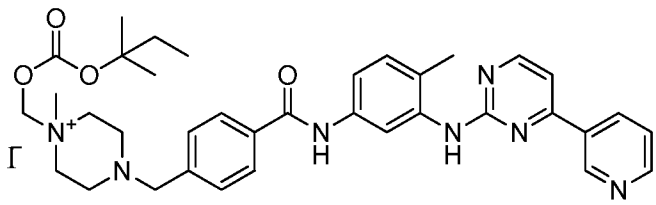
1026

1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methanesulfonate



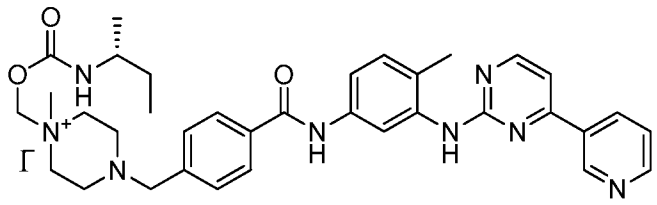
1027

1-((2,2-dimethylbutanoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



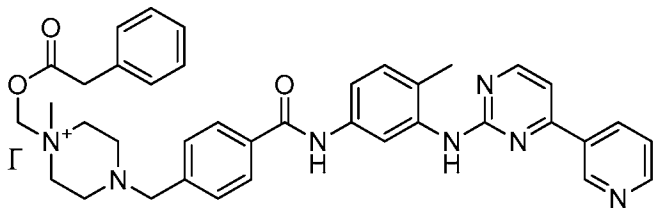
1028

1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((tert-pentyloxycarbonyloxy)methyl)piperazin-1-ium iodide



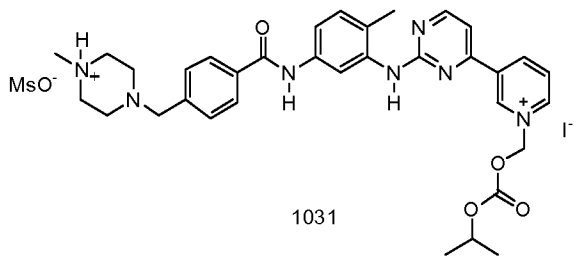
1029

(R)-1-((sec-butylcarbamoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide



**1030**

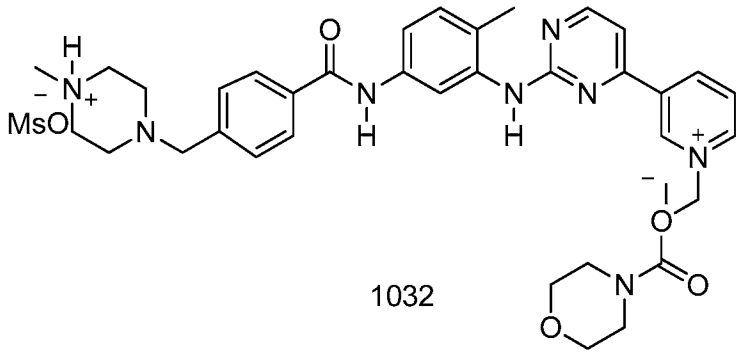
1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium iodide



1031

4-(4-((3-((4-(1-(((isopropoxycarbonyl)oxy)methyl)pyridin-1-ium-3-yl)pyrimidin-2-yl)amino)-4-methylphenyl)carbamoyl)benzyl)-1-methylpiperazin-1-ium

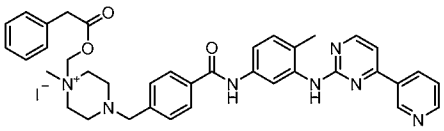
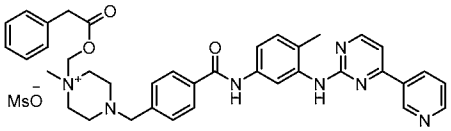
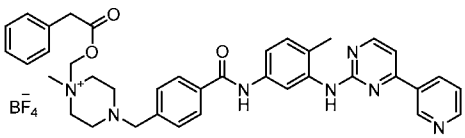
4-(4-((3-((4-(1-(((isopropoxycarbonyl)oxy)methyl)pyridin-1-ium-3-yl)pyrimidin-2-yl)amino)-4-methylphenyl)carbamoyl)benzyl)-1-methylpiperazin-1-ium monoiodide monomesylate

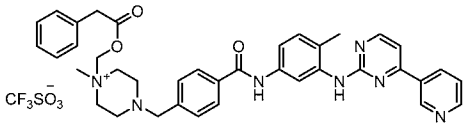
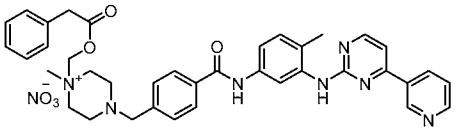
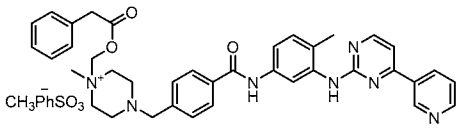
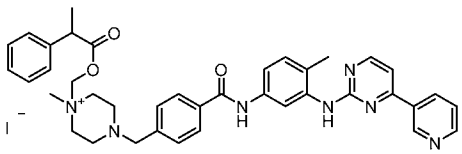


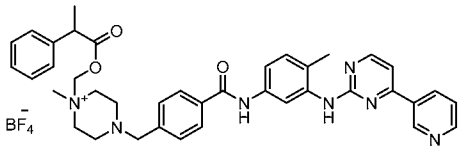
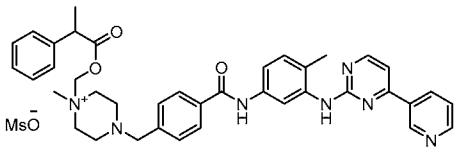
1032

3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl) methyl) benzamido)phenyl)amino)pyrimidin-4-yl)-1-(((morpholine-4-carbonyl)oxy)methyl)pyridin-1-ium monoiodide monomesylate

**Table 1:**

| No. | Structure | IUPAC name | m/z |
|---|---|---|---|
| 1030 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium iodide | 643 |
| 10737.02 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium methanesulfonate | 643 |
| 10737.04 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2- | 643 |

| | | | |
|---|---|---|---|
| | | phenylacetoxy)methyl)piperazin-1-ium tetrafluoroborate | |
| 10737.06 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium trifluoromethanesulfonate | 643 |
| 10737.07 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium nitrate | 643 |
| 10737.08 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium p-toluene sulfonate | 643 |
| 11124.01 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((2-phenylpropanoyl)oxy)methyl)piperazin-1-ium iodide | 657 |

| | | | |
|---|---|---|---|
| 11124.02 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((2-phenylpropanoyl)oxy)methyl)piperazin-1-ium tetrafluoroborate | 657 |
| 11124.03 |  | 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((2-phenylpropanoyl)oxy)methyl)piperazin-1-ium methanesulfonate | 657 |

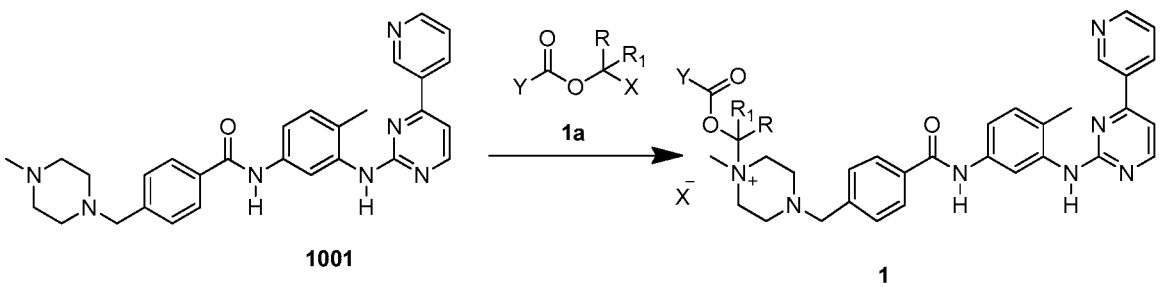
## A. SYNTHESIS OF THE COMPOUNDS OF THE PRESENT INVENTION

The present invention also relates to a process of synthesis of the compounds of the present invention;

The synthesis of the compounds of the present invention may be as enumerated below:

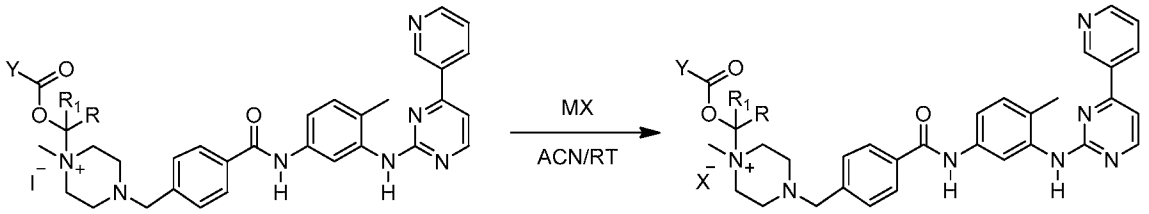
**Scheme A: General Scheme for synthesis of the compounds of the present invention:**

**Step1:-**



Imatinib (1001) when reacted with a suitable halomethyl reagent (Type I or II or III) **[1a]** in a solvent such as DCM at a temperature ranging from room temperature to refluxing followed by evaporation of excess of solvent yield final product **[1]** which may be further purified to desire level either by crystallization of by washing with a solvent such as ether.

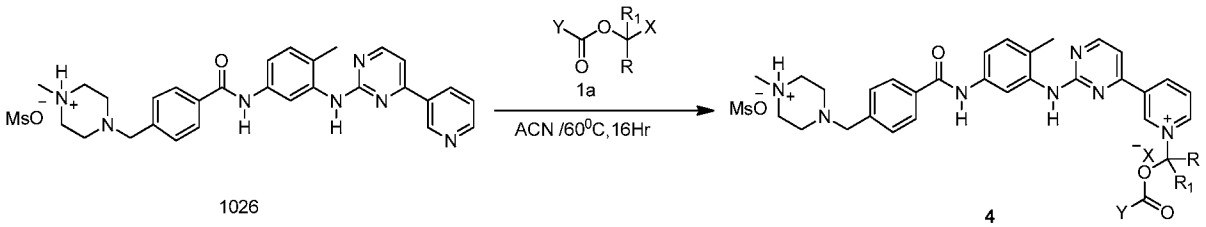
Step 2:-General Scheme for counter ion exchange:




2 3

A quaternary salt such as **[2]** may be prepared by the method describe above in step 1 with a suitable halomethyl formyl reagent such as iodo methyl formyl (Type I or Type II or Type III). Compound **[2]** may be treated with a suitable metal salt such as silver mesylate in a suitable solvent such as acetonitrile at a desired temperature ranging from ambient to refluxing which results in the precipitation of silver iodide and formation of desired product **[3]**. The insoluble silver halide maybe filtered out to get reasonably pure desire product **[3]**.

Scheme B:




1026 4

Imatinib mesyalte, 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methanesulfonate **[1026]** reacted with suitable halomethyl reagent (Type I or II or III) **[1a]** in dry solvent such as acetonitrile and at a temperature ranging from room temperature to refluxing followed by evaporation of excess

of solvent yield final product **[4]** which if required can be purified further either by crystallization or by solvent washing with a solvent such as ether.

The above methods are applicable to do anion exchange on all type of quaternary salts having any halide such as chloride, bromide or iodide as the counter ion. The non limiting list of silver salts that may be use includes silver acetate, silver mesylate, silver tosylate, silver oxalate, silver tartrate, silver triflate etc.

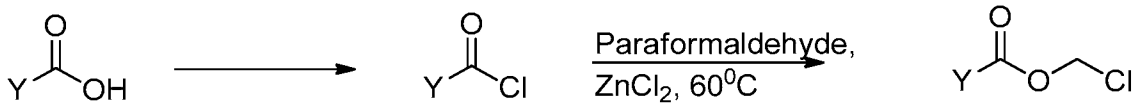
The compounds of formula II may be divided in three classes i.e. Type I, where Y = $OR^2$; Type II, where Y = $R^2$ and Type III, where Y = $NR^2R^3$ and may be synthesized by the general schemes as below.

**General methods for the preparation of Formula II:**

The compounds of formula II (Type I, II, III) may be prepared from respective acids, amines and alcohols directly. An acid with or without activation may be reacted with a corresponding aldehyde in presence of a Lewis acid may provide Type II reagent. An alcohol may be reacted with a halomethylhaloformate in presence of a base to provide Type I reagent. Similarly, an amine (primary or secondary) may be reacted with halomethyl haloacetate with or without the presence of base may provide Type III reagent.

**General Method to Synthesize Type II Reagents**

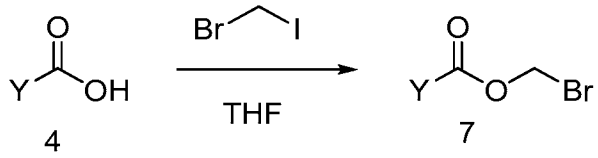
**Scheme C**




**4** **5** **6**

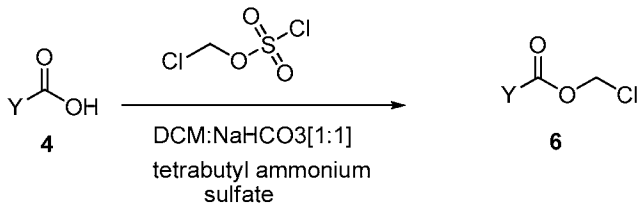
Lewis acids such as zinc chloride (dry), aldehydes such as paraformaldehyde and acid chlorides, **[5]**, may be reacted under anhydrous conditions and at appropriate temperatures, typically between -10°C and 60°C for a time ranging up to 24 hours. The reaction mixture may be diluted with solvents such as dichloromethane, washed with aqueous dilute base such as a solution of $Na_2HCO_3$. Standard work up and purifications yield the desired Reagents, **[6]**.

**]Scheme 2**




Metal salt of desired acid such as caesium salt of Acid **[4]**,may be treated with bromoiodomethane in Dry THF at appropriate temperatures,typically between 0 °C to RT for 16 hours and if required heating. The reaction mixture may be diluted with solvents such as ethyl acetate, washed with aqueous dilute base such as aqueous solution of $Na_2HCO_3$. Standard work up and purifications yield the desired Reagents **[7]**.

**Scheme E**

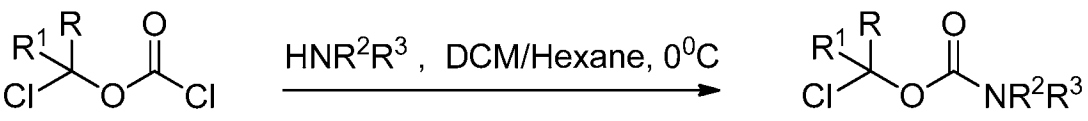



To a vigorously stirred, solution of acid **[4]** in a solvent such as dichloromethane at room temperature, a base such as sodium bicarbonate and tetrabutylammonium bisulfate in water was added, followed by the drop-wise addition of a solution of chloromethyl chlorosulfate in a solvent such as dichloromethane. After completion of reaction, organic layer was washed with 5% aqueous $Na_2CO_3$. Standard work up and purifications yields desired reagents, **[6]**.

l.

**General Method to Synthesize Type III Reagents**

**Scheme F**




**8** **9**

Corresponding primary or secondary amines may be reacted with substituted or unsubstituted chloro methylchloroformate, **[8]**, in a solvent such as hexane or DCM at 0 °C. The reaction mixture may be filtered and the filtrate may be washed with 1.0 N HCl. The organics may be evaporated to get the desired reagent, **[9]**. If required, further purification may be achieved using any general purification method practiced in organic chemistry laboratory such as precipitation or crystallization or preparative column purification.

As illustrated above, R and $R^1$ are each independently selected from H, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl and heteroaryl substituents; or R and $R^1$ taken together with the atom to which they are attached form a 3- to 7-membered ring, wherein the 3- to 7-membered ring optionally contains up to two heteroatom groups selected from O, N $R^4$, S, SO and $SO_2$, and is optionally substituted with 1 to 4 alkoxy, F or Cl substituents;

Y is selected from $R^2$, $OR^2$, $NH_2$, $NHR^2$, and $NR^2R^3$;

$R^2$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of said $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl substituents;

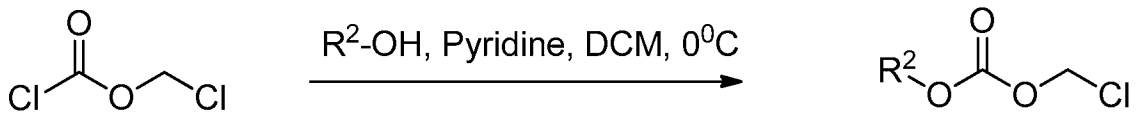
$R^3$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl; or

$R^2$ and $R^3$ may be taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered ring, wherein the 3- to 7-membered ring optionally contains up to

three heteroatom groups selected from O, $NR^4$, S, SO and $SO_2$, and is optionally substituted with alkoxy, F or Cl.

**General Method to Synthesize Type I Reagents**

**Scheme G**

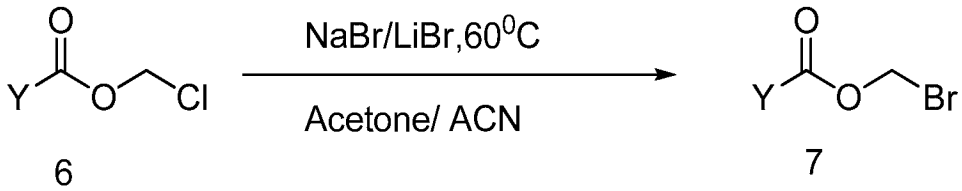



**10** **11**

To the solution of chloromethylchloroformate, **[10]**, in a solvent such as hexane, may be added solution of pyridine in hexane, drop wise under ice cooling. To this reaction mixture, the corresponding alcohol may be added at the same temperature. The reaction mixture may be stirred for a time ranging up to 24 hrs. Standard work up and purifications yield the desired corresponding carbonate reagent, **[11]**.

As illustrated above, $R^2$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of said $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl substituents.

**Scheme H: General Synthetic Scheme for halide exchange:**

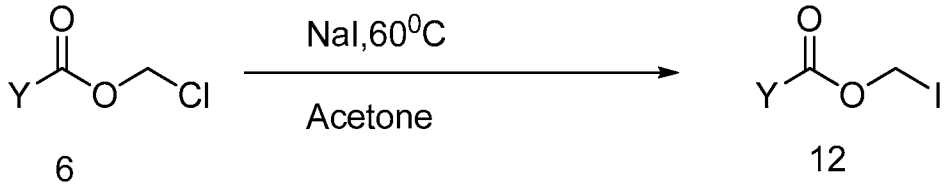



6 7

Reagents **[6]** when treated with bromide suitable reagent such as lithium bromide or sodium bromide at appropriate temperatures, typically in the range of 40 -80°C for a time ranging up

to 24 hours followed by standard work up and purification, yields desired bromo Reagents, [7].

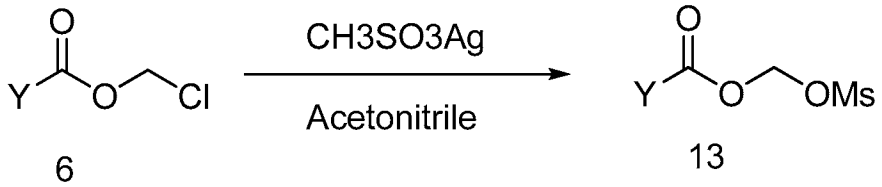
**Scheme I**




6 12

Reagents **[6]** when treated with a reagent such as sodium iodide at appropriate temperatures, typically ranging from room temperature to 60°C for a time ranging up to 24 hours followed by a standard work up and purification, yields desired iodo Reagents, **[12]**.

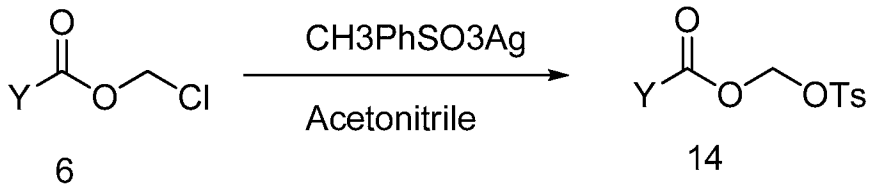
**Scheme J**




6 13

Reagents **[6]** when treated with silver salt of methane sulfonic acid at appropriate temperatures, typically ranging from room temperature to 60°C to 90°C for a time ranging up to 24 hours followed by standard work up and purification, yield desired ((methylsulfonyl)oxy) Reagents, **[14]**.

**Scheme K**




6 14

Reagents **[6]** when treated with silver salt of p-methyl benzene sulfonic acid at appropriate temperatures, typically ranging from room temperature to 60°C to 90°C for a time ranging up to 24 hours followed by standard work up and purification yield the desired ((methylsulfonyl)oxy) Reagents, **[14]**.

## B. COMPOSITION OF THE COMPOUNDS OF THE PRESENT INVENTION

The present invention further provides pharmaceutical compositions comprising a compound of formula (I) or its pharmaceutically acceptable salt thereof as an active ingredient along with pharmaceutically acceptable additives/ excipients/ adjuvants/ vehicles. The composition may be administered in a variety of ways including orally, nasally, buccally, sublingually, intravenously, transmucosally, parenterally, by inhalation, spray, transdermally, subcutaneously, intrathecally topically or rectally and may be formulated according to methods known in the art.

The effective dosage form for a mammal may be about 0.1- 100 mg/ kg of body weight of active compound, which may be administered as a single dose or in the form of individual doses, such as from 1 to 4 times a day.

The mammal may be an adult human.

The compounds of the present invention may optionally be administered with one or more additional drugs. Exemplary additional drugs include one or more compounds independently selected from the group comprising central nervous system drugs, such as cns/respiratory stimulants, analgesics, narcotic agonists, narcotic agonist/antagonists, nonsteroidal anti-inflammatory/analgesic agents, behavior-modifying agents, tranquilizers/sedatives, anesthetic agents, inhalants, narcotics, reversal agents, anticonvulsants, muscle relaxants, skeletal, muscle relaxants, smooth, euthanasia agent, cardiovascular agents, inotropic agents, antiarrhythmic drugs, anticholinergics, vasodilating agents, agents used in treatment of shock, alpha-adrenergic blocking agents, beta-adrenergic blocking agents, respiratory drugs, bronchodilators, sympathomimetics, antihistamines, antitussives, renal and urinary tract, agents for urinary incontinence/retention, urinary alkalinizers, urinary acidifiers, cholinergic stimulants, agents for urolithiasis, gastrointestinal agents, antiemetic agents, antacids, h2 antagonists, gastromucosal protectants, proton pump inhibitors, appetite stimulants, gi antispasmodics-anticholinergics, gastro intestinal stimulants, laxatives, saline, bulk producing, lubricant, surfactant, antidiarrheals, hormones/endocrine/reproductive agents, sex hormones, anabolic steroids, posterior pituitary hormones, adrenal cortical steroids, glucocorticoids, antidiabetic agents, thyroid drugs, thyroid hormones, misc. endocrine/reproductive drugs, prostaglandins, antiinfective drugs, antiparasitics, anticoccidial agents, antibiotics, anti-tuberculosis, aminocyclitols,cephalosporins, macrolides, penicillins, tetracyclines, lincosamides, quinolones, sulfonamides, miscellaneous antibacterials,

antifungal agents, antiviral agents, blood modifying agents, clotting agents, anticoagulants, erythropoietic agents, antineoplastics/immunosuppresives, alkylating agents, antidotes, bone/joint agents, dermatologic agents (systemic), vitamins and minerals/nutrients, systemic acidifiers, systemic alkalinizers, anti-cancer agents, anti-viral agents, etc.

## C. METHODS OF USE

The present invention further provides a method of prophylaxis and/or treatment of, and/or ameliorating the symptoms of diseases comprising administering a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising the compound of formula (I) as the active ingredient.

The compounds of the present invention are useful as c-ABL1 inhibitors and are useful in all disorders where alteration of the amount of c-ABL1 is required in mammals, including humans. The compounds of the present invention may also act as PGDFR inhibitors in mammals, including humans. The compounds of the present invention may also act as inhibitors of stem cell factor receptor (SCFR), also known as c-Kit, in mammals, including humans.

The compounds of the present invention may be used to treat mammals including humans, suffering from a tumoral disease a dose, effective against tumours.

Imatinib mesylate (Gleevec) has been shown to be effective against poxvirus infections by disabling host proteins essential to the virus life cycle (Nature Medicine, 2005, vol.11, 7, page 731-739) and without interfering with the acquisition of immune memory (Journal of Virology, 2011, vol.85, 1, p.21-31).

Similarly, by targeting the host gene products rather the virus itself, short-term administration of imatinib mesylate may be useful in treating Ebola virus infections (Science Translational Medicine, 2012, vol.4, 123, page 1-10).

Furthermore, Abl family kinases have been shown to regulate the susceptibility of cells to polyomavirus infection by modulating gangliosides required for viral attachment (Journal of Virology, 2010, vol.84, 9, p.4243-4251). Hence, Abl kinase inhibitor, e.g., imatinib mesylate may prove useful as therapeutics of human polyomaviruses.

The present application provides a method for preventing or treating a bacterial infection or a viral infection in a subject using a novel compounds as described herein.

In certain embodiments, the bacterial infection is caused by *Pseudomonas aeruginosa, Chlamydia trochomatis, Escherichia coli, Helicobacter pylori, Listeria monocytogenes, Salmonella typhimurium, Shigella flexneri,* or *Mycobacterium tuberculosis*.

In certain embodiments, *Mycobacterium tuberculosis* causes MDR-tuberculosis or XDR-tuberculosis.

In certain embodiments, the viral infection is caused by a Vaccinia virus, a variola virus, a polyoma virus, a Pox virus, a Herpes virus, a cytomegalovirus (CMV), a human immunodeficiency virus, JC virus, BK virus, Simian virus 40 (SV40), Monkeypox virus, Ebola virus, Marburg virus, Bunyavirus, Arenavirus, Alphavirus e.g., Venezualan equine encephalitis (VEE), Western equine encephalitis (WEE), Flavirus, West Nile virus or SARS Coronovirus.

In some embodiments, the compounds described in the present application have improved/ maintain desirable safety and toxicity profile relative to imatinib mesylate.

In some embodiments, the compounds described in the present application are more soluble than imatinib mesylate in saline and/or at biologically useful pH ranges.

In some embodiments, the compounds described in the present application have modified rate of conversion and thereby may cause a change in the dosage and/or dosing regimen relative to imatinib mesylate.

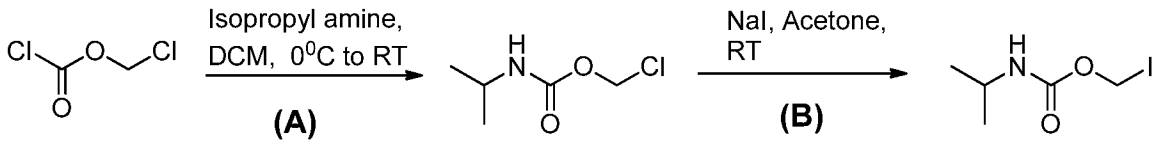
In some embodiments, the compounds described in the present application may be such that they are cleaved in certain therapeutically important location(s), thereby enabling specificity and selectivity and or targeted drug delivery.

All of the U.S. Patents and other publications cited herein are expressly incorporated by reference herein in each of their entireties.

From the foregoing description, one of ordinary skill in the art can easily ascertain the essential characteristics of the instant invention, and without departing from the spirit and scope thereof can make various changes and/or modifications of the invention to adapt it to various usages and conditions. Accordingly, these changes and/or modifications are properly, equitably and intended to be, within the full range of equivalence of the claims that follow.

**EXAMPLES:**

**EXAMPLE 1: Synthetic Procedure for the synthesis an exemplary Type III reagent**




**10** **15** **16**

**Step (A):**

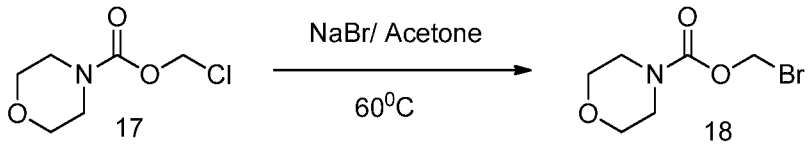
To the solution of chloromethylchloroformate **[10]** (1.0 g, 7.75 mmol, 1.0 eq) in DCM (y ml) was added a solution of isopropyl amine (0.95 g, 19.30 mmol, 2.5 eq) in DCM drop wise at 0°C. White solid precipitated out in the reaction mixture on addition. The resulting mixture was stirred for 2 hours at 0°C and then at RT for 1 hour. Reaction was monitored by TLC,. The reaction was worked up by diluting the reaction mixture with DCM, washing with saturated $NaHCO_3$ solution, followed by a wash with 2N HCl solution, again washing with saturated $NaHCO_3$ solution, and lastly with water. The organic layer was separated, dried over $Na_2SO_4$ and evaporated under reduced pressure to give chloromethyl isopropylcarbamate **[15]** as colorless oil (0.50 g, 44 %).

$^1H$ NMR [$CDCl_3$, 300 MHz]: δ 5.73 (s, 2 H), 4.73 (s, -NH), 3.78 - 3.91 (m, 1 H), 1.17 - 1.19 (d, 6 H)

**Step (B):**

Sodium iodide (0.6 g, 3.99 mmol, 3.0 eq) was added to a solution of chloromethyl isopropylcarbamate **[15]** (0.2 g, 1.33mmol, 1.0 eq) in acetone. The resulting reaction mixture was stirred at RT overnight. Reaction was monitored by TLC. The reaction was worked up by filtering out precipitated solid and evaporating the acetone layer under vacuum. The solid obtained was dissolved in DCM and filtered to get rid of residual solid. The DCM layer thus obtained was evaporated under reduced pressure to get a crude product, which was purified using silica gel column chromatography (2% MeOH: DCM, 100 - 200 mesh yield pure iodomethyl isopropylcarbamate **[16]** as colorless sticky material (0.12 g, 37 %). $^1H$ NMR [$CDCl_3$, 300 MHz]: δ 5.96 (s, 2 H), 4.65 (s, -NH), 3.80 - 3.91 (m, 1 H), 1.17 - 1.19 (d, 6 H).

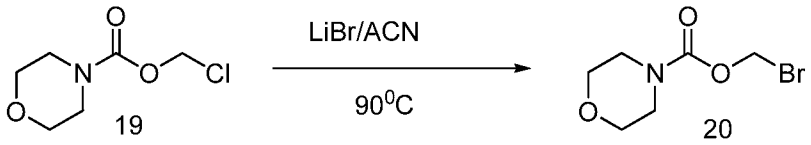
**EXAMPLE 2**




Chloromethyl morpholine-4-carboxylate **[17]** (0.3 g, 1.67 mmol, 1.0 eq) and sodium bromide (0.86 g, 8.3 mmol, 5.0 eq) was taken in acetone (10ml). The reaction was refluxed at 60$^0$C for 24 h. Reaction progress was monitored by TLC/$^1$H NMR. The reaction was filtered off and filtrate was evaporated to dryness under reduced pressure to yield light brown gel, bromomethyl morpholine-4-carboxylate**[18]** (0.30 g, 80%)

$^1$H NMR (CDCl3): δ ppm 5.92 (s, 2H), 3.72 (t, 4H), 3.54 δ(t, 4H)s

**EXAMPLE 3:**



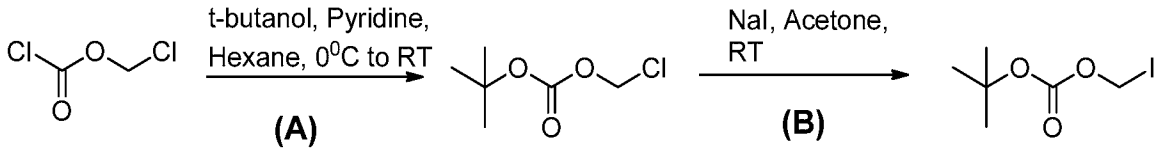

**Procedure:**

Chloromethyl morpholine-4-carboxylate **[19]** (0.3 g, 1.67 mmol, 1.0 eq) and lithium bromide (0.72 g, 8.3 mmol, 5.0 eq) was taken in acetonitrile (10ml). The reaction was refluxed at 90$^0$C for 30 h. Reaction progress was monitored by TLC/$^1$H NMR. The reaction was filtered off and filtrate was evaporated to dryness under reduced pressure to yield light brown gel, bromomethyl morpholine-4-carboxylate **[20]** (0.30 g, 80%)

$^1$H NMR (CDCl3): δ ppm 5.92 (s, 2H), 3.72 (t, 4H), 3.54 (t, 4H)

Other methyl formyl reagents were synthesized using the synthetic procedures disclosed above and herein with various substituted or unsubstituted alcohols, phenols, amines and acids to get various structures.

**EXAMPLE 4: Example of a typical Synthetic Procedure for the synthesis of Type I reagents**




**10** **21** **22**

**Procedures:**

Step **(A)**:

To a solution of chloromethylchloroformate **[10]** (7.75 mmol, 1 eq) in hexane was added a solution of pyridine (19.3 mmol, 2.5 eq) in hexane drop wise under ice cooling. After the complete addition, a white solid precipitate formed. *t*-Butanol (11.62 mmol, 1.5 eq) was added in hexane at the same temperature. After the addition of *t*-butanol the reaction mixture became a clear solution. The resulting mixture was stirred for 2 hours under ice cooling and then 1 hour at room temperature (RT). Reaction completion was monitored by TLC, which showed one non-polar spot compared to starting material. The reaction was worked up by diluting the reaction mixture with hexane and washing with saturated $NaHCO_3$ solution, followed by 2N HCl solution, followed by a second washing with saturated $NaHCO_3$ solution, and lastly by water. The organic layer was separated, dried over $Na_2SO_4$ and evaporated under reduced pressure to give the reagent *tert*-butyl (chloromethyl) carbonate **[21]** as a colorless sticky liquid (0.900 g, 70%).

$^1H$ NMR: [$CDCl_3$, 300 MHz]:- δ 5.774 (s, 2 H), 1.518 (s, 9 H).

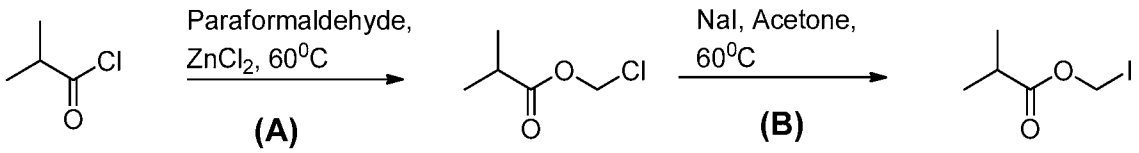
**Step (B):**

To a solution of *tert*-butyl (chloromethyl) carbonate **[21]** (9.87 mmol, 1 eq) dissolved in acetone was added sodium iodide (29.61 mmol, 3 eq). The resulting reaction mixture was stirred overnight at RT. The TLC showed consumption of starting material and one new non polar spot compared to starting material. The reaction was worked up by filtering out any precipitated solid and evaporating the acetone layer. The solid obtained was dissolved in DCM. The solution was filtered once again to eliminate any solid not dissolved in the DCM. The DCM layer obtained was evaporated. The crude product was passed through column

chromatography by using 100-200 mesh size silica and 1% MeOH-DCM as a solvent system to yield the product *tert*-butyl (iodomethyl) carbonate **[22]** as colorless liquid (136 mg, 30%).

$^1$H NMR [$CDCl_3$, 300 MHz]: δ 5.90 (s, 2 H), 1.518 (s, 9 H).

**EXAMPLE 5: Synthetic Procedure for an exemplary Type II reagent**




**23** **24** **25**

**Step (A):**

An appropriate Lewis acid such as zinc chloride (catalytic amount- 0.50 g) was fused in a dried 2-neck round bottomed flask under inert atmosphere. *Iso*-butyryl chloride **[23]** (46.72 mmol, 1 eq) and paraformaldehyde (47.0 mmol, 10 eq) are added to the prepared Lewis Acid at RT. The reaction mixture was heated to $60^0$ C overnight. The reaction was monitored by TLC. The reaction was stopped by addition of DCM and washed with saturated $NaHCO_3$ then brine. The organic layer was separated, dried over $Na_2SO_4$ and evaporated under reduced pressure to yield the product, chloromethyl isobutyrate **[24],** as colorless oil (2.0 g, 31 %).

$^1$H NMR [$CDCl_3$, 300 MHz]: δ 5.71 - 5.76 (d, 2 H), 2.54-2.64 (m, 1 H), 1.17 - 1.21 (d, 6 H)

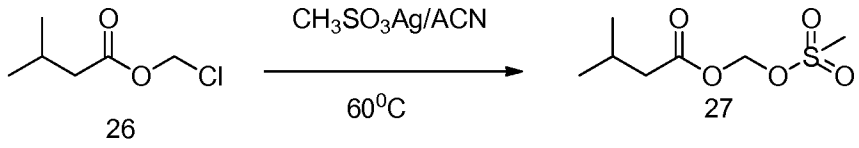
**Step (B):**

Sodium iodide (43.9 mmol, 3 eq) was added to a solution of chloromethyl isobutyrate **[24]** (14.6 mmol, 1 eq) in acetone. The resulting reaction mixture was stirred at RT overnight. Reaction completion was monitored by TLC. The reaction was worked up by filtering out precipitated solid and evaporation of excess of acetone under reduced pressure. A solid was obtained and washed with DCM while filtering under suction using a Buchner funnel. The DCM layer obtained was evaporated to provide crude product which was further purified

using silica gel column chromatography (100 - 200 mesh) and DCM as an eluent. The product, iodomethyl isobutyrate **[25]**, (1.6 g, 50% yield) was obtained as a brownish liquid.

$^1$H NMR [$CDCl_3$, 300 MHz]: δ 6.21 (s, 2 H), 2.54-2.64 (m, 1 H), 1.17 - 1.21 (d, 6 H).

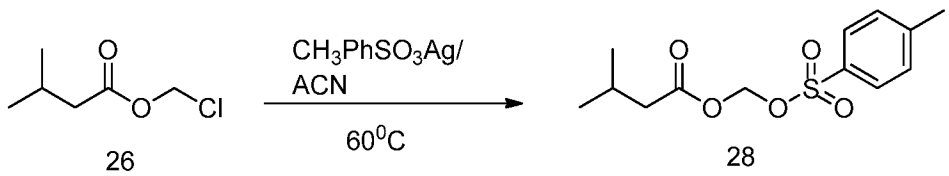
**EXAMPLE 6: Synthesis of ((methylsulfonyl)oxy)methyl 3-methylbutanoate:-**




**Procedure:**

Silver salt of methane sulfonic acid [0.34 g, 1.6 mmol, 0.5 eq] was taken in acetonitrile (8 ml) and chloromethyl 3-methylbutanoate **[26]** (0.5 g, 3.3 mmol, 1.0 eq) was added to it. The resulting solution was heated to 60$^0$Ctemperature ranging from 30 to 80°C, preferably 60°C for 1 to 10 hour, preferably 5 hour for 5 h. Reaction progress was monitored by TLC. After completion, the reaction was filtered and solvent was evaporated under vacuum to yield colorless oil. The crude compound was purified by silica gel column chromatography (10% EtOAc: CyHex, 100-200 mesh) which afforded **[27]** ((methylsulfonyl)oxy)methyl 3-methylbutanoate [0.25 g, 40%] as a colorless oil.

**EXAMPLE 6a: Synthesis of ((methylsulfonyl)oxy)methyl 3-methylbutanoate:-**



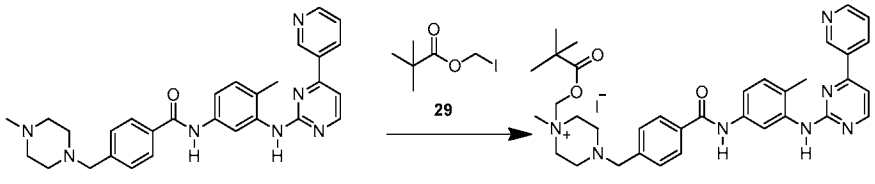

**Procedure:**

Silver salt of para-toluene sulfonic acid [0.3 g, 1.0 mmol, 0.5 eq] was taken in acetonitrile (8 ml) and chloromethyl 3-methylbutanoate **[26]** (0.48 g, 3.0 mmol, 1.0 eq) was added to it. The resulting solution was heated to 60$^0$Ctemperature ranging from 30 to 80°C, preferably 60°C for 1 to 10 hour, preferably 5 hour for 5 h. Reaction progress was monitored by TLC. After completion, the reaction was filtered and solvent was evaporated under vacuum to yield

colorless oil. The crude compound was purified by silica gel column chromatography (10% EtOAc: CyHex, 100-200 mesh) which afforded **[28]** ((methylsulfonyl)oxy)methyl 3-methylbutanoate [0.26 g, 35%] as a colorless oil.

## Synthesis of modified forms of Imatinib

**EXAMPLE 6b:**

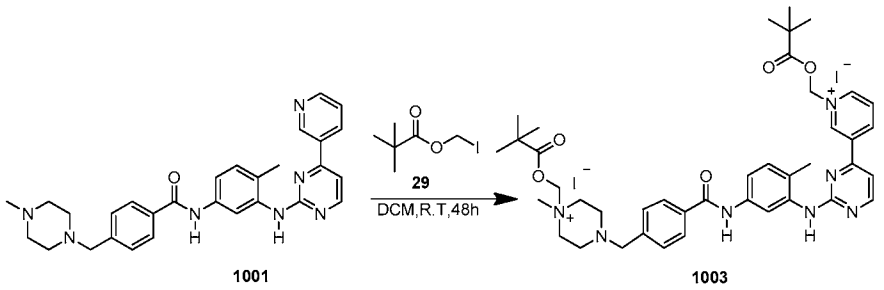



Imatinib, N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, **[1001]** (0.100 g, 0.2 mmol,1.0 eq) was dissolved in dichloromethane (10 ml) in a 25 ml two-necked round-bottomed flask, and iodomethyl pivalate **[29]** (0.049 g, 0.2 mmol, 1.0 eq) was added at RT. After stirring for 3 – 4 hours, the precipitate formed was filtered and washed with DCM to give the product, 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((pivaloyloxy)methyl)piperazin-1-ium iodide, **[1002]** as a yellow solid (0.04 g, 27%).

m/z: 608.

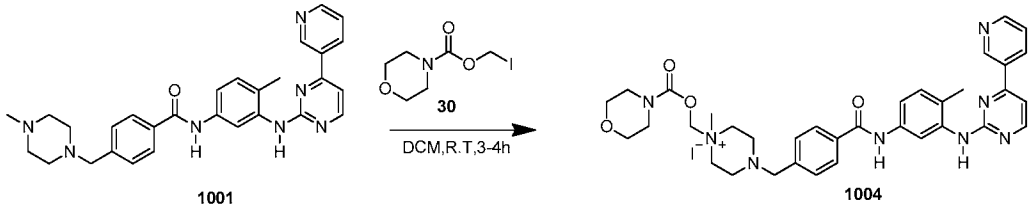
$^1$H NMR [DMSO, 300 MHz]: δ ppm 1.24 (s, 9 H), 2.20 (s, 3 H), 2.7 (m, 4 H), 3.10 (s, 3 H), 3.07 (s, 3 H), 3.48 (br s, 4 H), 3.71 (s, 2 H), 5.39 (s, 2 H), 7.19 (d, 1 H), 7.42 - 7.54 (m, 5 H), 7.9 (d, 2 H), 8.06 (d, 1 H), 8.45 - 8.52 (m, 2 H), 8.60 (dd, 1 H), 9.0 (s, 1 H), 9.27 (d, 1 H), 10.18 (s, 1 H)

## EXAMPLE 7



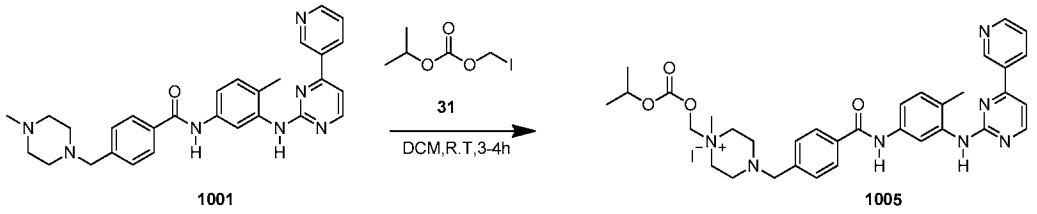

Imatinib **[1001]** (0.10 g, 0.2 mmol, 1.0 eq) was dissolved in DCM (10 ml) in a 25 ml two-necked round-bottomed flask and iodomethyl pivalate **[29]** (0.185 g, 0.77 mmol, 3.8 eq) was added while stirring at RT. After 48h stirring, the precipitate formed was filtered under vacuum and washed with DCM to give the product, 1-methyl-4-(4-((4-methyl-3-((4-(1-((pivaloyloxy)methyl)pyridin-1-ium-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((pivaloyloxy)methyl)piperazin-1-ium diiodide **[1003]**, as a yellow solid (0.05 g, 25% ). m/z: 361.

## EXAMPLE 8




Imatinib, N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, **[1001]** (0.100 g, 0.2 mmol,1.0 eq) was dissolved in dichloromethane (10 ml) in a 25 ml two-necked round-bottomed flask, and iodomethyl carbamate **[30]** (0.055 g, 0.2 mmol, 1.0 eq) in dichloromethane (5ml) was added at RT. After stirring for 3 – 4 hours, the precipitate formed was filtered and washed with DCM to give the product, 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((morpholine-4-carbonyl)oxy)methyl)piperazin-1-ium iodide, **[1004]** as a yellow solid (0.060 g, 50%). m/z : 637

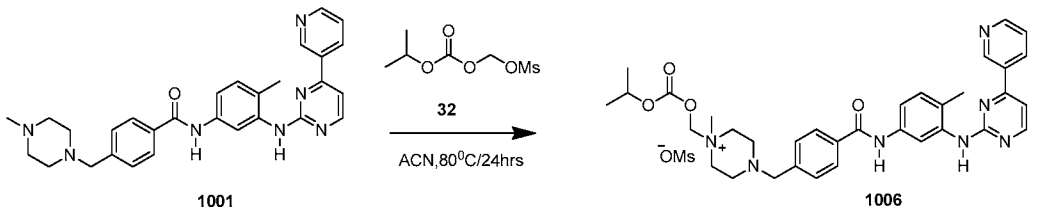
**EXAMPLE 9:**




1001 1005

Imatinib, N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, **[1001]** (0.100 g, 0.2 mmol,1.0 eq) was dissolved in dichloromethane (10 ml) in a 25 ml two-necked round-bottomed flask, and iodomethyl isopropyl carbonate **[31]** (0.047 g, 0.2 mmol, 1.0 eq) in dichloromethane (5ml) was added at RT. After stirring for 3 – 4 hours, the precipitate formed was filtered and washed with DCM to give the product, 1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide, **[1005]** as a yellow solid (0.035 g, 40%). m/z : 610

**EXAMPLE 10:**

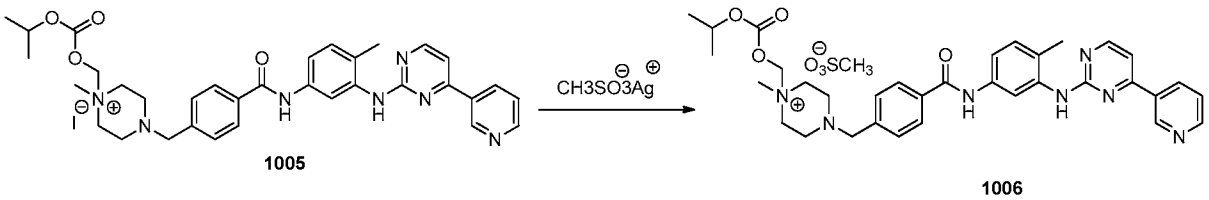



1001 1006

To a suspension of Imatinib, N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, **[1001]** (0.100 g, 0.2 mmol,1.0 eq) in acetonitrile (10 ml) in a 25 ml two-necked round-bottomed flask, and ((isopropoxycarbonyl)oxy)methyl methanesulfonate **[32]** (0.043 g, 0.2 mmol, 1.0 eq) in acetonitrile (5ml) was added at RT. The resulting suspension was heated at $80^0$C for 24hrs,

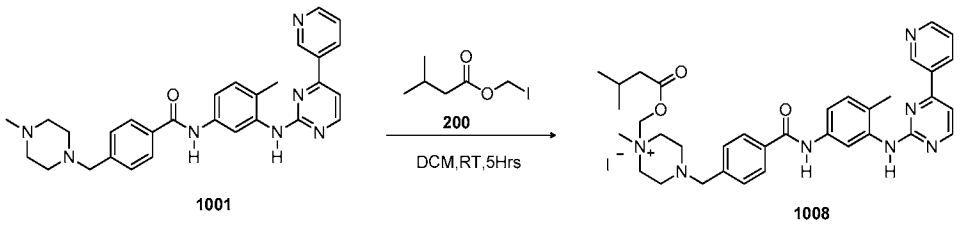
The progress of the reaction was monitored by TLC. Then it was cooled to room temperature and evapourated to dryness.The resulting residue was redissolved in dichloromethane(1ml) and reprecipitated by adding n-pentane,precipitate was filtered and dried to yield crude product, 1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide, **[1006]** as a yellow solid (0.034 g, 27%).The characterization was done by Mass spectroscopy. m/z : 610

**EXAMPLE 11a:**



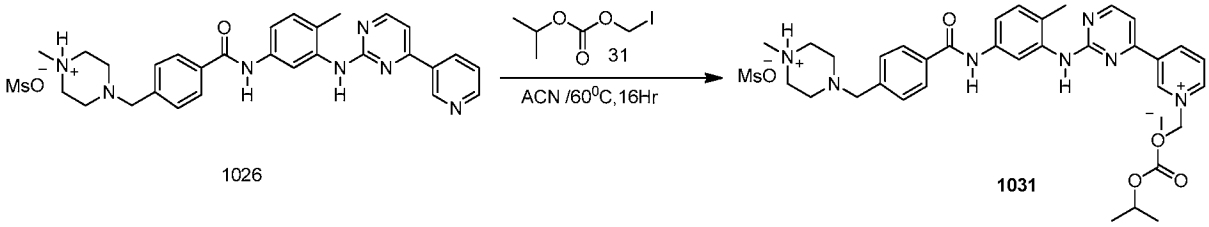

To a stirred solution of (1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium) iodide[1005] (0.0163 g, 0.027 mmol, 1.0 eq) in ACN (2 ml) was added silver(I) methanesulfonate (0.0054 g, 0.027 mmol, 1.0 eq) at RT. The reaction mixture was stirred at RT for 2 h. The reaction was filtered to get rid of silver iodide. Filtrate was concentrated under vacuum, which was triturated with dry ether (2x 5 ml), ether removed by decantation and product dried under vacuum to get a pale yellow solid 1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methane sulfonate[1006] (0.012 g, 66%). m/z : 610

**EXAMPLE 11b:**



Imatinib **[1001]** (0.100 g, 0.2 mmol,1.0 eq) was dissolved in dichloromethane (10 ml) in a 25 ml two-necked RBF followed by addition of iodomethyl 3-methylbutanoate **[200]** (0.049 g, 0.2 mmol, 1.0 eq) at RT. Reaction mixture was stirred for 4-5 hours, the yellow precipitate thus formed was filtered and washed with DCM to give the product, 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((3-methylbutanoyl)oxy)methyl)piperazin-1-ium iodide **[1008]** as a yellow solid (0.080 g, 55%). m/z: 608.

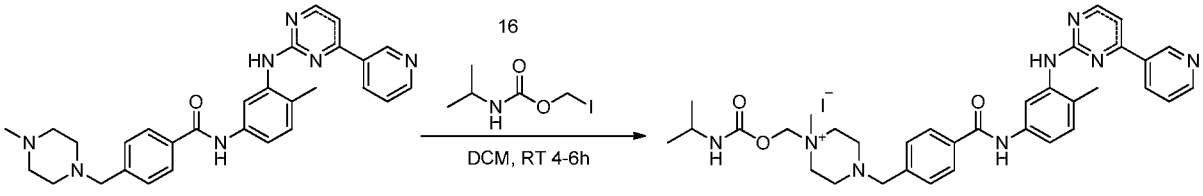
**EXAMPLE 12:**




1026 1031

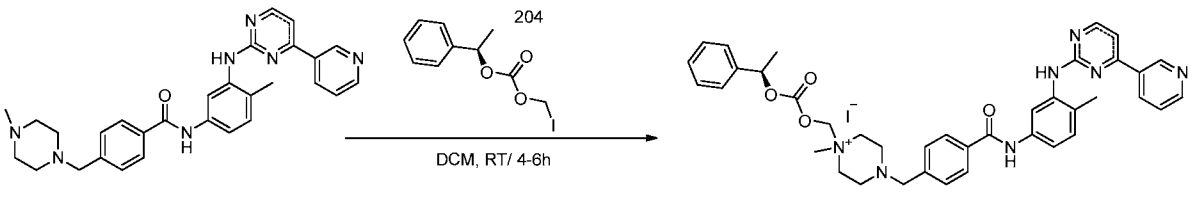
Imatinib mesyalte, 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methanesulfonate **[1026]** (0.100 g, 0.169 mmol, 1.0 eq) was taken in dry acetonitrile(6 ml) in a flame dried 2 neck RB flask equipped with refluxing condenser. To this suspension iodomethyl isopropyl carbonate **[31]** (0.041 g, 0.169 mmol, 1 eq) was added and heated the reaction mixture at $60^0$C for 16 Hrs.During the reaction progress the suspension was turned into a light yellow clear solution.The progress of the reaction was monitored by TLC and $^1$H NMR. After 16Hrs the solvent was evaporated to dryness and washed the resulting crude reaction mass with diethyl ether(10ml x 2) to give the product, 11-(((isopropoxycarbonyl)oxy)methyl)-3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-1-iummonoiodide monomethanesulfonate, **[1031]** as a brown gel (0.105 g, 74 %). m/z: 611.

1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((3-methylbutanoyl)oxy)methyl)piperazin-1-ium iodide, **[1008]** was synthesized using (procedure similar to that used for the synthesis of **[1002])** using**[1001]**), iodomethyl 3-methylbutanoate **[200]** and DCM as solvent.



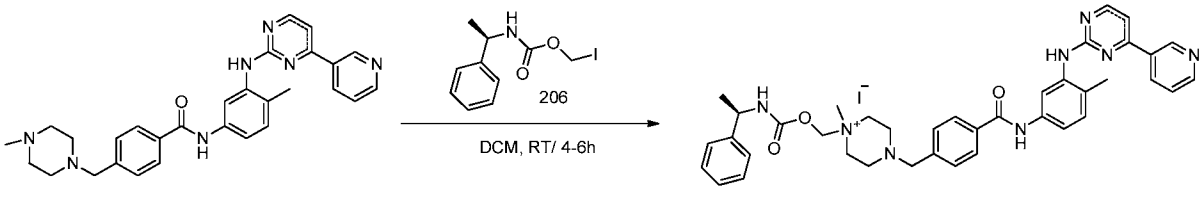

1001 1009

1-(((isopropylcarbamoyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1009]** was synthesized using (procedure similar to that used for the synthesis of **[1002]**using**[1001]**), iodomethyl isopropylcarbamate **[16]** and DCM as solvent.



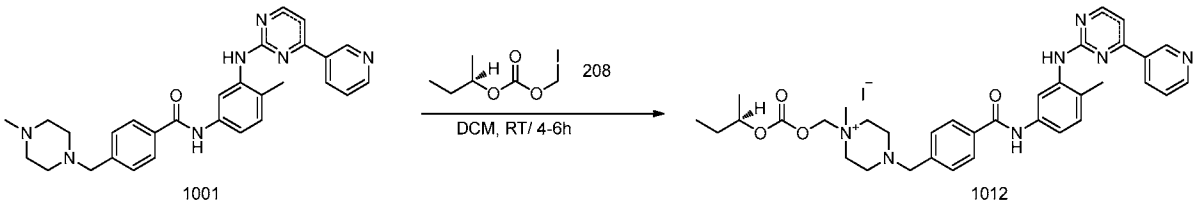

1001 1010

(R)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((((1-phenylethoxy)carbonyl)oxy)methyl)piperazin-1-ium iodide **[1010]** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001])**, (R)-iodomethyl (1-phenylethyl) carbonate **[204]** and DCM as solvent.

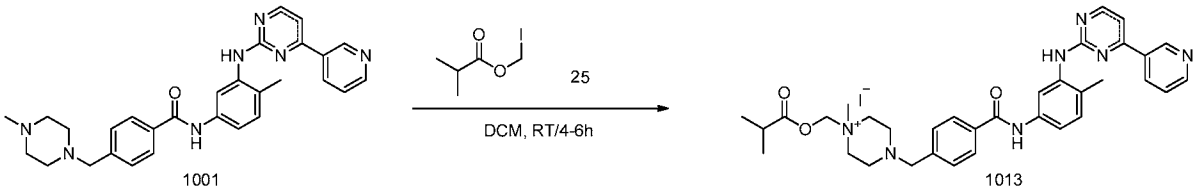



1001 1011

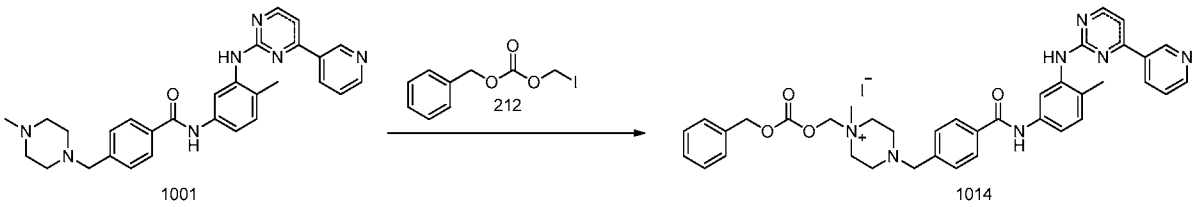
(R)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((((1-phenylethyl)carbamoyl)oxy)methyl)piperazin-1-ium iodide **[1011]** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001])**, (R)-iodomethyl (1-phenylethyl)carbamate **[206]** and DCM as solvent.



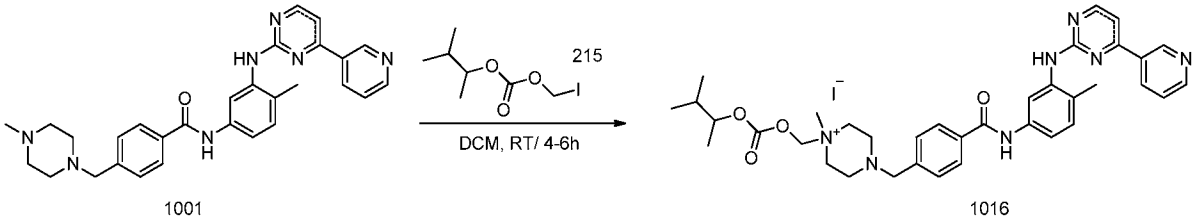

(R)-1-(((sec-butoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1012] ]** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001])** , (R)-sec-butyl (iodomethyl) carbonate **[208]** and DCM as solvent.



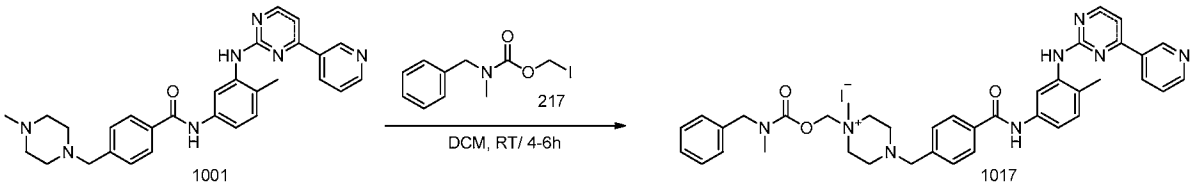

1-((isobutyryloxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1013]** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001]**), iodomethyl isobutyrate **[25]** and DCM as solvent.



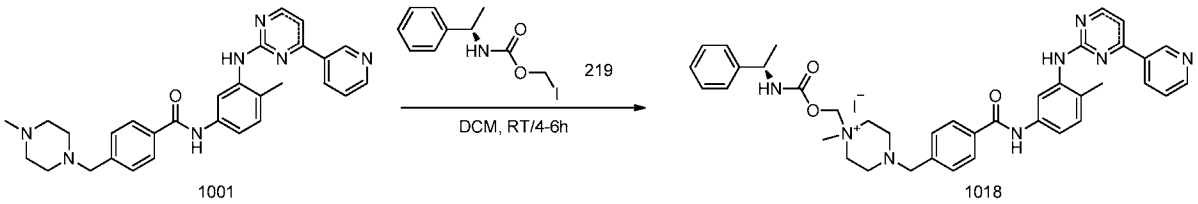

1-((((benzyloxy)carbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1014]** was synthesized using( procedure similar to that used for the synthesis of **[1002]** using **[1001])**, benzyl (iodomethyl) carbonate **[212]** and DCM as solvent.



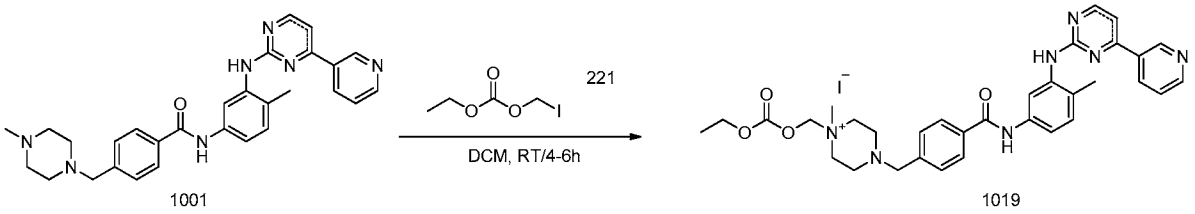

1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((((3-methylbutan-2-yl)oxy)carbonyl)oxy)methyl)piperazin-1-ium iodide **[1016]** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001])**, iodomethyl (3-methylbutan-2-yl) carbonate **[215]** and DCM as solvent.




1-(((benzyl(methyl)carbamoyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1017** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001]**), iodomethyl benzyl(methyl)carbamate **[217]** and DCM as solvent.

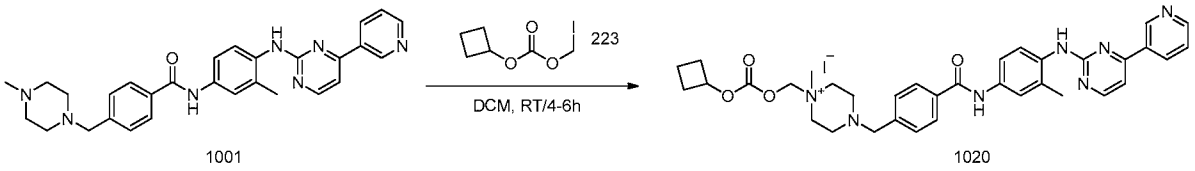



(S)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((((1-phenylethyl)carbamoyl)oxy)methyl)piperazin-1-ium iodide **[1018]** was synthesized using (procedure similar to that used for the synthesis of **[1002])** using **[1001]**), (S)-iodomethyl (1-phenylethyl)carbamate **[219]** and DCM as solvent.



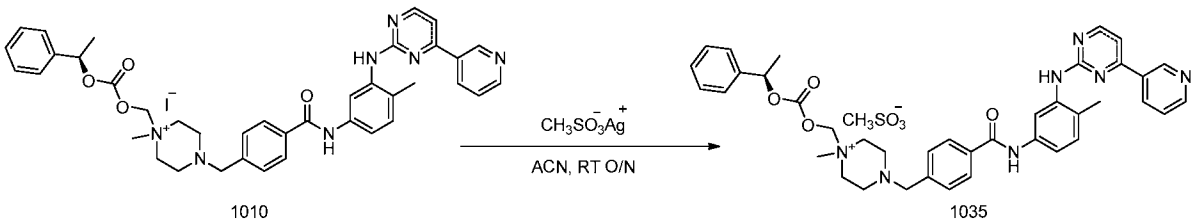

1001 1019

1-(((ethoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1019]** was synthesized using (procedure similar to that used for the synthesis of **[1002])** using **[1001])** ethyl (iodomethyl) carbonate **[221]** and DCM as solvent.




1001 1020

1-(((cyclobutoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((3-methyl-4-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide **[1020]** was synthesized using (procedure similar to that used for the synthesis of **[1002]** using **[1001])**, cyclobutyl (iodomethyl) carbonate **[223]** and DCM as solvent.

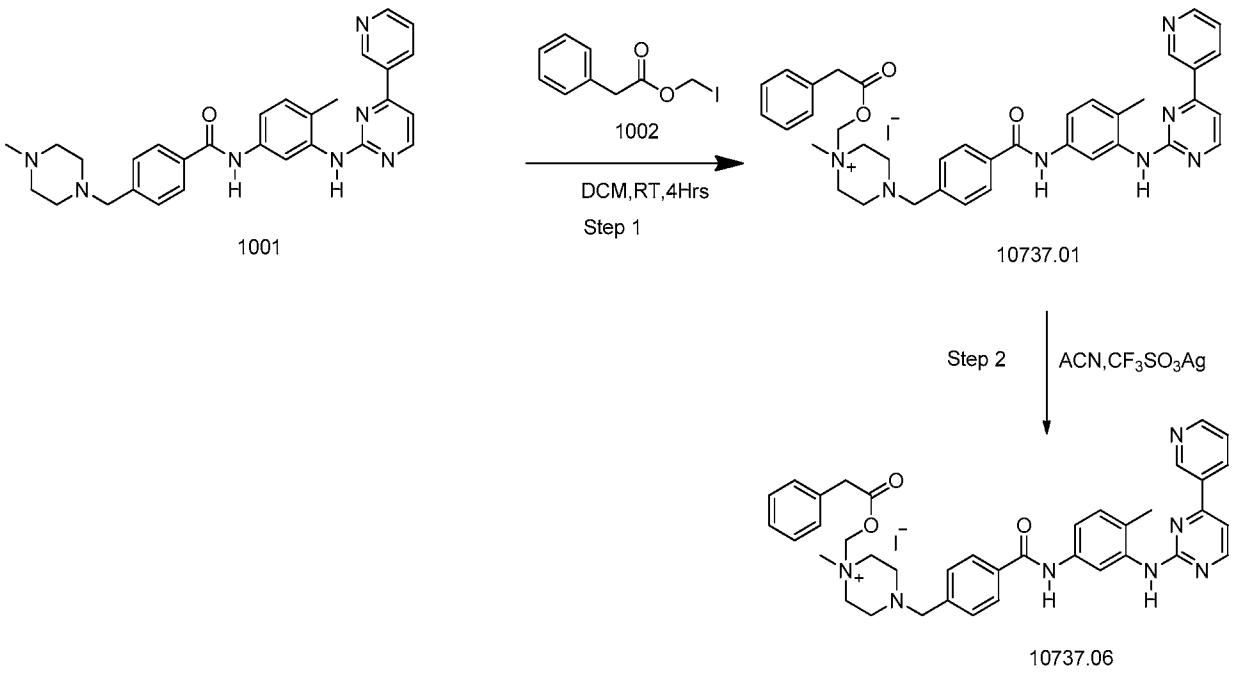



1010 1035

(R)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((((1-phenylethoxy)carbonyl)oxy)methyl)piperazin-1-ium methanesulfonate **[1035]** was synthesized using (procedure similar to that used for the synthesis of **[1006],** using **[1005])**, Silver methanesulfonate and ACN as solvent.

**EXAMPLE 13:**

**1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium trifluoromethanesulfonate [10737.06]**




**Step 1:**

Imatinib, N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide, **[1001]** (0.5 g, 1.0 mol,1.0 eq) was dissolved in dry dichloromethane (40 ml) in a 100 ml two-necked round bottom flask, to which was added iodomethyl 2-phenylacetate **[1002]** (0.28 g,1.0 mol, 1.0 eq) dissolved in 10 ml DCM dropwise at room temperature. After stirring for 3-4 hours, a yellow precipitate formed. The precipitate was filtered and washed with excess of DCM (dichloromethane) to yield the product, 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium iodide **[10737.01]** as a yellow solid [0.5g, 64%]; m/z:-643.

**Step 2:**

To a stirred solution of 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium iodide **[10737.01]** (0.08 g, 0.1mol, 1.0 eq) in CAN [acetonitrile] (10 ml) was added silver(I) trifluoromethane sulfonate (0.026 g, 0.1 mmol, 1.0 eq) at RT. The reaction mixture was stirred at RT for 30 min. The reaction was filtered to get rid of the silver iodide precipitate. The filtrate was concentrated under vacuum, which was triturated with dry ether (2 x 5 ml). The ether was removed by decantation and the resulting product was dried under vacuum to yield 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium trifluoromethanesulfonate **[10737.06]** as a light yellow solid [0.045 g, 50%]; m/z : 643.

**Synthesis of 10737.02, 10737.04, 10737.07, 10737.08** was achieved by using procedure described in Example 13, step 2 above and using the corresponding silver salts (silver nitrate or silver tosylate or silver tetrafluoroborate or silver mesylate etc.) and 10737.01 as starting material.

**Synthesis of 11124.01, 11124.02 and 11124.03** was achieved by using the procedure described in Example 13 using iodomethyl 2-phenylpropanoate instead of iodomethyl 2-phenylacetate **[1002].**

**Example 14: Antiviral potency of imatinib against VEE virus**

Primary antiviral screens were conducted to determine EC50 and cellular toxicity to define a therapeutic index by neutral red assay. Secondary assay determines EC90 using more refined concentrations of inhibitor and virus yield reduction. A low level of virus innoculum that produces maximum cell death at a specified time (≥3 days) were used for virus assay, typically 50-100 $CCID_{50}$.

Table 1:

| Drug | Virus | Virus Family | NIAID Category | Genome Type | EC50 (micromolar) | Therapeutic Index |
|---|---|---|---|---|---|---|
| imatinib | VEE | *alphaviridae* | B | ssRNA(+) | **6** | **4** |

**Example 15: Antiviral potency of imatinib against polyoma viruses**

PCR amplifications were set up in a reaction volume of 50 µL that contained the TaqMan Universal PCR Master Mix (PE Biosystems), 5 µL of tissue lysate, 300 nmol/L each forward and reverse primer, 200 nmol/L probe, 300 µmol/L dNTPs, 5 mmol/L magnesium, and 1.25

U of Taq Gold polymerase. Thermal cycling was begun with an initial denaturation step at 95°C for 12 min that was followed by 45 cycles at 95°C for 15 s (denaturation) and 60°C for 1 min (reannealing and extension).

Table 2:

| Drug | Virus | Genome Type | EC50 (micromolar) | Therapeutic Index |
|---|---|---|---|---|
| imatinib | JCV | dsDNA | **1.25** | **10** |
| imatinib | BKV | dsDNA | **2.1** | **10** |

**Pharmacokinetic properties of the compounds of the compounds of the present invention**

The compounds of the present invention were compared for their pharmacokinetic properties with that of imatinib. The data of the compounds are present at **Table 3.**

**PK protocol**

Female Sprague Dawley (SD) rats 3 per group after overnight fasting were dosed orally (via gavage) with imatinib and its modified drugs in distilled water (5ml/ kg) at a dose level of 3mg/ kg. Blood was collected by serial bleeding at 0.16 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h and 24 h in heparinized tubes. Blood samples were centrifuged at 10,000 rpm for 10 min. at 4 °C to obtain the plasma, which were aspirated into separate labeled tubes and stored at – 80 °C. 400 ng/ ml of Verapamil in acetonitrile was used as the drug extraction solvent for extracting drug from plasma. Extraction solvent was added to plasma was vortexed and shaken on shaker for 10 min, centrifuged at 10000 rpm for 10 min at 4 °C. Supernatant was kept for analysis. Acetonitrile and plasma calibration curves were generated and percentage of imatinib recovery from plasma determined. Quantitative analysis of imatinib levels in each sample was done by liquid chromatography tandem mass spectrometry using multiple reaction monitoring (API3200 LC-MS/MS). $C_{max}$, $T_{max}$, AUC and $t_{1/2}$ were calculated using Graph Pad PRISM version 5.04.

**Table 3: PK Parameters for compounds**

3 mpk, Distilled Water (Rat, triplicate)

| Patent Ref # | AUC (nM*hr) |
|---|---|
| SR-03 (SPR-618) 1006 | 523 |
| SR-05 (SPR_634) | 295 |
| SR-07 (SPR-619) | 470 |
| SR-10 (SPR-631) 1005 | 1574 |
| SR-11 (SPR-621) 1010 | 2712 |
| SR-13.1 (SPR632) 1013 | 356 |
| SR-14* (SPR-136) 1002 | 5233 |
| Standard (SPR-10627) (imatinib) | 1753 |
| 11124.01 | 5102 |

*Vehicle = PEG400

MTS cell viability assay (K562 cell line):

The compounds of the present invention were tested for their MTS cell viability assay. The results are presented are Table 4:

K562 cells were the first human immortalised myelogenous leukemia line to be established. K562 cells are of the erythroleukemia type, and the line is derived from a 53 year old female CML patient. The cells are non-adherent and rounded, are positive for the bcr:abl fusion gene.

K562 cell line is maintained in RPMI1640 with 10% fetal Bovine Serum. 2500 cells/well of K562 cells were plated in 96 well tissue culture plate. Cells were incubated for 48 hours with

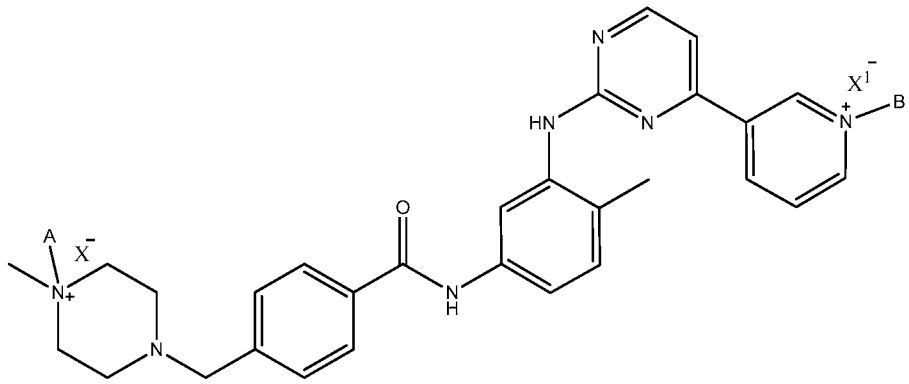
serially diluted compound (final concentration from 20μM -0.002μM) for 48 hr. MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium), obtained from Promega was added to the wells and plates were incubated at 370C in 5% CO2 for 4 hrs.The MTS compound is bio-reduced by cells into a colored formazan product that is soluble in tissue culture medium. The quantity of formazan product as measured by the amount of 490nm absorbance is directly proportional to the number of living cells in culture. Theabsorbance was read at 490nm (Spectramax microplate reader). The Percentage inhibition was calculated and plotted against the concentration of inhibitor and data was fit to Non Linear Regression curve fit (sigmoidal dose response curve with variable slope-four parameters) using Graph pad prism 5.

Table 4: Activity of the compounds of the present invention in K562 cell lines

| | % Inhibition - K562 cell line (myelogenous leukemia) | | |
|---|---|---|---|
| Compound # | 20uM | 2uM | 0.2uM |
| 1001 | 67 | 64 | 48 |
| 1011 | 70 | 63 | 45 |
| 1028 | 76 | 63 | 40 |

## CLAIMS

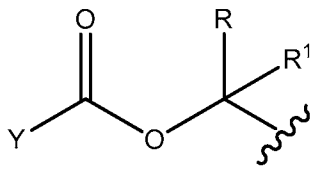
1. A compound of Formula **(I)** or a pharmaceutically acceptable salt thereof:



**(I)**

wherein:

A and B are independently selected from absent, H or a moiety of Formula **(II)**, with the proviso that at least one of A and B is a moiety of Formula (**II**);



**(II)**

wherein:

R and $R^1$ are each independently selected from H, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein said $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl and heteroaryl substituents; or R and $R^1$ taken together with the atom to which they are attached form a 3- to 7-membered ring, wherein said 3- to 7-membered ring optionally contains up to two heteroatom groups selected from O, N $R^4$, S, SO and $SO_2$, and is optionally substituted with 1 to 4 alkoxy, F or Cl substituents;

Y, independently for each occurrence, is selected from $R^2$, $OR^2$, $NH_2$, $NHR^2$, and $NR^2R^3$;

$R^2$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein said $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl substituents;

$R^3$ is selected from alkoxy, aryl, heteroaryl, $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl, wherein in each of the $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl optionally up to three carbon atoms are replaced by a heteroatom group independently selected from O, $NR^4$, S, SO and $SO_2$ (i.e., thereby making a heteroalkyl or heterocyclyl substituent), and wherein said $C_1$-$C_8$ alkyl and $C_3$-$C_7$ cycloalkyl are each optionally substituted with from 1 to 4 $C_1$-$C_8$ alkyl, alkoxy, aryl or heteroaryl; or

$R^2$ and $R^3$ may be taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered ring, wherein said 3- to 7-membered ring optionally contains up to three heteroatom groups selected from O, $NR^4$, S, SO and $SO_2$, and is optionally substituted with alkoxy, F or Cl;

$R^4$ is, independently for each occurrence, selected from H or $C_1$-$C_8$ alkyl; and

X and $X^1$ are each independently an anion or absent, provided that X is absent only when A is absent, and $X^1$ is absent only when B is absent.

2. The compound according to claim 1, wherein R and $R^1$ are each independently selected from H and $C_1$-$C_8$ alkyl.

3. The compound according to claim 2, wherein R and $R^1$ are both H.

4. The compound according to any preceding claim, wherein $R^2$ and $R^3$ are independently selected from $C_1$-$C_8$ alkyl and aralkyl.

5. The compound according to any preceding claim, wherein $R^2$ and $R^3$ are independently selected from methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, *sec*-butyl, 3-methylbut-2-yl, 1-phenylethyl, benzyl or cyclobutyl.

6. The compound according to any preceding claim, wherein $R^4$, independently for each occurrence, is selected from H and $C_1$-$C_8$ alkyl.

7. The compound according to any preceding claim, wherein X and $X^1$ are each independently halide or sulfonate.

8. The compound according to any preceding claim, wherein X and $X^1$ are each independently iodide or mesylate.

9. The compound according to any preceding claim, wherein X is mesylate and $X^1$ is iodide.

10. The compound according to any preceding claim, wherein A and B are each independently H or a moiety of Formula **(II)**.

11. The compound according to claim 8, wherein A is H and B is a moiety of Formula **(II)**.

12. The compound according to claim 8, wherein A is a moiety of Formula **(II)** and B is H.

13. The compound according to any one of claims 1-7, wherein A is a moiety of Formula **(II)** and B is absent.

14. The compound according to any one of claims 1-7, wherein A is absent and B is a moiety of Formula **(II)**.

15. The compound according to any one of the preceding claims, wherein Y, independently for each occurrence, is $OR^2$ or R2 or $NR^2R^3$.

16. The compound according to claim 15, wherein Y=$OR^2$.

17. The compound according to claim 16, wherein Y is a moiety that would remain after displacing chlorine from:

i. chloromethyl isopropyl carbonate;
ii. benzyl chloromethyl carbonate;
iii. chloromethyl morpholinomethyl carbonate;
iv. chloromethyl isobutyl carbonate;
v. chloromethylmethyl carbonate;
vi. (S)-sec-butyl chloromethyl carbonate;
vii. (R)-sec-butyl chloromethyl carbonate;
viii. chloromethyl ((3S,5R)-3,5-dimethylmorpholino)methyl carbonate;
ix. chloromethyl 2-methylcyclopropyl carbonate;
x. chloromethyl2-methoxyethyl carbonate;
xi. chloromethyl propyl carbonate;
xii. chloromethyl cyclobutyl carbonate;
xiii. chloromethyl cyclopropyl carbonate;
xiv. chloromethyl 2,2-dimethylcyclobutyl carbonate;
xv. chloromethyl cyclopentyl carbonate;
xvi. chloromethyl oxetan-3-yl carbonate;
xvii. (S)-chloromethyl tetrahydrofuran-3-yl carbonate;
xviii. chloromethyl cyclohexylmethyl carbonate;
xix. chloromethyl 3-methoxycyclohexyl carbonate;
xx. (R)-chloromethyl tetrahydrofuran-3-yl carbonate;
xxi. chloromethyl ethoxymethyl carbonate;
xxii. chloromethyl oxepan-4-yl carbonate;
xxiii. (1R,2S,4S)-bicyclo[2.2.1]heptan-2-yl chloromethyl carbonate;
xxiv. chloromethyl 2,3-dihydro-1H-inden-1-yl carbonate;
xxv. benzyl chloromethyl carbonate;
xxvi. (S)-chloromethyl 1-phenylethyl carbonate;
xxvii. chloromethyl cyclohexyl carbonate;
xxviii. chloromethyl isobutyl carbonate;
xxix. chloromethyl 4-methylcyclohexyl carbonate;
xxx. chloromethyl 2-(methylthio)ethyl carbonate;
xxxi. chloromethyl 3-methylcyclohexyl carbonate;
xxxii. chloromethylpentan-2-yl carbonate;
xxxiii. chloromethyl neopentyl carbonate;
xxxiv. methyl 1-((chloromethoxy)carbonyloxy)cyclopropanecarboxylate;

xxxv. chloromethyl cyclopropylmethyl carbonate;

xxxvi. chloromethyl 2,2-diethoxyethyl carbonate;

xxxvii. chloromethyl cyclopentylmethyl carbonate;

xxxviii. methyl 2-((chloromethoxy)carbonyloxy)propanoate;

xxxix. (S)-chloromethyl 2,2,4-trimethylcyclopent-3-enyl carbonate;

xl. chloromethyl 1,3-dioxolan-2-yl carbonate;

xli. chloromethyl (2,6-dimethylcyclohexyl)methyl carbonate;

xlii. chloromethyl 2-(tetrahydro-2H-pyran-2-yl)ethyl carbonate;

xliii. chloromethyl(tetrahydro-2H-pyran-4-yl)methyl carbonate;

xliv. chloromethyl tetrahydro-2H-pyran-4-yl carbonate;

xlv. chloromethyl 1-methylcyclopentyl carbonate;

xlvi. chloromethyl 1-cyclopentylethyl carbonate;

xlvii. chloromethyl 3-methylcyclopentyl carbonate;

xlviii. chloromethyl 3,3-dimethylcyclohexyl carbonate;

xlix. chloromethyl 2,5-dimethylcyclohexyl carbonate;

l. chloromethyl 1-(4-methylcyclohexyl)ethyl carbonate;

li. chloromethyl (3-methyloxetan-3-yl)methyl carbonate;

lii. chloromethyl (3-methyloxetan-3-yl)methyl carbonate;

liii. chloromethyl 2-isopropoxyethyl carbonate;

liv. (chloromethyl carbonic) 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoic anhydride;

lv. 4-((chloromethoxy)carbonyloxy)-2-hydroxy-4-oxobutanoic acid;

lvi. chloromethyl 4-formyl-2-methoxyphenyl carbonate;

lvii. chloromethyl 3-oxobutan-2-yl carbonate;

lviii. methyl 4-((chloromethoxy)carbonyloxy)benzoate;

lix. (R)-2-amino-3-((chloromethoxy)carbonyloxy)propanoic acid;

lx. 3-tert-butyl-4-methoxyphenyl chloromethyl carbonate;

lxi. (R)-2-amino-3-(4-((chloromethoxy)carbonyloxy)phenyl)propanoic acid;

lxii. (R)-2-amino-4-((chloromethoxy)carbonyloxy)-4-oxobutanoic acid;

lxiii. (E)-chloromethyl 3,7-dimethylocta-2,6-dienyl carbonate;

lxiv. methyl 4-((chloromethoxy)carbonyloxy)benzoate;

lxv. chloromethyl 2-(4-methylcyclohex-3-enyl)propan-2-yl carbonate;

lxvi. chloromethyl 3,7-dimethylocta-1,6-dien-3-yl carbonate;

lxvii. 4-allyl-2-methoxyphenyl chloromethyl carbonate;

lxviii. chloromethyl (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl carbonate;

lxix. propyl 4-((chloromethoxy)carbonyloxy)benzoate; or

lxx. (E)-chloromethyl 3,7-dimethylocta-2,6-dienyl carbonate.

18. A compound according to claim 15, wherein Y=$R^2$.

19. A compound according to claim 18, wherein Y is a moiety that would remain after displacing chlorine from:

i. chloromethyl cyclohexanecarboxylate;

ii. chloromethyl 2-cyclohexylacetate;

iii. chloromethyl 4-methylcyclohexanecarboxylate;

iv. chloromethyl 1-methylcyclohexanecarboxylate;

v. chloromethyl cyclopentanecarboxylate;

vi. chloromethyl 1-(trifluoromethyl)cyclopentanecarboxylate;

vii. chloromethyl cyclobutanecarboxylate;

viii. chloromethyl 2-ethylhexanoate;

ix. chloromethyl 3-cyclopentylpropanoate;

x. chloromethyl cyclopropanecarboxylate;

xi. chloromethyl pentanoate;

xii. chloromethyl 2-methylpentanoate;

xiii. chloromethyl 3,5,5-trimethylhexanoate;

xiv. chloromethyl 2,2-dimethylbutanoate;

xv. chloromethyl 2-methylbutanoate;

xvi. chloromethyl hexanoate;

xvii. chloromethyl 2-ethylbutanoate;

xviii. chloromethyl butyrate;

xix. chloromethyl 3-phenylpropanoate;

xx. chloromethyl 2-phenylpropanoate;

xxi. (R)-chloromethyl 2-phenylpropanoate;

xxii. (S)-chloromethyl 2-phenylpropanoate;

xxiii. (1r,4r)-chloromethyl 4-methylcyclohexanecarboxylate;

xxiv. chloromethyl 4-methoxycyclohexanecarboxylate;

xxv. chloromethyl 4,4-difluorocyclohexanecarboxylate;

xxvi. chloromethyl 3-methoxycyclohexanecarboxylate;

xxvii. (2R)-chloromethyl 2-methylcyclopentanecarboxylate;
xxviii. (R)-chloromethyl 2-methylbutanoate;
xxix. (S)-chloromethyl 2-methylbutanoate;
xxx. (S)-chloromethyl 2-methoxy-2-phenylacetate;
xxxi. (S)-chloromethyl 2-phenylpropanoate;
xxxii. (S)-chloromethyl 2-phenylbutanoate;
xxxiii. (S)-chloromethyl 3-phenylbutanoate;
xxxiv. bis(chloromethyl) 2,2-dimethylmalonate;
xxxv. bis(chloromethyl) oxalate;
xxxvi. chloromethyl 2-cyclopropylacetate;
xxxvii. chloromethyl 2-cyclobutylacetate;
xxxviii.chloromethyl 2-cyclopentylacetate;
xxxix. chloromethyl 2-(tetrahydrofuran-3-yl)acetate;
xl. chloromethyl 2-(tetrahydro-2H-pyran-4-yl)acetate;
xli. chloromethyl 2-methylcyclopropanecarboxylate;
xlii. chloromethyl 2-(1-methylcyclobutyl)acetate;
xliii. chloromethyl 2-(1-methylcyclopropyl)'acetate;
xliv. chloromethyl propionate;
xlv. chloromethyl acetate;
xlvi. chloromethyl isobutyrate;
xlvii. chloromethyl 2-isopropyl-3-methylbutanoate;
xlviii. chloromethyl 3,5-dimethylcyclohexanecarboxylate;
xlix. chloromethyl 2-propylpentanoate;
l. chloromethyl 4-methoxybenzoate;
li. chloromethyl 4-methylbenzoate;
lii. chloromethyl 3-methylbenzoate;
liii. chloromethyl 2,2,2-trifluoroacetate;
liv. chloromethyl 5,5-dimethyl-3-oxohexanoate;
lv. bis(chloromethyl) cyclopropane-1,1-dicarboxylate;
lvi. chloromethyl 1,2-dihydrocyclobutabenzene-1-carboxylate;
lvii. chloromethyl 2-cyclopentenylacetate;
lviii. chloromethyl 2-phenylbutanoate;
lix. chloromethyl 2,2-difluoroacetate;
lx. chloromethyl 4-fluorobenzoate;

lxi. chloromethyl 3-cyclohexylpropanoate;
lxii. chloromethyl 2-cyclohexylacetate;
lxiii. chloromethyl 3-(tetrahydro-2H-pyran-4-yl)propanoate;
lxiv. chloromethyl 2-(tetrahydro-2H-pyran-3-yl)acetate;
lxv. chloromethyl 3-(tetrahydro-2H-pyran-3-yl)propanoate; and
lxvi. chloromethyl nicotinates.

20. A compound of formula (I) according to claim 15, wherein $Y=NR^2R^3$.

21. A compound of formula (I) according to claim 20, wherein Y is a moiety that would remain after displacing chlorine from:
i. chloromethyl isopropylcarbamate;
ii. chloromethyl diisopropylcarbamate;
iii. chloromethyl dimethylcarbamate;
iv. chloromethyl isobutylcarbamate;
v. chloromethyl methylcarbamate;
vi. chloromethyl ethyl(isopropyl)carbamate;
vii. chloromethylisobutyl(methyl)carbamate;
viii. (S)-chloromethyl sec-butylcarbamate;
ix. chloromethyl methylcarbamate;
x. chloromethyl isopropyl(methyl)carbamate;
xi. chloromethyl propylcarbamate;
xii. chloromethyl 2-methoxyethylcarbamate;
xiii. chloromethyl methyl(propyl)carbamate;
xiv. chloromethyl diisobutylcarbamate;
xv. chloromethyl tert-butyl(isopropyl)carbamate;
xvi. chloromethyl di-sec-butylcarbamate;
xvii. chloromethyl aziridine-1-carboxylate;
xviii. chloromethyl 2-methylcyclopropylcarbamate;
xix. chloromethyl cyclopropylcarbamate;
xx. chloromethyl cyclopropylmethyl(propyl)carbamate;
xxi. chloromethyl cyclopropyl(methyl)carbamate;
xxii. chloromethyl azetidine-1-carboxylate;
xxiii. chloromethyl cyclobutylcarbamate;

xxiv. chloromethyl 2,2-dimethylcyclobutylcarbamate;

xxv. chloromethyl 3-methoxyazetidine-1-carboxylate;

xxvi. chloromethyl cyclobutyl(methyl)carbamate;

xxvii. chloromethyl oxetan-3-ylcarbamate;

xxviii. (S)-chloromethyl 2-methylpyrrolidine-1-carboxylate;

xxix. chloromethyl cyclopentylcarbamate;

xxx. chloromethl cyclopentyl(methyl)carbamate;

xxxi. chloromethyl tetrahydrofuran-3-ylcarbamate;

xxxii. chloromethyl piperidine-1-carboxylate;

xxxiii. (2R,6S)-chloromethyl 2,6-dimethylpiperidine-1-carboxylate;

xxxiv. (R)-chloromethyl 2-methylpiperidine-1-carboxylate;

xxxv. chloromethyl piperidine-1-carboxylate;

xxxvi. chloromethyl 3-methoxycyclohexylcarbamate;

xxxvii. chloromethyl cyclohexylmethylcarbamate;

xxxviii. chloromethyl cyclohexylmethyl(methyl)carbamate;

xxxix. chloromethyl morpholine-4-carboxylate;

xl. (3S,5R)-chloromethyl 3,5-dimethylmorpholine-4-carboxylate;

xli. (3R,5S)-chloromethyl 3,5-dimethylmorpholine-4-carboxylate;

xlii. (2S,6R)-chloromethyl 2,6-dimethylmorpholine-4-carboxylate;

xliii. chloromethyl 4-methylpiperazine-1-carboxylate;

xliv. chloromethylazepane-1-carboxylate;

xlv. chloromethylcycloheptylcarbamate;

xlvi. chloromethyl oxepan-4-ylcarbamate;

xlvii. chloromethyl (1R,2S,4S)-bicyclo[2.2.1]heptan-2-ylcarbamate;

xlviii. chloromethyl 2,3-dihydro-1H-inden-1-ylcarbamate;

xlix. chloromethyl benzylcarbamate;

l. (S)-chloromethyl 1-phenylethylcarbamate;

li. ethyl 2-((chloromethoxy)carbonylamino)-3-methylbutanoate;

lii. ethyl 2-((chloromethoxy)carbonylamino)-3-phenylpropanoate;

liii. (S)-diethyl 2-((chloromethoxy)carbonylamino)pentanedioate;

liv. ethyl((chloromethoxy)carbonylamino)propanoate;

lv. ethyl 2-amino-6-((chloromethoxy)carbonylamino)hexanoate;

lvi. ethyl 2-((chloromethoxy)carbonylamino)-4-methylpentanoate;

lvii. ethyl 2-((chloromethoxy)carbonylamino)-3-methylpentanoate;

lviii. (S)-dimethyl 2-((chloromethoxy)carbonylamino)succinate;

lix. (S)-ethyl 2-((chloromethoxy)carbonylamino)-5-guanidinopentanoate;

lx. (S)-ethyl 4-amino-2-((chloromethoxy)carbonylamino)-4-oxobutanoate;

lxi. (S)-ethyl 2-amino-5-((chloromethoxy)carbonylamino)pentanoate;

lxii. (S)-ethyl 5-amino-2-((chloromethoxy)carbonylamino)-5-oxopentanoate;

lxiii. ethyl 2-((chloromethoxy)carbonylamino)-4-(methylthio)butanoate;

lxiv. 1-chloromethyl 3-methyl 2-methyl-5,6-dihydropyridine-1,3(2H)-dicarboxylate;

lxv. (S)-chloromethyl (1-methylpyrrolidin-2-yl)methyl carbonate;

lxvi. (R)-chloromethyl (1-methylpyrrolidin-2-yl)methyl carbonate;

lxvii. (S)-(1-benzylpyrrolidin-2-yl)methyl chloromethyl carbonate;

lxviii. chloromethyl 1H-pyrrole-1-carboxylate;

lxix. chloromethyl 2-nicotinoylhydrazinecarboxylate;

lxx. (6S)-3-chloro-7-((chloromethoxy)carbonylamino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

lxxi. (6S)-7-((chloromethoxy)carbonylamino)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

lxxii. (6S)-7-((chloromethoxy)carbonylamino)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

lxxiii. (6R,7R)-7-((chloromethoxy)carbonylamino)-3-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

lxxiv. chloromethyl 3-(4-chlorophenyl)-1H-pyrazole-1-carboxylate;

lxxv. chloromethyl 3-(4-fluorophenyl)-1H-pyrazole-1-carboxylate;

lxxvi. chloromethyl 3-phenyl-1H-pyrazole-1-carboxylate;

lxxvii. chloromethyl 3-(4bromophenyl)-1H-pyrazole-1-carboxylate;

lxxviii. chloromethyl 2-cyano-1H-pyrrole-1-carboxylate;

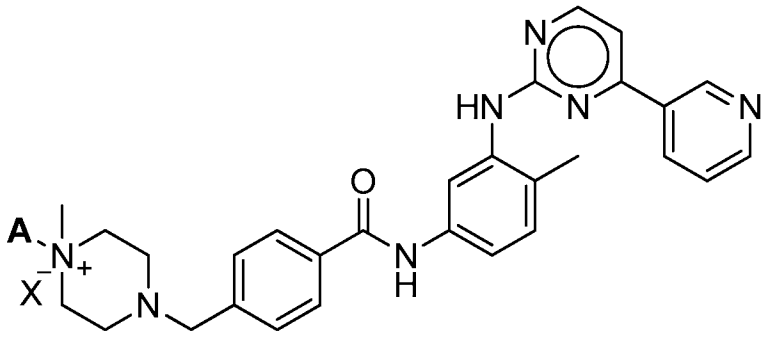
lxxix. chloromethyl 4-oxopiperidine-1-carboxylate;

lxxx. 1-chloromethyl 3-ethyl 2-oxopiperidine-1,3-dicarboxylate;

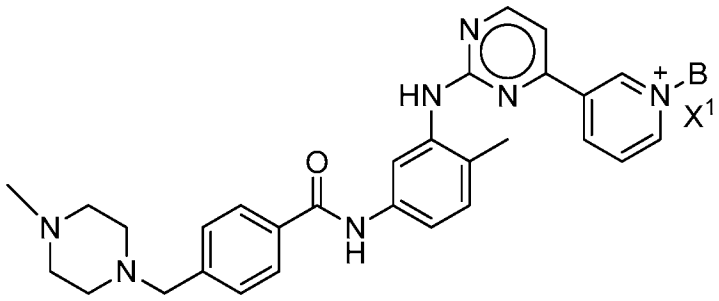
lxxxi. chloromethyl 2,2,6,6-tetramethyl-4-oxopiperidine-1-carboxylate; or

lxxxii. chloromethyl 2-oxopiperidine-1-carboxylate.

22. A compound according to claim 1, represented by Formula (III) or Formula (IV):

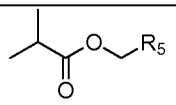
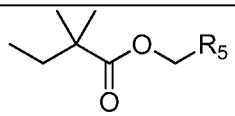
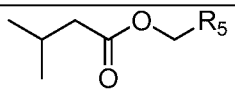
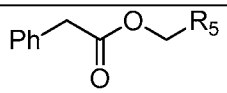
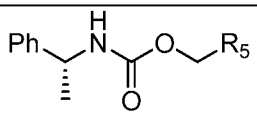
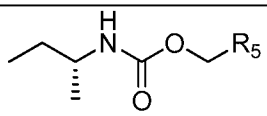
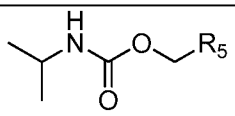
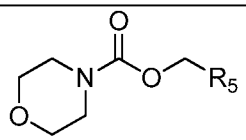
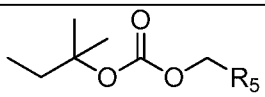
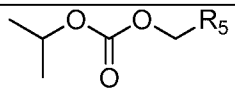
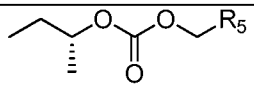
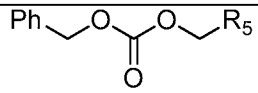
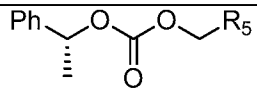
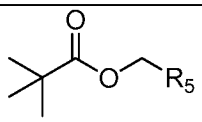
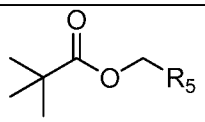
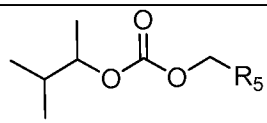
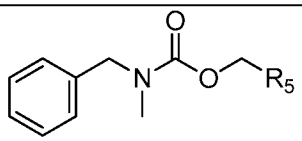
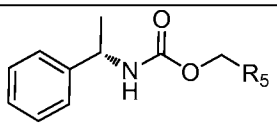
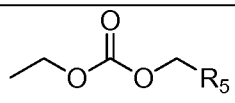
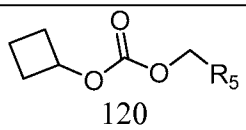
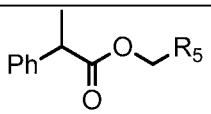


Formula **(III)**



Formula **(IV)**

Where A or B =

| | | | |
|---|---|---|---|
|  101 |  102 |  103 |  104 |
|  105 |  106 |  107 |  108 |
|  109 |  110 |  111 |  112 |
|  113 |  114 |  115 |  116 |
|  117 |  118 |  119 |  120 |
|  121 | | | |

where $R^5$ represents a nitrogen atom of the imatinib moiety linked to A or B;

and

X can be iodide, chloride, bromide, mesylate, tosylate, or any other pharmaceutically acceptable anion.

23. A compound according to claim 1, selected from:

i. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((pivaloyloxy)methyl)piperazin-1-ium iodide;

ii. 1-methyl-4-(4-((4-methyl-3-((4-(1-((pivaloyloxy)methyl)pyridin-1-ium-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((pivaloyloxy)methyl)piperazin-1-ium diiodide;

iii. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((morpholine-4-carbonyl)oxy)methyl)piperazin-1-ium iodide;

iv. 1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium iodide;

v. 1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methane sulfonate;

vi. 1-(((isopropoxycarbonyl)oxy)methyl)-1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium p-tolyl sulfonate;

vii. 1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((3-methylbutanoyloxy)methyl)piperazin-1-ium iodide;

viii. 1-((isopropylcarbamoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

ix. (R)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-(((1-phenylethoxy)carbonyloxy)methyl)piperazin-1-ium iodide;

x. (R)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((1-phenylethylcarbamoyloxy)methyl)piperazin-1-ium iodide;

xi. (R)-1-((sec-butoxycarbonyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xii. 1-(isobutyryloxymethyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xiii. 1-((benzyloxycarbonyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xiv. (R)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-(((1-phenylethoxy)carbonyloxy)methyl)piperazin-1-ium iodide;

xv. 1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-(((3-methylbutan-2-yloxy)carbonyloxy)methyl)piperazin-1-ium iodide;

xvi. 1-((benzyl(methyl)carbamoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xvii. (S)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((1-phenylethylcarbamoyloxy)methyl)piperazin-1-ium iodide;

xviii. 1-((ethoxycarbonyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xix. 1-((cyclobutoxycarbonyloxy)methyl)-1-methyl-4-(4-(3-methyl-4-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xx. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)piperazin-1-ium methanesulfonate;

xxi. 1-((2,2-dimethylbutanoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xxii. 1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((tert-pentyloxycarbonyloxy)methyl)piperazin-1-ium iodide;

xxiii. (R)-1-((sec-butylcarbamoyloxy)methyl)-1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)piperazin-1-ium iodide;

xxiv. 1-methyl-4-(4-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenylcarbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium iodide;

xxv. 4-(4-((3-((4-(1-(((isopropoxycarbonyl)oxy)methyl)pyridin-1-ium-3-yl)pyrimidin-2-yl)amino)-4-methylphenyl)carbamoyl)benzyl)-1-methylpiperazin-1-ium monoiodide monomesylate;

xxvi. 3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl) methyl) benzamido)phenyl)amino)pyrimidin-4-yl)-1-(((morpholine-4-carbonyl)oxy)methyl)pyridin-1-ium monoiodide monomesylate;

xxvii. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium methanesulfonate;

xxviii. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium tetrafluoroborate;

xxix. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium trifluoromethanesulfonate;

xxx. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium nitrate;

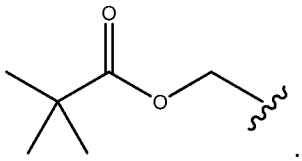
xxxi. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-((2-phenylacetoxy)methyl)piperazin-1-ium p-toluene sulfonate;

xxxii. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((2-phenylpropanoyl)oxy)methyl)piperazin-1-ium iodide;

xxxiii. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((2-phenylpropanoyl)oxy)methyl)piperazin-1-ium tetrafluoroborate; and

xxxiv. 1-methyl-4-(4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzyl)-1-(((2-phenylpropanoyl)oxy)methyl)piperazin-1-ium methanesulfonate.

24. The compound according to any preceding claim, wherein neither A nor B is



25. A composition comprising a compound according to any preceding claim.

26. A composition comprising a compound according to claim 25 further comprising one or more pharmaceutically acceptable excipients.

27. A compound or composition according to any proceding claim, for administration to a mammal in the dose of 0.1-100 mg/ kg of body weight of the compound of Formula (I).

28. The compound according to claim 1, for conjoint administration with one or more compounds independently selected from the group comprising central nervous system drugs, such as cns/respiratory stimulants, analgesics, narcotic agonists, narcotic agonist/antagonists, nonsteroidal anti-inflammatory/analgesic agents, behavior-modifying agents, tranquilizers/sedatives, anesthetic agents, inhalants, narcotics, reversal agents, anticonvulsants, muscle relaxants, skeletal, muscle relaxants, smooth, euthanasia agent, cardiovascular agents, inotropic agents, antiarrhythmic drugs, anticholinergics, vasodilating agents, agents used in treatment of shock, alpha-adrenergic blocking agents, beta-adrenergic blocking agents, respiratory drugs, bronchodilators, sympathomimetics, antihistamines, antitussives, renal and urinary tract, agents for urinary incontinence/retention, urinary alkalinizers, urinary acidifiers, cholinergic stimulants, agents for urolithiasis, gastrointestinal agents, antiemetic agents, antacids, h2 antagonists, gastromucosal protectants, proton pump inhibitors, appetite stimulants, gi antispasmodics-anticholinergics, gi stimulants, laxatives, saline, bulk producing, lubricant, surfactant, antidiarrheals, hormones/endocrine/reproductive agents, sex hormones, anabolic steroids, posterior pituitary hormones, adrenal cortical

steroids, glucocorticoids, antidiabetic agents, thyroid drugs, thyroid hormones, misc. endocrine/reproductive drugs, prostaglandins, antiinfective drugs, antiparasitics, anticoccidial agents, antibiotics, anti-tuberculosis, aminocyclitols,cephalosporins, macrolides, penicillins, tetracyclines, lincosamides, quinolones, sulfonamides, miscellaneous antibacterials, antifungal agents, antiviral agents, blood modifying agents, clotting agents, anticoagulants, erythropoietic agents, antineoplastics/immunosuppresives, alkylating agents, antidotes, bone/joint agents, dermatologic agents (systemic), vitamins and minerals/nutrients, systemic acidifiers, systemic alkalinizers, anti-cancer agents, anti-viral agents.

29. Use of a compound or composition according to any one of claims 1-27 for altering c-ABL in mammals, including humans.

30. Use of a compound or composition according to any one of claims 1-27 for inhibition of PGDFR.

31. Use of a compound or composition according to any one of claims 1-27 for inhibition of SCFR.

32. A method of treating a mammal suffering from a tumoral disease, such as a human, which comprises administering to such a mammal an effective amount of a compound or composition according to any one of claims 1-27.

33. A method for preventing or treating a bacterial infection or a viral infection in a subject, comprising administering a compound or composition of any one of claims 1-27 to the subject.

34. The method of claim 33, wherein the bacterial infection is caused by *Pseudomonas aeruginosa, Chlamydia trochomatis, Escherichia coli, Helicobacter pylori, Listeria monocytogenes, Salmonella typhimurium, Shigella flexneri,* or *Mycobacterium tuberculosis*.

35. The method of claim 33, wherein the viral infection is caused by a Vaccinia virus, a variola virus, a polyoma virus, a Pox virus, a Herpes virus, a cytomegalovirus (CMV), a human immunodeficiency virus, JC virus, BK virus, Simian virus 40 (SV40), Monkeypox virus, Ebola virus, Marburg virus, Bunyavirus, Arenavirus, Alphavirus e.g., Venezualan

equine encephalitis (VEE), Western equine encephalitis (WEE), Flavirus, West Nile virus or SARS Coronavirus.

36. The method of any one of claims 32-35, wherein the compound or composition is administered orally, nasally, buccally, sublingually, intravenously, transmucosally, rectally, topically, transdermally, subcutaneously, by inhalation, or intrathecally.

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2013/063560**

**A. CLASSIFICATION OF SUBJECT MATTER**

**C07D 401/14(2006.01)i, A61K 31/506(2006.01)i, A61P 35/00(2006.01)i, A61P 31/12(2006.01)i**

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 401/14; C07D 403/14; A01N 35/02; C07F 9/12; C07D 403/02; A01N 35/00; C07F 9/58; A61K 31/506; A61P 35/00; A61P 31/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: imatinib, tumor, cancer, prodrug

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2011-081408 A2 (CELLTRION CHEMICAL RESEARCH INSTITUTE et al.) 07 July 2011<br>See the whole document | 1-4,22-23,28 |
| A | WO 2008-076265 A1 (GILEAD SCIENCES, INC. et al.) 26 June 2008<br>See the whole document | 1-4,22-23,28 |
| PX | WO 2012-137225 A1 (SPHAERA PHARMA PVT. LTD et al.) 11 October 2012<br>See abstract; B.2.(pp. 67, 70, 71); scheme 50, 51 | 1-4,22-23,28 |

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

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 January 2014 (24.01.2014) | **24 January 2014 (24.01.2014)** |

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# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/US2013/063560**

**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.: 32-36
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 32-36 pertain to methods for treatment of the human body by therapy as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1 (iv) of the Regulations nder the PCT, to search.

2. ☒ Claims Nos.: 11-12, 16-21, 26, 34-35
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:
Claims 11-12, 16-21, 26, 34-35 are unclear, since they refer to claims which are not searchable due to not being drafted in accordance with the third sentence of Rule 6.4(a)

3. ☒ Claims Nos.: 5-10, 13-15, 24-25, 27, 29-33, 36
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 addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any 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/US2013/063560**

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2011-081408 A2 | 07/07/2011 | CN102666530 A | 12/09/2012 |
| | | EP 2519518 A2 | 07/11/2012 |
| | | EP 2519518 A4 | 22/05/2013 |
| | | JP 2013-515766A | 09/05/2013 |
| | | KR 10-1138840 B1 | 10/05/2012 |
| | | KR 20110075302A | 06/07/2011 |
| | | US 2012-0295917 A1 | 22/11/2012 |
| | | WO 2011-081408 A3 | 10/11/2011 |
| WO 2008-076265 A1 | 26/06/2008 | AR 064307A1 | 25/03/2009 |
| | | AU 2007-334541 A1 | 26/06/2008 |
| | | CA 2670730 A1 | 26/06/2008 |
| | | CN 101657460 A | 24/02/2010 |
| | | EP 2125841 A1 | 02/12/2009 |
| | | JP 2010-513276 T | 30/04/2010 |
| | | JP 2010-513276A | 30/04/2010 |
| | | RU 2009126633 A | 20/01/2011 |
| | | TW 200848060 A | 16/12/2008 |
| | | US 2010-0098641 A1 | 22/04/2010 |
| WO 2012-137225 A1 | 11/10/2012 | None | |