IMIDAZOPYRAZINES AS CYCLIN DEPENDENT KINASE INHIBITORS

Field of the Invention

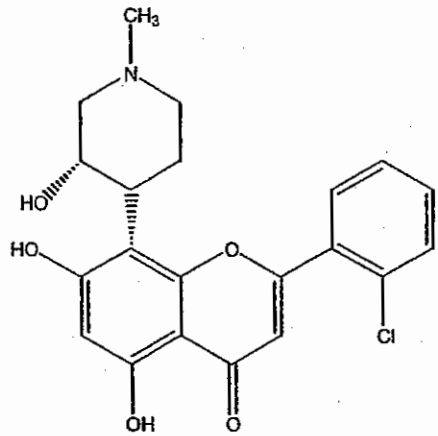
The present invention relates to imidazo[1,2-a]pyrazine compounds useful as protein kinase inhibitors (such as for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like), pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, and fungal diseases. This application claims the benefit of priority from U.S. provisional patent application Serial No. 60/412,997, filed September 23, 2002.

Background of the Invention

Protein kinase inhibitors include kinases such as, for example, the inhibitors of the cyclin-dependent kinases (CDKs), mitogen activated protein kinase (MAPK/ERK), glycogen synthase kinase 3 (GSK3beta), and the like. The cyclin-dependent kinases are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Individual CDK's, such as, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK7, CDK8 and the like, perform distinct roles in cell cycle progression and can be classified as either G1, S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer cells, and misregulation of CDK function occurs with high frequency in many important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. Checkpoints serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorgenesis. The CDK2 pathway influences tumorgenesis at the level of tumor suppressor function (e.g. p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator, cyclin E, and the inhibitor, p27, of CDK2 are either over – or underexpressed,

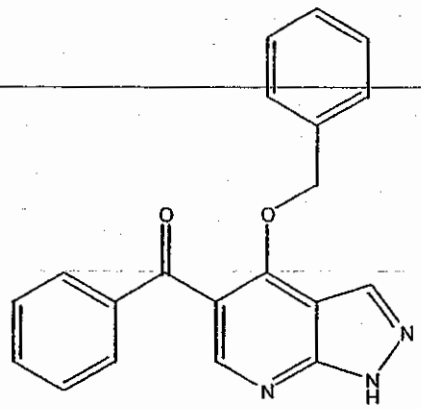
respectively, in breast, colon, nonsmall cell lung, gastric, prostate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased CDK2 activity levels and poor overall survival. This observation makes CDK2 and its regulatory pathways compelling targets for the development years, a number of adenosine 5'-triphosphate (ATP) competitive small organic molecules as well as peptides have been reported in the literature as CDK inhibitors for the potential treatment of cancers. U.S. 6,413,974, col. 1, line 23- col. 15, line 10 offers a good description of the various CDKs and their relationship to various types of cancer.

CDK inhibitors are known. For example, flavopiridol (Formula I) is a nonselective CDK inhibitor that is currently undergoing human clinical trials, A. M. Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.



Formula I

Other known inhibitors of the CDKs include, for example, olomoucine (J. Vesely *et al*, *Eur. J. Biochem.*, (1994) 224, 771-786) and roscovitine (I. Meijer *et al*, *Eur. J. Biochem.*, (1997) 243, 527-536). U.S. 6,107,305 describes certain pyrazolo[3,4-b] pyridine compounds as CDK inhibitors. An illustrative compound from the '305 patent has the Formula II:



Formula II

K. S. Kim *et al, J. Med. Chem.* 45 (2002) 3905-3927 and WO 02/10162 disclose certain aminothiazole compounds as CDK inhibitors.

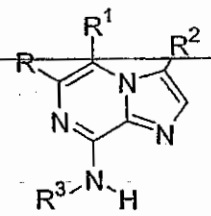
Pyrazolopyrimidines are known. For Example, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem. Pharm. Bull., (1962)* 10 620 disclose various pyrazolopyrimidines.

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with CDKs. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of imidazo[1,2-a]pyrazine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

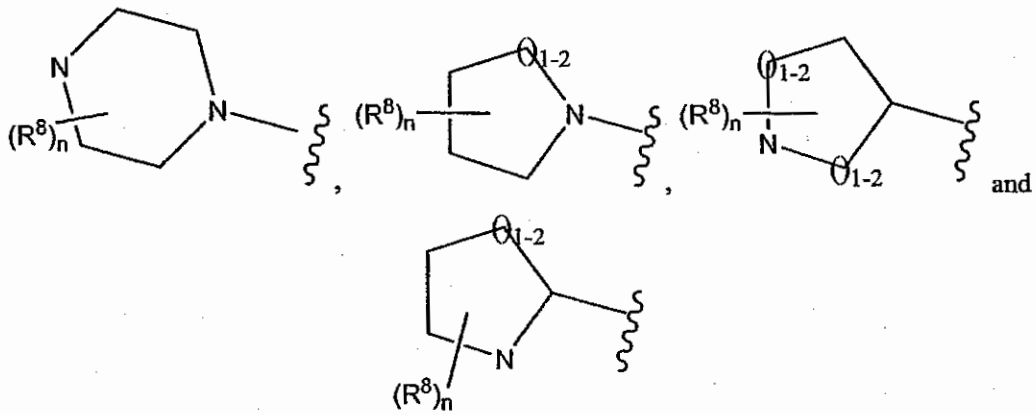
In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula III:



Formula III

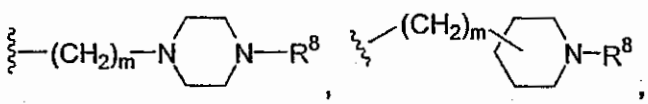
wherein:

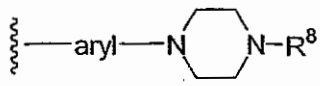
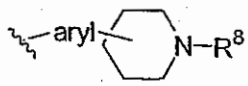
R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, $-C(O)R^7$,

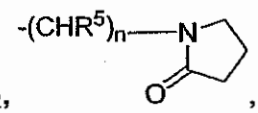
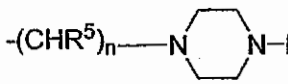
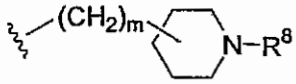


wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^1 is H, halogen, or alkyl;

R^2 is selected from the group consisting of R^9, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, $-CF_3$, $-C(O)R^7$, alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected, 

 and , wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n$-cycloalkyl, , $-(CHR^5)_n$-heterocycloalkyl, $-(CHR^5)_n$-$CH(aryl)_2$, , $-(CHR^5)_n$-OR^6, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-(CH_2)_m$-NR^8, and , wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4;

n is 1-4; and

p is 0-3.

The compounds of Formula III can be useful as protein kinase inhibitors and can be useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

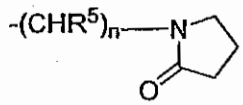
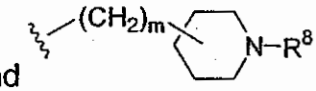
Detailed Description

In one embodiment, the present invention discloses imidazo[1,2-a]pyrazine compounds which are represented by structural Formula III, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

In another embodiment, R is selected from the group consisting of H, halogen, aryl, heteroaryl, alkenyl and $-C(O)R^7$, wherein each of said aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, CF_3, CN, $-OCF_3$, and $-OR^6$.

In another embodiment, R^1 is H or lower alkyl.

In another embodiment, R^2 is selected from the group consisting of halogen, alkyl, aryl, heteroaryl, alkenyl and $-C(O)R^7$, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, CF_3, CN, $-OCF_3$, and $-OR^6$.

In another embodiment, R^3 is selected from the group consisting of H, aryl, heteroaryl, $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n-OR^6$, $-C(O)R^6$, cycloalkyl, $-CH(aryl)_2$,  and , wherein each of said aryl and heteroaryl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, CF_3, CN, $-C(O_2)R^5$ and $-S(O_2)R^6$.

In another embodiment, R^5 is H or lower alkyl.

In another embodiment, m is 0 to 2.

In another embodiment, n is 1 to 3.

In an additional embodiment, R is selected from the group consisting of H, phenyl and heteroaryl.

In an additional embodiment, R^1 is H, Br or methyl.

In an additional embodiment, R^2 is F, Cl, Br, I, aryl, alkenyl, heteroaryl or CF_3.

In an additional embodiment, R^3 is phenyl, (pyrid-2-yl)methyl, (pyrid-3-yl)methyl, (pyrid-4-yl)methyl, 2-[(pyrid-3-yl)]ethyl, 2-[(pyrid-4-yl)]ethyl, 2-ylpropanol, 3-ylpropyl-10pyrrolidin-2-one, or $-C(O)CH_3$, wherein said pyridyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Cl, Br, CF_3, lower alkyl, methoxy and CN.

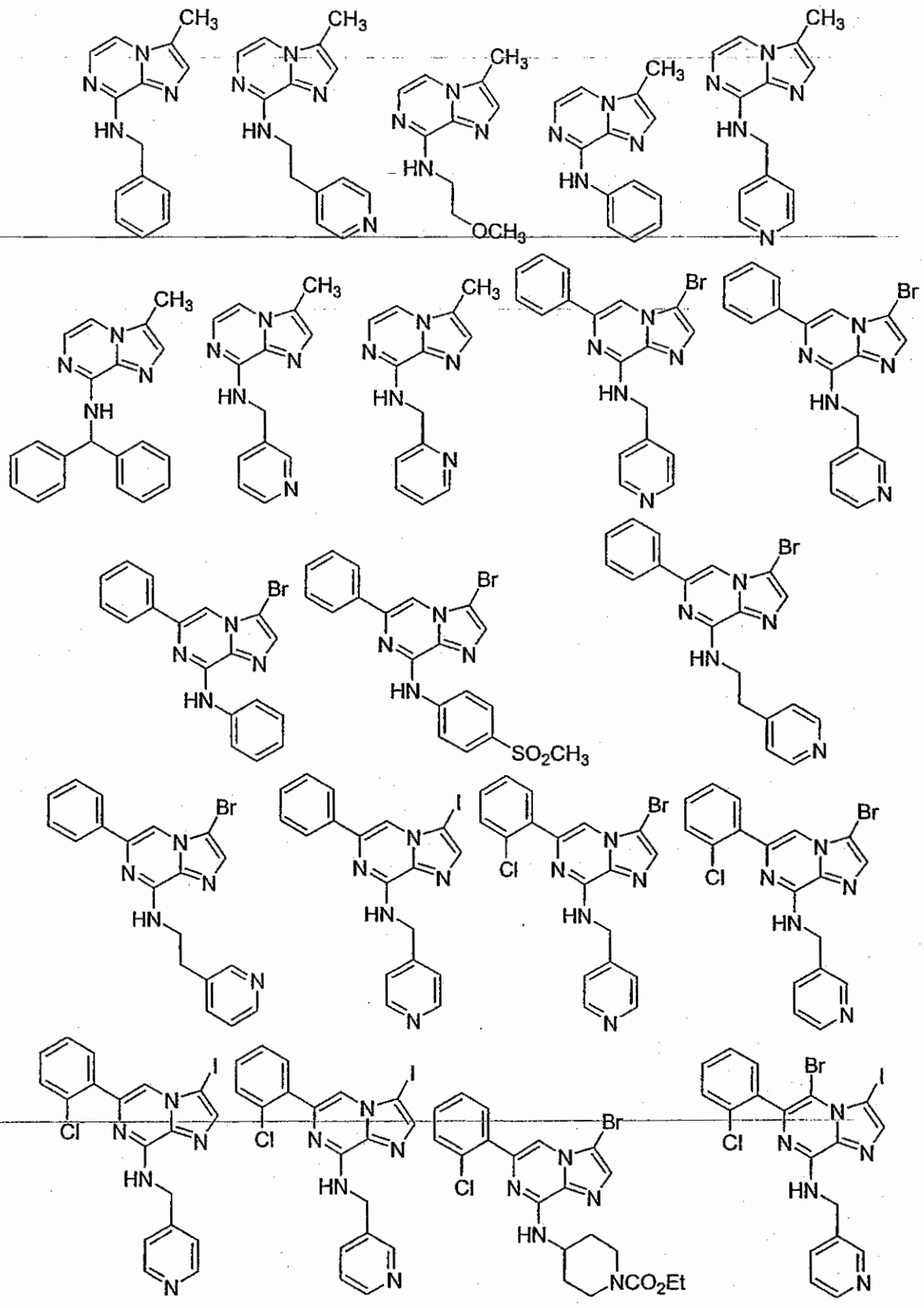
In an additional embodiment, R^5 is H.

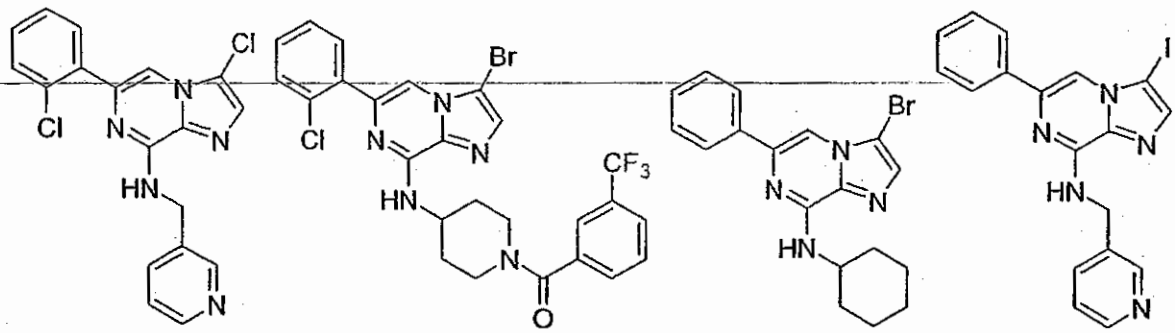
In an additional embodiment, m is 0.

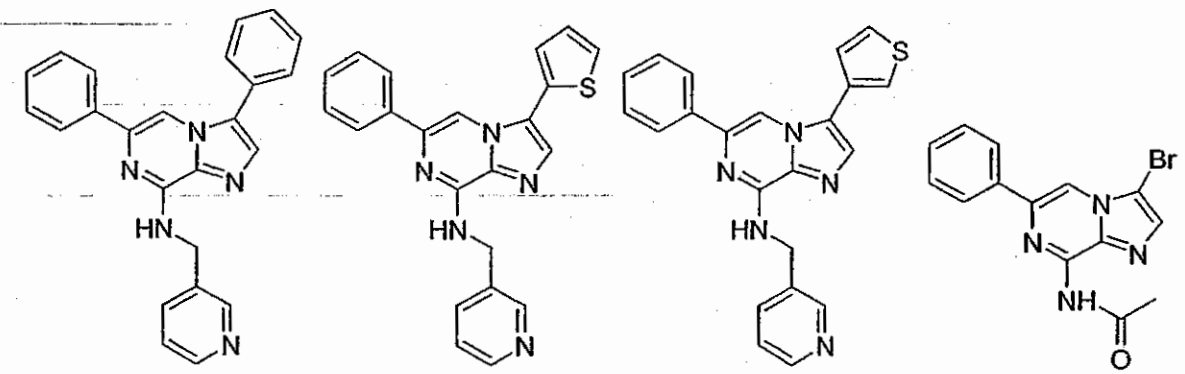
In an additional embodiment, n is 1 or 2.

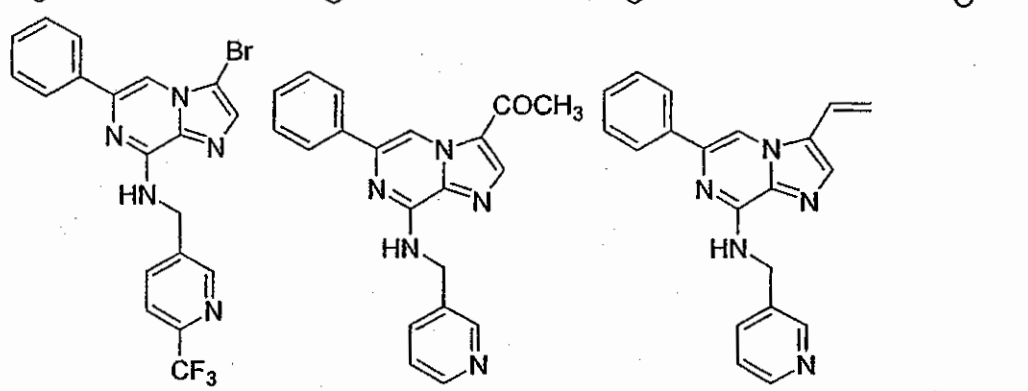
An inventive group of compounds is shown in **Table 1.**

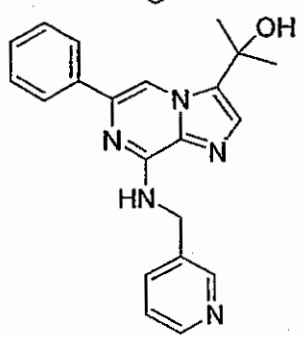
Table 1

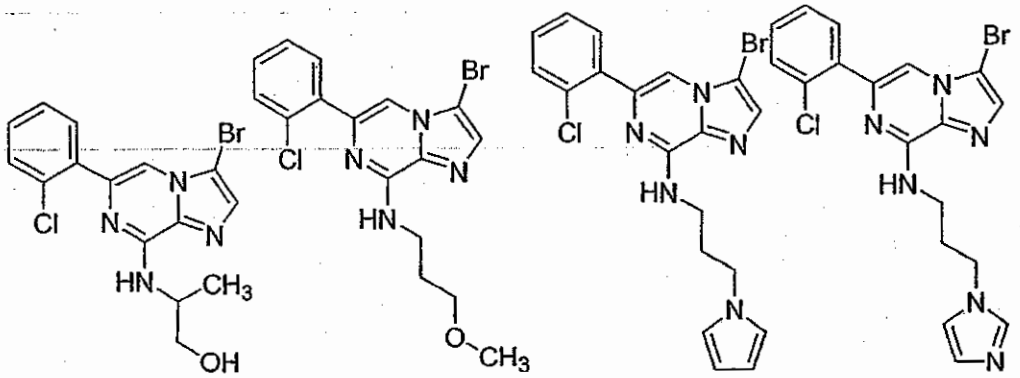




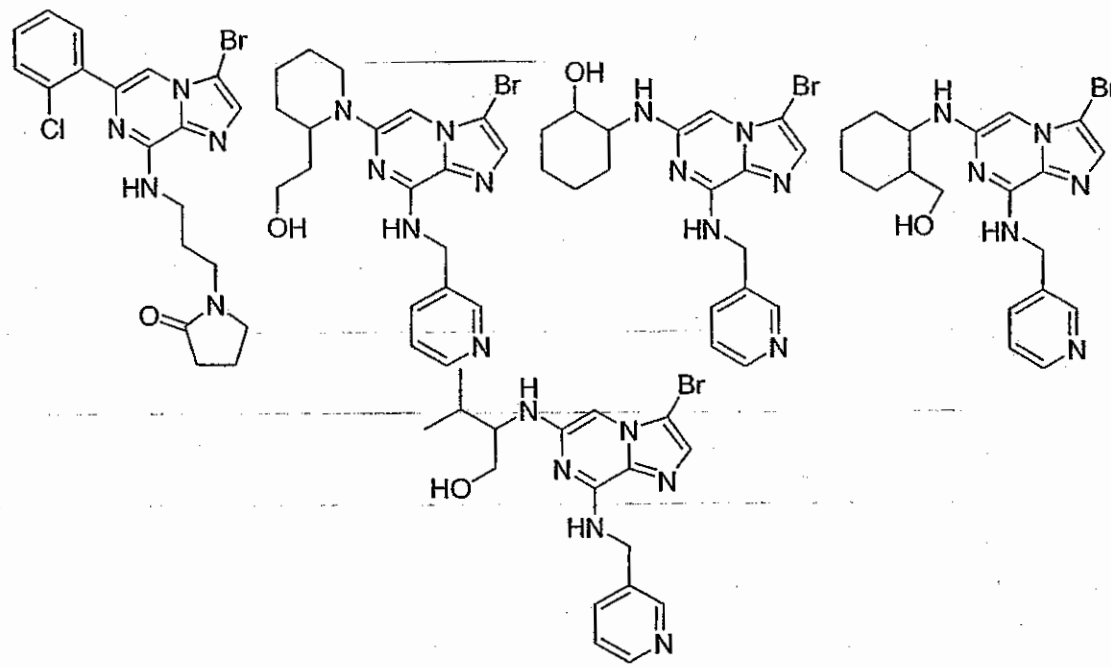






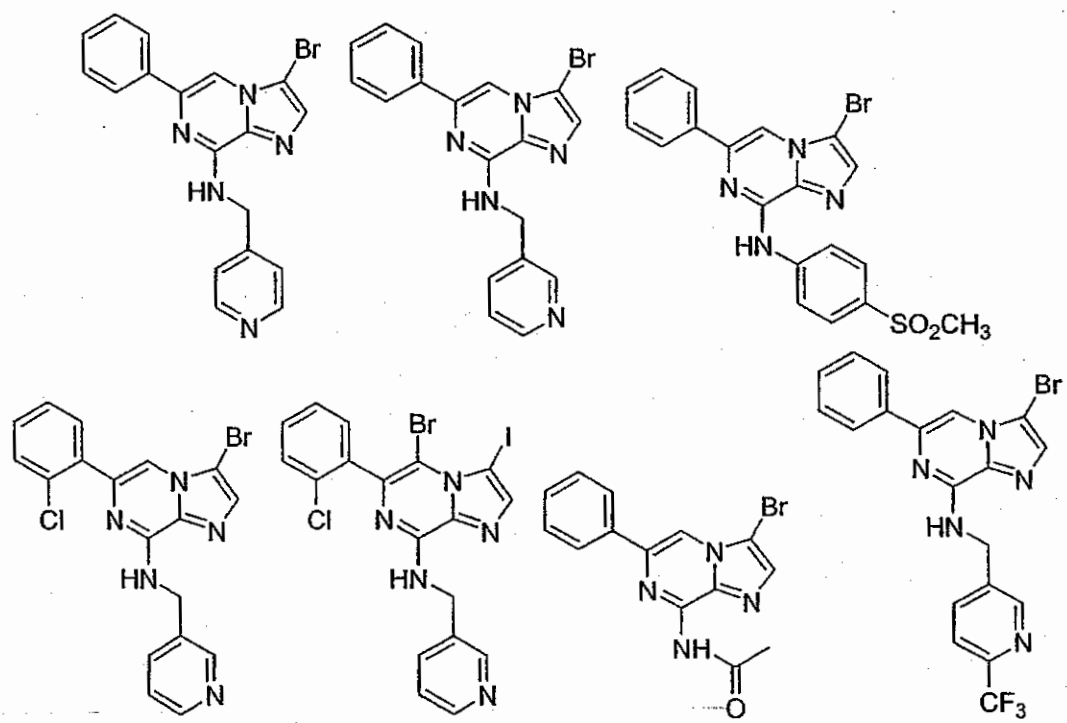


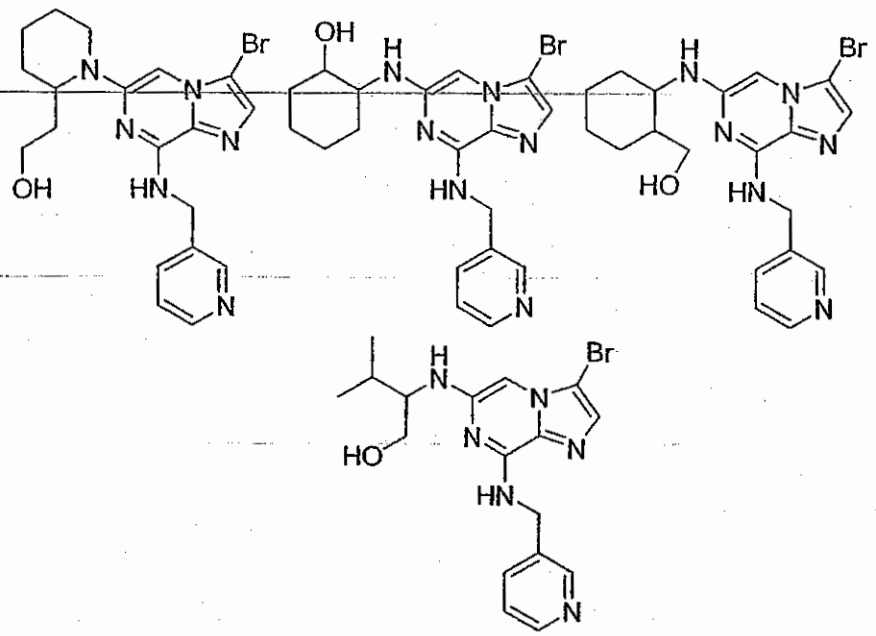
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Another embodiment discloses compounds of the formula:

of the formula:





and

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have

about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term “heteroaryl” also refers to partially saturated

heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

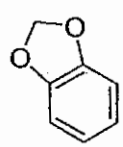
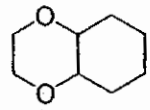
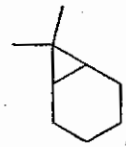
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine.

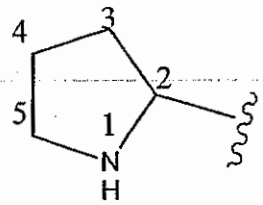
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and

are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



and
.

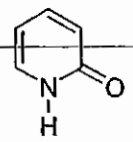
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:

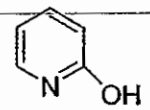


there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



and



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy,

ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula III, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any

product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula III or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula III can form salts which are also within the scope of this invention. Reference to a compound of Formula III herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable

(i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula III may be formed, for example, by reacting a compound of Formula III respectively 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, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts 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 dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are

considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula III, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). 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 can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula III can be inhibitors of protein kinases such as, for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like. The cyclin dependent kinases (CDKs) include, for example, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 and CDK8. The novel compounds of Formula III are expected to be useful in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974 cited earlier, the disclosure of which is incorporated herein.

More specifically, the compounds of Formula III can be useful in the treatment of a variety of cancers, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of CDKs in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of Formula III may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that CDK5 is involved in the phosphorylation of tau protein (*J. Biochem,* (1995) 117, 741-749).

Compounds of Formula III may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of Formula III, as modulators of apoptosis, will be useful in the treatment of cancer (including but

not limited to those types mentioned hereinabove), viral infections (including but not limited to herpevirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formula III, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formula III may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formula III may also be useful in inhibiting tumor angiogenesis and metastasis.

Compounds of Formula III may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf 1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

Another aspect of this invention is a method of treating a mammal (*e.g.*, human) having a disease or condition associated with the CDKs by administering a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound to the mammal.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula III. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more of anti-cancer treatments such as radiation therapy, and/or one or more anti-cancer agents selected from the group consisting of cytostatic agents, cytotoxic agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin)); taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11), camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methoxtrexate); alkylating agents (such as temozolomide (TEMODAR™ from Schering-Plough Corporation, Kenilworth, New Jersey), cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASAR™(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl-]-1-piperidinyl]-2-oxoehtyl]-1-piperidinecarboxamide, or SCH 66336 from Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); signal transduction inhibitors (such as, Iressa (from Astra Zeneca Pharmaceuticals, England), Tarceva (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC™ (C-abl kinase inhibitor from Novartis Pharmaceuticals, East Hanover, New Jersey); interferons such as, for example, intron (from Schering-Plough Corporation), Peg-Intron (from Schering-Plough

Corporation); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, cytoxan, and gemcitabine.

Other anti-cancer (also known as anti-neoplastic) agents include but are not limited to Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaeuticals, France), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. For example, the CDC2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Compounds of Formula III may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of Formula III may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. Such

techniques are within the skills of persons skilled in the art as well as attending physicians.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate thereof, and an amount of one or more anti-cancer treatments and anti-cancer agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one anticancer therapy and/or anti-cancer agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. The retention time and observed parent ion are given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Thin layer chromatography: TLC

dichloromethane: CH_2Cl_2

ethyl acetate: AcOEt or EtOAc

methanol: MeOH

trifluoroacetate: TFA

triethylamine: Et_3N or TEA

butoxycarbonyl: N-Boc or Boc

nuclear magnetic resonance spectroscopy: NMR

liquid chromatography mass spectrometry: LCMS

high resolution mass spectrometry: HRMS

milliliters: mL

millimoles: mmol

microliters: µl

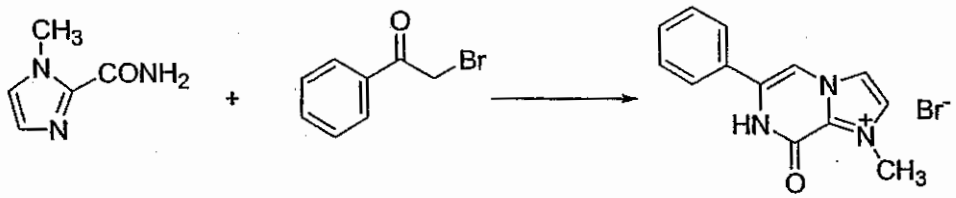
grams: g

milligrams: mg

room temperature or rt (ambient): about 25°C.

EXAMPLES

PREPARATIVE EXAMPLE 1:



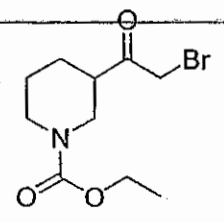
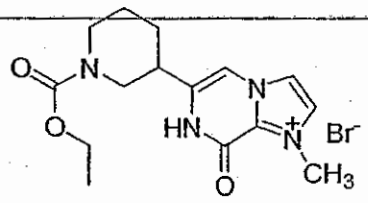
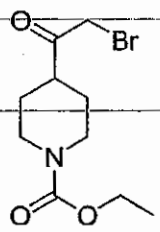
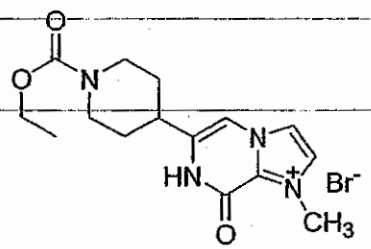
A mixture of 1-methylimidazole-2-carboxamide (3.00 g, 24 mmol) and phenacyl bromide (5.73 g, 29 mmol) in anhydrous CH_3CN (90 mL) was stirred and refluxed under N_2 for 1 day. The mixture was filtered, the solid was washed on filter with CH_3CN (2 x 30 mL) and dried in a vacuum. White solid (5.86 g, 80 %) was obtained.

PREPARATIVE EXAMPLE 1.1 and 1.2:

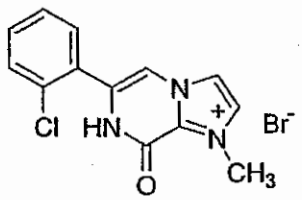
By essentially the same procedure given in Preparative Example 1, compounds given in Column 2 of Table 1.1 can be prepared by combining 1-methylimidazole-2-carboxamide with the bromoketones given in Column 1.

TABLE 1.1

Prep. Example	Column 1	Column 2

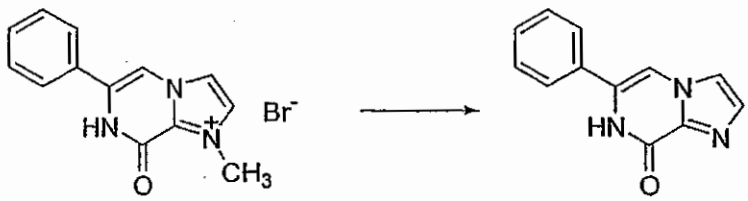
1.1		
1.2		

PREPARATIVE EXAMPLE 2:



This compound was prepared by essentially same procedure set forth in Preparative Example 1.

PREPARATIVE EXAMPLE 3:

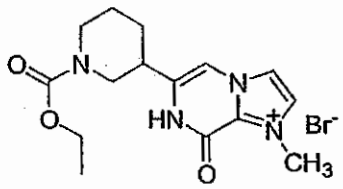
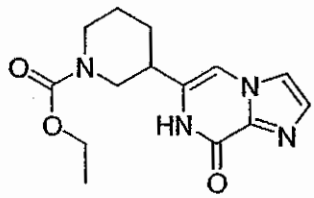
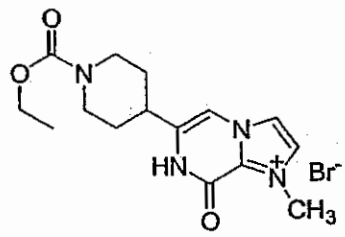
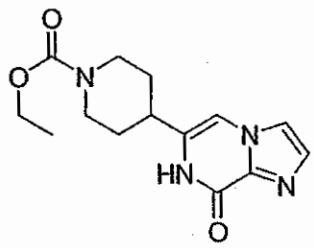


A mixture of the product from Preparative Example 1 (4.62 g, 15 mmol) and imidazole (25.50 g, 375 mmol) was stirred under N_2 at 175°C for 20 hr, then it was cooled to 100°C and poured into stirred ice-cold water (400mL). The mixture was stirred for 15 min, and then filtered. The solid was washed on filter with water (2 x 100 mL) and dried in a vacuum at 100°C. White solid (2.43 g, 77 %) was obtained.

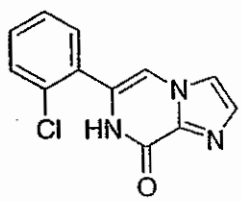
PREPARATIVE EXAMPLE 3.1 and 3.2:

By essentially the same procedure given in Preparative Example 3, compounds given in Column 2 of Table 2.1 can be prepared from compounds given in Column 1.

TABLE 2.1

Prep. Example	Column 1	Column 2
3.1		
3.2		

PREPARATIVE EXAMPLE 4:



Method 1:

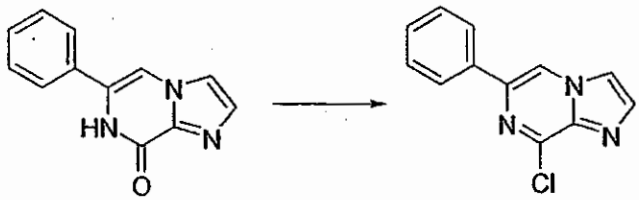
This compound was prepared by essentially same procedure set forth in Preparative Example 3. LCMS; MH^+ = 246.

Method 2:

Pyridinium hydrochloride (378.6g, 3.28moles) was placed in a 2L round bottomed flask and heated under reflux under a gentle stream of nitrogen until all

of the material had melted. The title compound from Preparative Example 2 [31.64g crude, prepared from 1-methylimidazole-2-carboxamide (10g, 79.9mmoles) essentially as described in Preparative Example 2] was added in one portion and the mixture was heated under reflux at 215°C for 15 min. The hot solution was poured into a mixture of 1.6L of ice and conc. NH_4OH (500mL). The pH was ~10.5. The mixture was evaporated to dryness and stored in the freezer. The resulting material was triturated with MeOH (4L), filtered and the solids were washed with additional MeOH (2L). The combined filtrates were evaporated to dryness to give a solid (49.75g). The latter was broken up and triturated with distilled water (250mL) and then filtered. The filtrate was discarded and the solid was dissolved in hot MeOH (850mL).and added to silica gel (~800mL) and Sea Sand (~350mL) and the mixture was evaporated to dryness. The resulting mixture was introduced as a plug on to a silica gel column (40x9cm) and the latter was eluted with CH_2Cl_2 (4L), followed by 1%-2.5% MeOH in CH_2Cl_2 and then neat MeOH, to give the title compound (8.06g, 41%): FABMS: m/z 246.0 (MH^+); HRFABMS: m/z 246.0434 (MH^+), $C_{12}H_9ClN_3O$ requires: m/z 246.0434.

PREPARATIVE EXAMPLE 5:

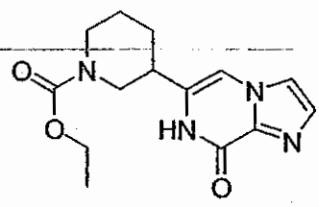
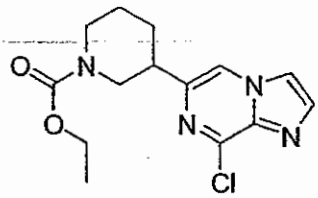
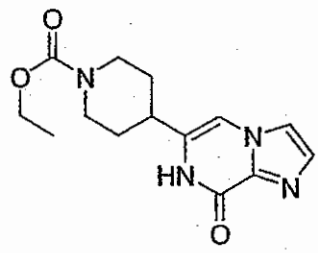
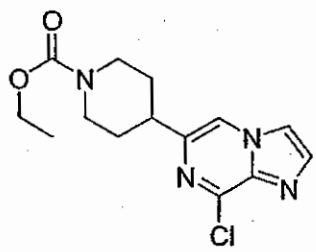


A mixture of the product from Preparative Example 3 (1.20 g, 5.71 mmol) and pyridine (0.32 mL, 4.0 mmol) in $POCl_3$ (6.5 mL) was stirred and refluxed under N_2 for 5 hrs. The mixture was poured into 100 mL of ice, a solution of NaOH (10 g) in H_2O (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 x 50 mL). The extracts were dried over Na_2SO_4, filtered and the solvent was evaporated. Column chromatography on silica gel with CH_2Cl_2/EtOAc (2:1) afforded off-white solid (520 mg, 40 %).

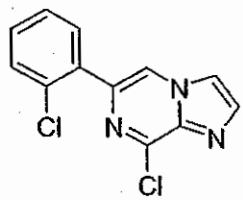
PREPARATIVE EXAMPLE 5.1 and 5.2:

By essentially the same procedure given in Preparative Example 5, compounds given in Column 2 of Table 3.1 can be prepared from compounds given in Column 1.

TABLE 3.1

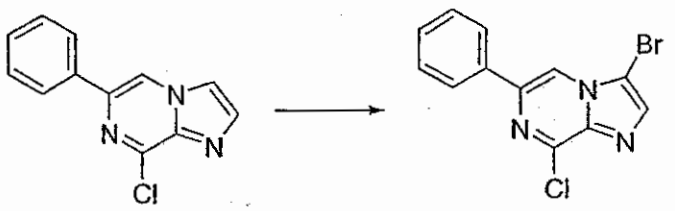
Prep. Example	Column 1	Column 2
5.1		
5.2		

PREPARATIVE EXAMPLE 6:



This compound was prepared by essentially same procedure set forth in Preparative Example 5. Off-white solid; LCMS; $MH^+ = 264$.

PREPARATIVE EXAMPLE 7:

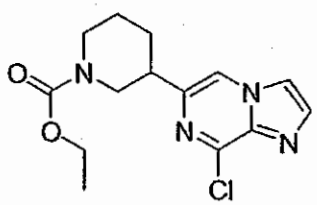
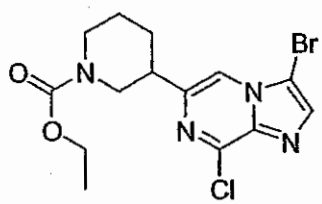
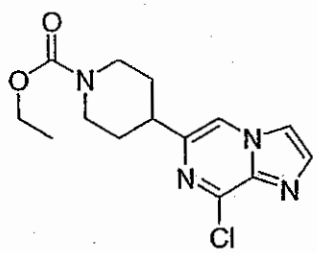
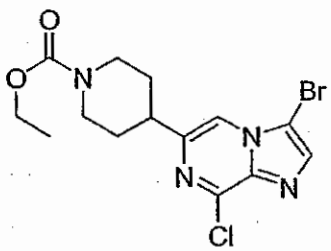


A solution of N-Bromosuccinimide ("NBS") (180 mg, 1.0 mmol) in anhydrous CH_3CN (5 mL) was added under N_2 to a stirred solution of the product from Preparative Example 5 (230 mg, 1.0 mmol) in anhydrous CH_3CN (5 mL) and CH_2Cl_2 (3 mL). The mixture was stirred at 25°C for 5 hr and the solvent was then evaporated. Chromatography on silica gel with CH_2Cl_2/EtOac (10:1) afforded white solid (294 mg, 96 %).

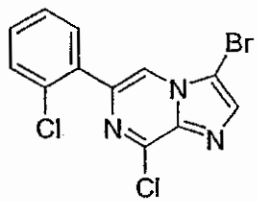
PREPARATIVE EXAMPLE 7.1 and 7.2:

By essentially the same procedure given in Preparative Example 7, compounds given in Column 2 of Table 4.1 can be prepared from compounds given in Column 1.

TABLE 4.1

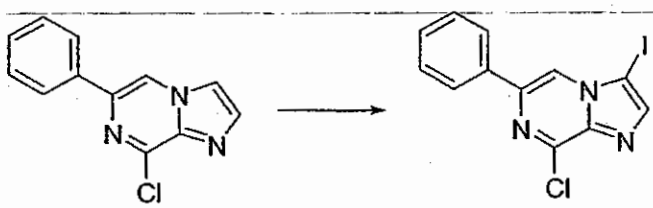
Prep. Example	Column 1	Column 2
7.1		
7.2		

PREPARATIVE EXAMPLE 8:



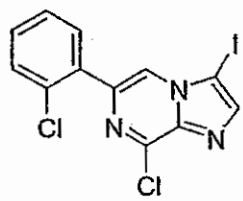
This compound was prepared by essentially same procedure set forth in Preparative Example 7. White solid; LCMS; MH^+ = 342.

PREPARATIVE EXAMPLE 9:



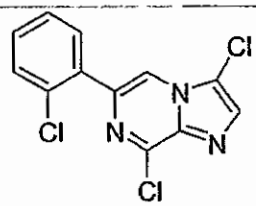
A solution of N-iodosuccinimide ("NIS") (450 mg, 2.0 mmol) in anhydrous CH_3CN (10 mL) was added under N_2 to a stirred solution of the product from Preparative Example 5 (460 mg, 2.0 mmol) in anhydrous CH_3CN (6 mL) and 1,2-dichloroethane (10 mL). The mixture was refluxed for 30 hr and the solvent was then evaporated. Chromatography on silica gel with CH_2Cl_2/EtOac (10:1) afforded white solid (602 mg, 85 %).

PREPARATIVE EXAMPLE 10:



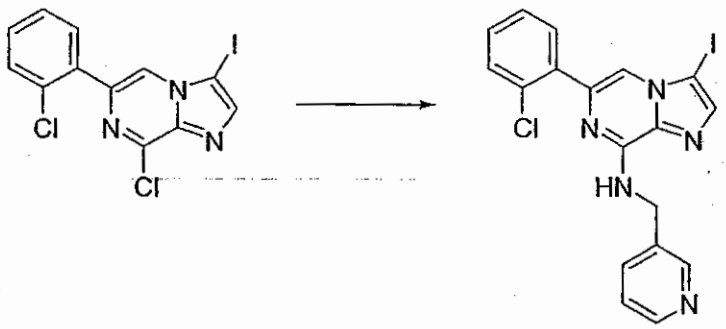
This compound was prepared by essentially same procedure set forth in Preparative Example 9. White solid; LCMS; MH^+ = 390.

PREPARATIVE EXAMPLE 11:



This compound was prepared by essentially same procedure set forth in Preparative Example 9. White solid.

EXAMPLE 11:

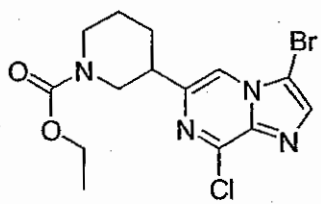
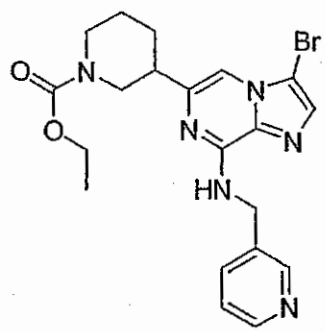


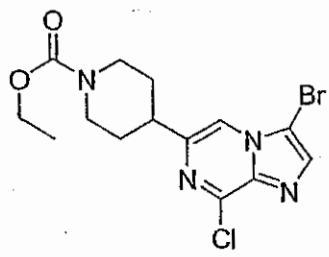
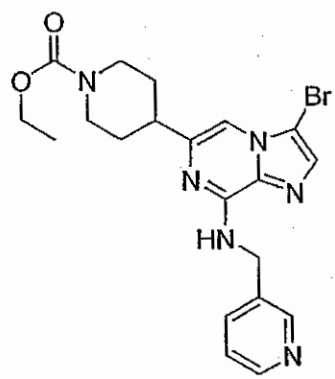
A mixture of the product from Preparative Example 10 (78 mg, 0.20 mmol), 3-(aminomethyl)pyridine (24 mg, 0.22 mmol), diisopropylethylamine (0.5 mL), and anhydrous dioxane (1.0 mL) was stirred at 90°C under N_2 for 48 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH/conc. aqueous NH_4OH (50:1:0.1). White solid (67 mg, 78 %) was obtained. LCMS; MH^+ = 462, m.p. 173-175°C.

EXAMPLES 11.1 and 11.2:

By essentially the same procedure given in Preparative Example 11, compounds given in Column 2 of Table 5.1 can be prepared from compounds given in Column 1.

TABLE 5.1

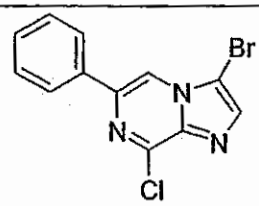
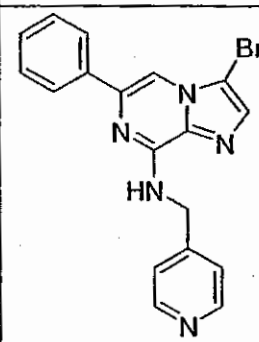
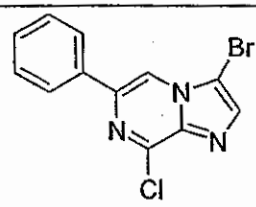
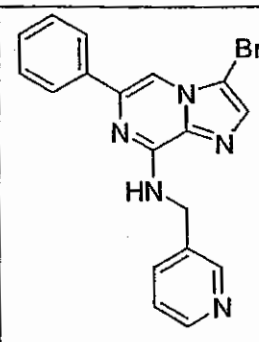
Example	Column 1	Column 2
11.1		

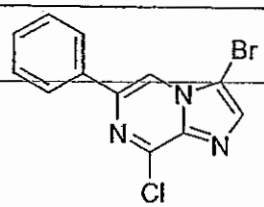
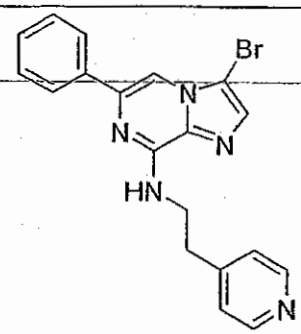
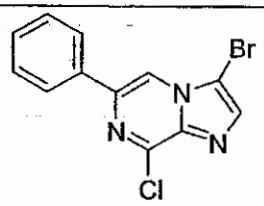
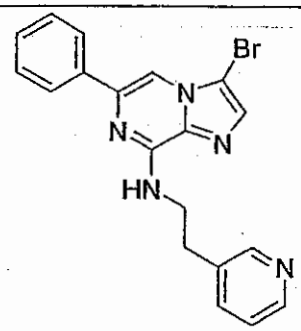
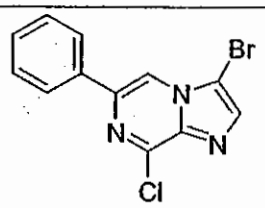
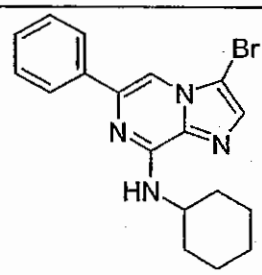
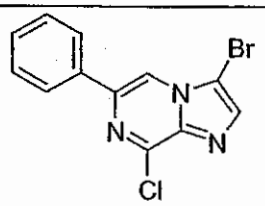
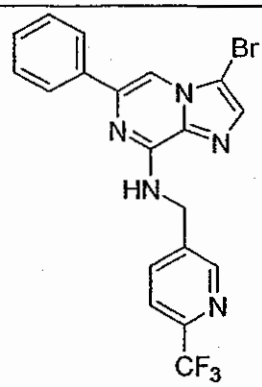
11.2		

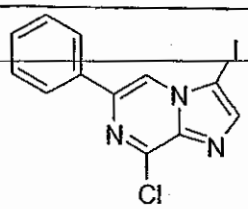
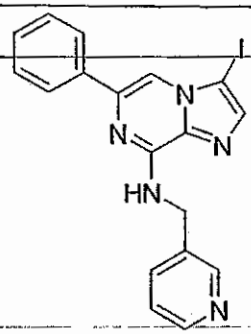
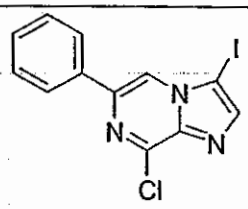
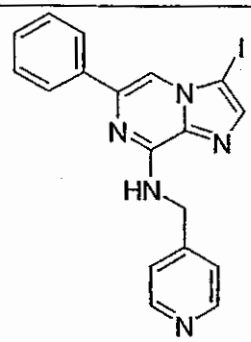
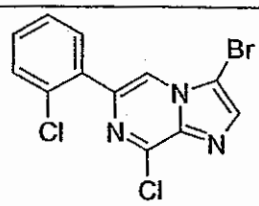
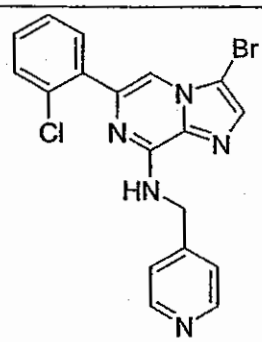
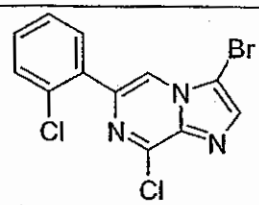
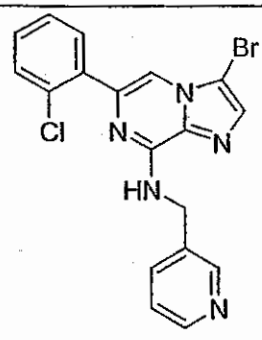
EXAMPLE 12-25:

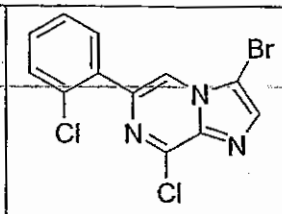
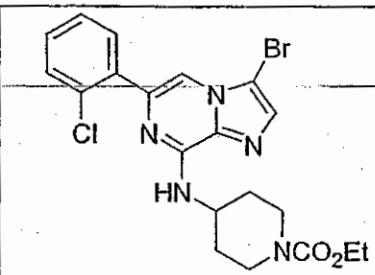
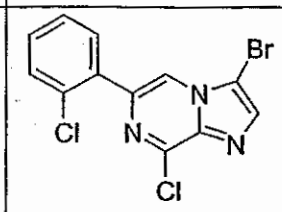
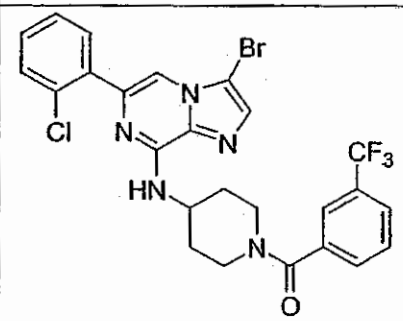
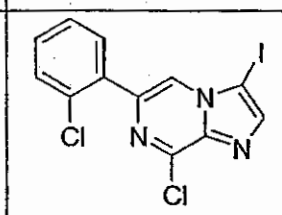
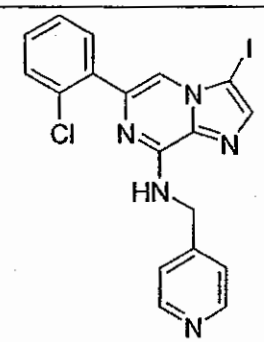
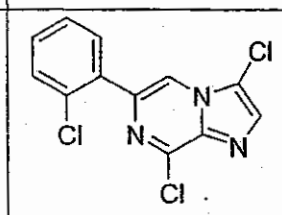
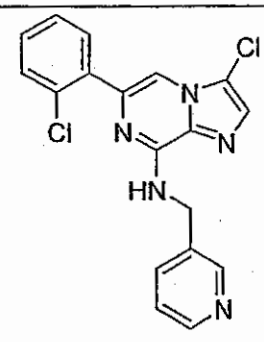
By essentially same procedure set forth in Example 11, the compounds shown in column 3 of Table 2 were prepared.

TABLE 2

Example	Column 2	Column 3	DATA
12			LCMS: (M+2H)+ = 382, M.P. > 205°C.
13			LCMS: (M+2H)+ = 382, M.P: 185-188°C.

14			LCMS: MH+ = 394, M.P: 177-179°C.
15			LCMS: MH+ = 394, M.P: 120-122°C.
16			LCMS: MH+ = 371, M.P: 145-146°C.
17			LCMS: MH+ = 449, M.P: 177-179°C.

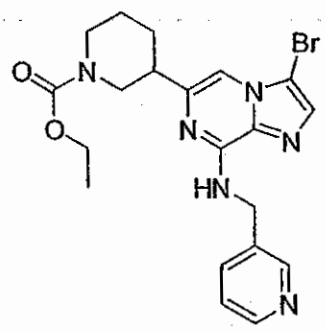
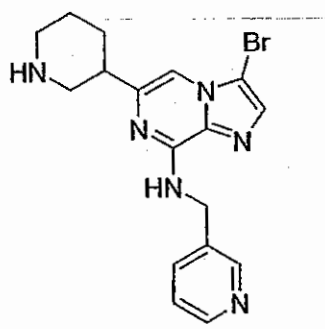
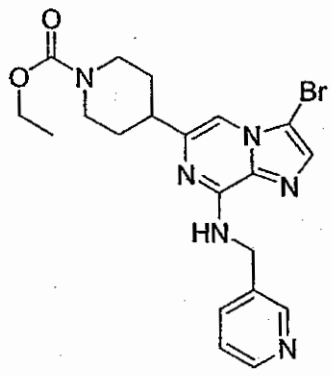
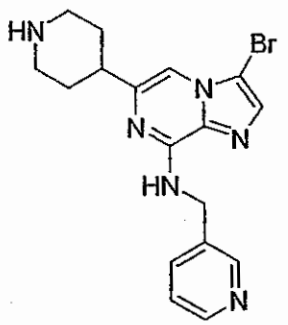
18			LCMS: MH+ = 428, M.P: 204-206°C.
19			LCMS: MH+ = 428, M.P: 139-141°C.
20			LCMS: MH+ = 415, M.P: 150-152°C.
21			LCMS: MH+ = 415, M.P: 146-147°C.

22			LCMS: MH+ = 479, M.P: 78-80°C.
23			LCMS: MH+ = 578, M.P: 175-177°C.
24			LCMS: MH+ = 462, M.P: 162-164°C.
25			LCMS: MH+ = 370, M.P: 127-129°C.

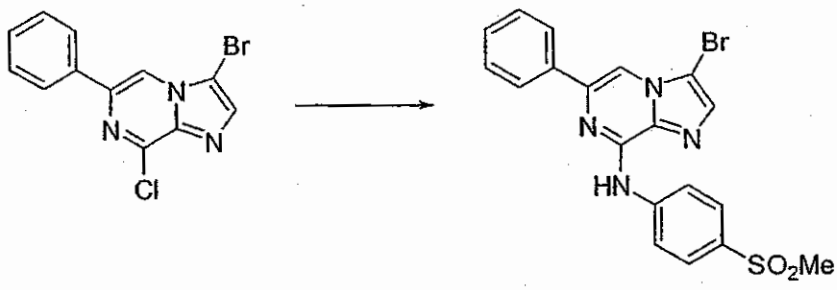
EXAMPLES 25.1 and 25.2:

Compounds given in Column 2 of Table 6.1 are prepared from compounds given in Column 1 by acidic hydrolysis (HCl in H_2O), followed by neutralization (K_2CO_3) and column chromatography.

TABLE 6.1

Example	Column 1	Column 2
25.1		
25.2		

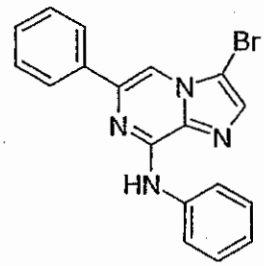
EXAMPLE 26:



A mixture of the product from Preparative Example 7 (81 mg, 0.20 mmol) and 4-methylsulfonylaniline hydrochloride (55 mg, 0.32 mmol) in

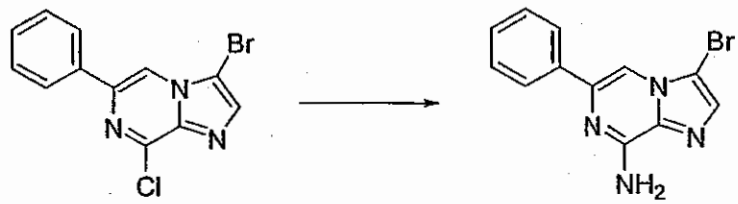
diisopropylethylamine (1.5 mL) was stirred at 110oC for 3 days. The solvent was evaporated and the residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH/conc. aqueous NH_4OH (20:1:0.1). White solid (22 mg, 20 %) was obtained. M. P. 251-254°C, LCMS: $(M+2H)^+$ = 445.

EXAMPLE 27:



This compound was prepared by essentially same procedure set forth in Example above. M. P. 169-170°C, LCMS: $(M+2H)^+$ = 367.

PREPARATIVE EXAMPLE 28:



Product from Preparative Example 7 (185 mg, 0.60 mmol) was stirred with conc. Aqueous NH_4OH (3 mL) and 2 M NH_3 in 2-propanol (6 mL) in a closed pressure tube at 90°C for 24 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH/conc. Aqueous NH_4OH (20:1:0.1). Slightly yellow solid (138 mg, 80 %) was obtained. M. P. 215-217°C, LCMS: MH^+ = 291.

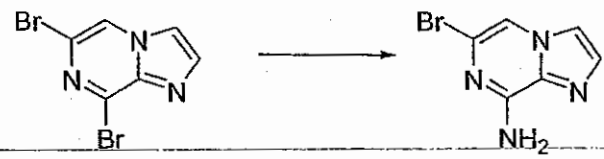
PREPARATIVE EXAMPLE 29:



A mixture of 2-amino-3,5-dibromopyrazine (Aldrich, 6.0g, 24.0 mmol) and 50% aqueous solution of chloroacetaldehyde (Aldrich, 4.8 mL) in 2-propanol (30 mL) was stirred and refluxed under N_2 for 24 hr. CH_2Cl_2 (300 mL) and triethylamine (12 mL) were added and the solvent was evaporated. The residue

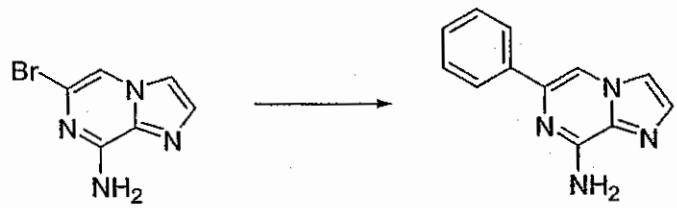
was suspended in 10:1 H_2O:2-propanol (200 mL), filtered, and the solid was washed on filter with 10:1 H_2O:2-propanol (2x100 mL). It was dried in a vacuum to yield pale beige solid (4.81g, 74 %).

PREPARATIVE EXAMPLE 30:



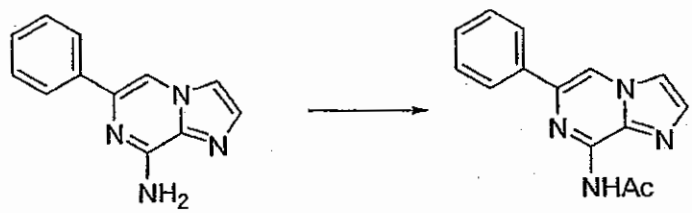
A mixture of the product from Preparative Example 29 (1.80 g, 6.45 mmol) and concentrated aqueous NH_4OH (27.0 mL) was stirred in a closed pressure vessel at 90°C for 24 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc. White solid (1.01 g, 73 %) was obtained. LCMS: MH^+ = 213.

PREPARATIVE EXAMPLE 31:



A mixture of the product from Preparative Example 30 (500 mg, 2.36 mmol), phenyl boronic acid (431 mg, 3.53 mmol), $Pd(PPh_3)_4$ (277 mg, 0.24 mmol), and Na_2CO_3 (2.50 g, 23.6 mmol) in 1,2-dimethoxyethane (30 mL) and H_2O (8 mL) was stirred and refluxed under N_2 for 24 hr. The mixture was poured into H_2O (500 mL), extracted with CH_2Cl_2 (4 x 50 mL) and the extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated and the residue was purified by column chromatography on silica gel with $PhCH_3$/7N NH_3 in MeOH (10:1). This afforded a slightly impure product as a pale orange solid, which was used for the next step.

PREPARATIVE EXAMPLE 32:



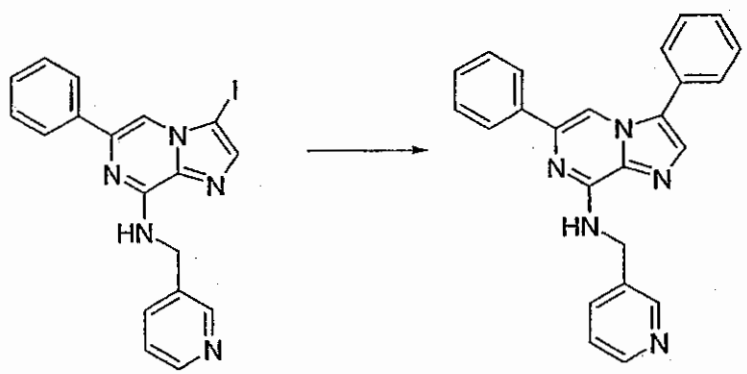
A mixture of the product from Preparative Example 31 (210 mg, 1.0 mmol), acetyl chloride (0.286 mL, 4.0 mmol), and pyridine (0.657 mL, 8.0 mmol) in 1,2-dichloroethane (5 mL) was stirred and refluxed for 72 hr. The mixture was poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 x 20 mL). The extracts were dried over Na_2SO_4, filtered and the solvent was evaporated. Chromatography on silica gel with EtOAc as eluent afforded 141 mg (56 %) of pale yellow solid.

PREPARATIVE EXAMPLE 33:



A solution of NBS (72 mg, 0.40 mmol) in anhydrous CH_3CN (2.0 mL) was added under N_2 to a stirred solution of the product from Preparative Example 32 (100mg, 0.40 mmol) in anhydrous CH_3CN (2.0 mL) and CH_2Cl_2 (6.0 mL). The mixture was stirred at 25°C for 48 hr and the solvent was then evaporated. Chromatography on silica gel with CH_2Cl_2/EtOAc (4:1) afforded pale yellow solid (41 mg, 31 %). M. P. 163-165°C, LCMS: $(M+2H)^+ = 333$.

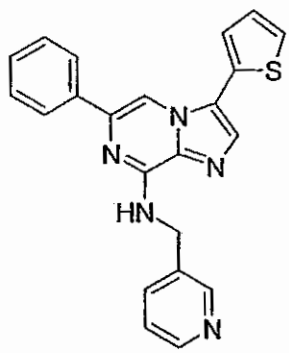
EXAMPLE 34:

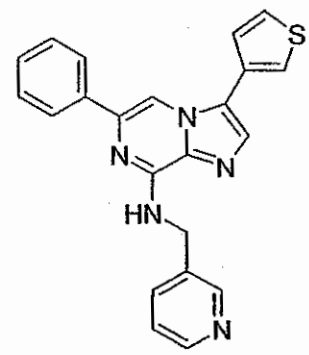


A mixture of the product from Example 17 (85 mg, 0.20 mmol), phenyl boronic acid (37 mg, 0.30 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and Na_2CO_3 (212 g, 2.00 mmol) in 1,2-dimethoxyethane (3.2 mL) and H_2O (0.8 mL) was stirred

and refluxed under N_2 for 24 hr. The mixture was poured into H_2O (100 mL), extracted with CH_2Cl_2 (4 x 15 mL) and the extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (30:1) to afford colorless waxy solid (46 mg, 61%). M. P. 138-140°C, LCMS: $(M+2H)^+ = 378$.

EXAMPLES 35 AND 36:

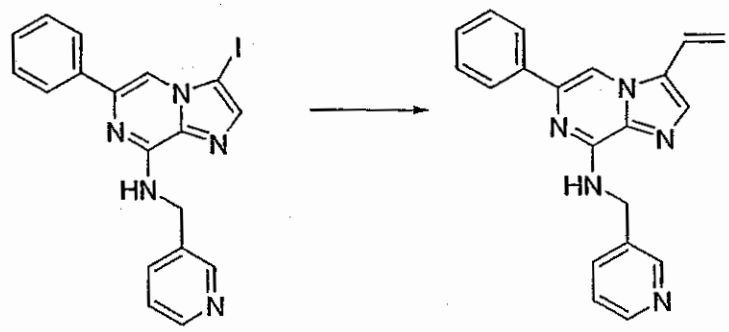




35 36

These compounds were prepared by essentially same procedure set forth in Example 34 above. Compound 35: M. P. 168-169°C, LCMS: $MH^+ = 384$; Compound 36: M. P. 154-156°C, LCMS: $MH^+ = 384$.

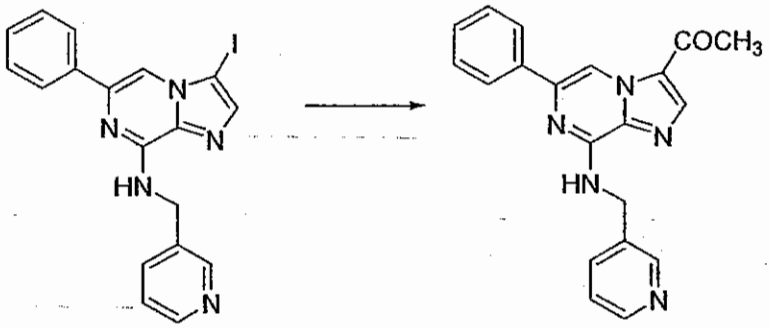
EXAMPLE 37:



A mixture of the product from Example 17 (214 mg, 0.50 mmol), tributyl(vinyl)tin (174 mg, 0.55 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), in 1,4-dioxane (10 mL) was stirred and refluxed under N_2 for 24 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel

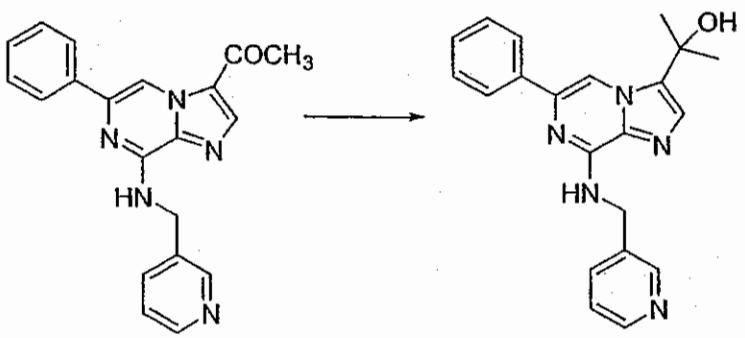
with CH_2Cl_2/MeOH/conc. Aqueous NH_4OH (40:1:0.1). Pale yellow solid (123 mg, 75 %) was obtained. M. P. 138-141°C, LCMS: MH^+ = 328.

EXAMPLE 38:



A mixture of the product from Example 17 (214 mg, 0.50 mmol), tributyl(ethoxyvinyl)tin (199 mg, 0.55 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), in 1,4-dioxane (10 mL) was stirred and refluxed under N_2 for 24 hr. 5 M HCl (1.0 mL) was added, the mixture was stirred for 5 min, then triethylamine (5 mL) was added and the solvent was evaporated. The residue was purified by column chromatography on silica gel with EtOAc/MeOH (10:1) and then triturated with cyclohexane (10 mL). Pale yellow solid (104 mg, 65 %) was obtained. M. P. 192-194°C, LCMS: MH^+ = 344.

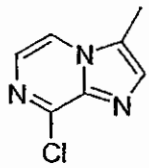
EXAMPLE 39:



MeMgI (3.0 M in Et_2O, 0.20 mL, 0.60 mmol) was added to a stirred solution of the product from Example 38 (51 mg, 0.15 mmol) in anhydrous Et_2O (3 mL) and CH_2Cl_2 (6 mL). The mixture was stirred at 25°C for 3 hr and then poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The extracts were dried over

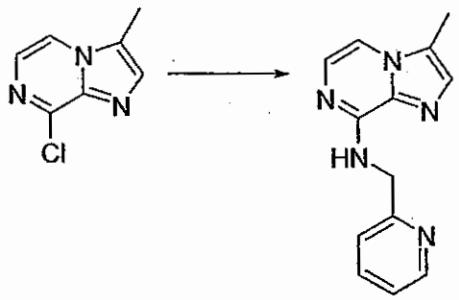
Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (20:1) to afford pale yellow solid (27 mg, 50%). M. P. 184-185°C, LCMS: MH^+ = 360.

PREPARATIVE EXAMPLE 40:



This compound was made according to the literature procedure (*J. Med. Chem.* **1983**, *26*, 357.and *J. Med. Chem.* **1992**, *35, 3845.*).

EXAMPLE 41:

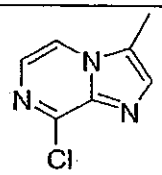
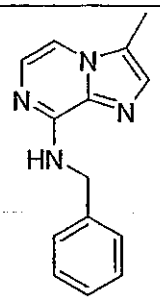
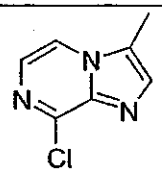
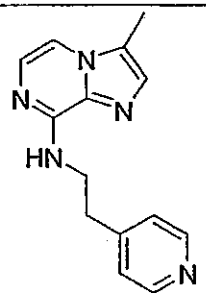
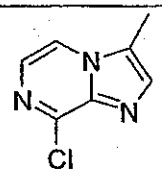
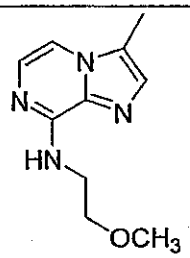
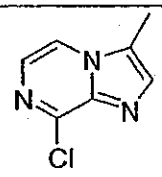
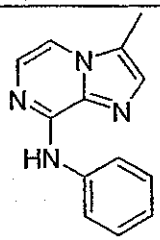


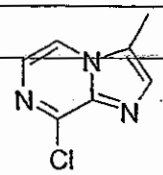
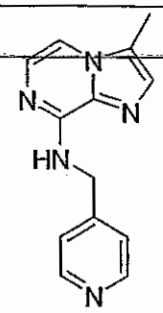
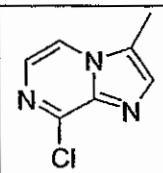
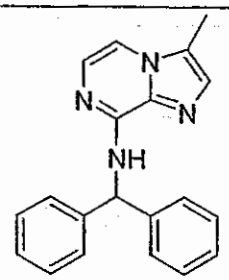
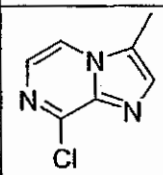
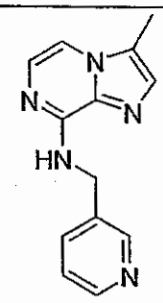
A mixture of the product from Preparative Example 40 (50 mg, 0.30 mmol), 2-(aminomethyl)pyridine (45 mg, 0.42 mmol), and diisopropylethylamine (0.20 mL) in anhydrous 1,4-dioxane (0.50 mL) was stirred under N_2 at 100°C for 24 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH/conc. aqueous NH_4OH (2:1:0.1). White solid (45 mg, 63 %) was obtained. M. P. 125-127°C, LCMS: MH^+ = 240.

EXAMPLES 42-48:

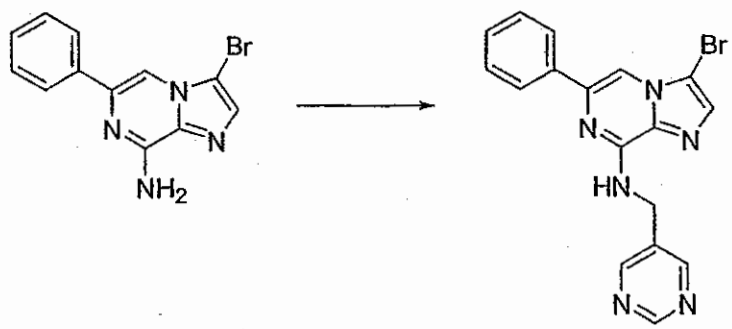
By essentially same procedure set forth in Preparative Example 41, compounds given in column 3 of Table 3 were prepared.

TABLE 3

Example	Column 2	Column 3	DATA
42			M. P. 152-154°C, LCMS: MH^+ = 239.
43			M. P. 130-132°C, LCMS: MH^+ = 254.
44			M. P. 104-105°C, LCMS: MH^+ = 207.
45			M. P. 182-184°C, LCMS: MH^+ = 225.

46			M. P. 183-185°C, LCMS: MH^+ = 240.
47			M. P. 186-188°C, LCMS: MH^+ = 315.
48			M. P. 143-145°C, LCMS: MH^+ = 240.

XAMPLE 49:



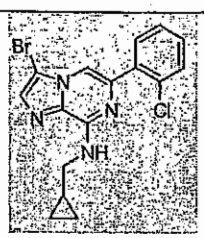
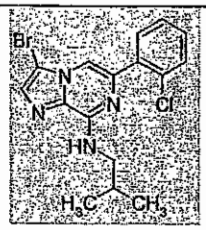
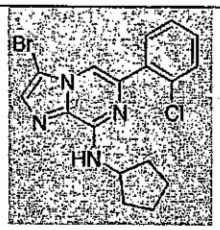
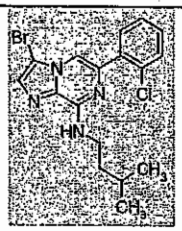
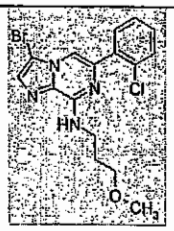
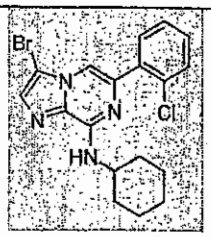
A mixture of the product from Preparative Example 28 (1.16 g, 4.00 mmol), pyrimidine-5-carboxaldehyde (540 mg, 5.00 mmol), and $Ti(OiPr)_4$ (4.54 g, 16.0 mmol) in anhydrous THF (20 mL) was stirred under N_2 at 50°C for 3 hr. The

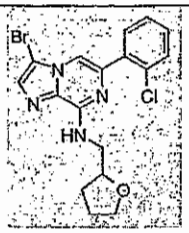
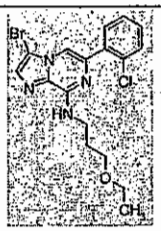
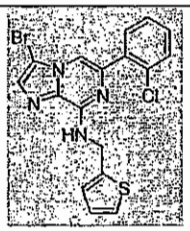
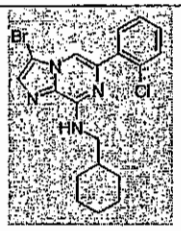
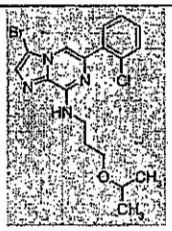
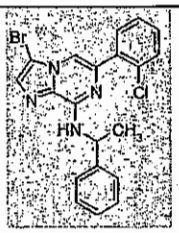
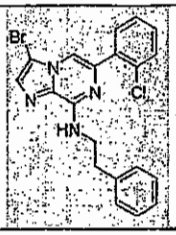
mixture was cooled to 25°C, $NaBH_3CN$ (1.26 g, 20.0 mmol) was added, and the mixture was stirred at 25°C for 30 min. The mixture was poured into 5% aqueous NaOH (500 mL), saturated aqueous NaCl (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3x100 mL). The combined extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH/conc. aqueous NH_4OH (20:1:0.1). Pale yellow solid (410 mg, 27 %) was obtained. M. P. 201-203°C, LCMS: MH^+ = 383.

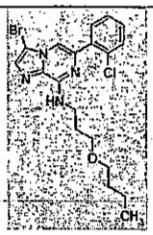
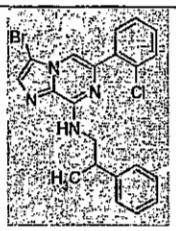
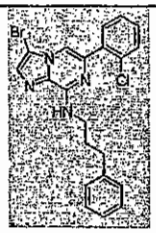
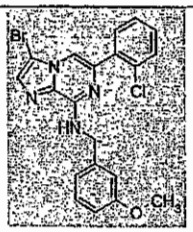
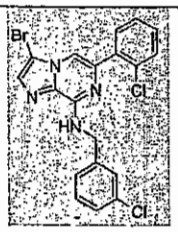
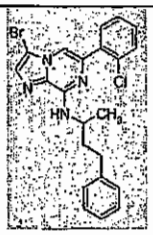
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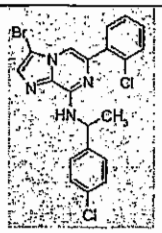
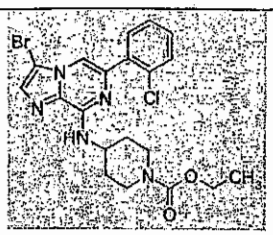
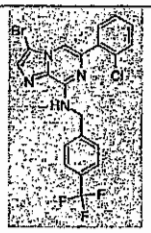
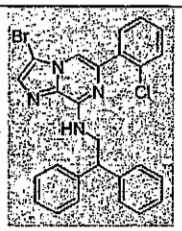
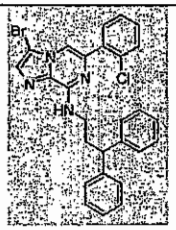
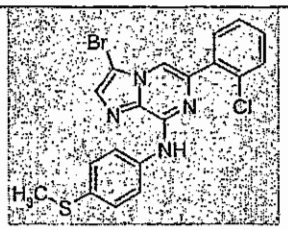
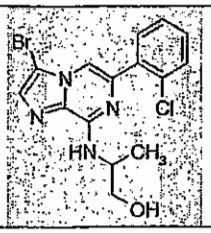
A stock solution of the title compound from Preparative Example 8 (1.2g) in anhydrous CH_3CN (120mL) was prepared and an aliquot (1mL, 10mg, 0.0291mmoles) was placed in each of the wells of an X-Block containing PS-DMAP resin (77.6mg, 0.1164mmoles). Freshly prepared 1M solutions of a library of 96 primary amines (0.0873mL, 0.0873mmoles) were added to each of the 96 wells of the X-Block. The unit was sealed and heated at 60-70°C for 26h. The block was cooled, opened and filtered into a new X-Block containing PS-Isocyanate resin (35mg, 0.073mmoles) and PS-Trisamine resin (35mg, 0.15mmoles) and the PS-DMAP resin was washed with CH_3CN (0.5mL/well). The X-Block was sealed and shaken at 25°C for 71h. The block was opened, filtered and each well was washed with CH_3CN (0.5mL). The wells were evaporated to dryness on a Speedvac concentrator. The samples were analyzed by LCMS and samples that were <90% pure were further purified as needed by preparative LCMS. The samples were each dissolved in 60% DMSO-CH_3CN (1mL) and 0.8mL of each were injected onto the preparative HPLC (using a Phenomenex Luna 5n C-18(2) column; 60x21.2mm; 5n micron: flow rate of 20mL/min; gradient elution using water-CH_3CN-1% aqueous formic acid) and the fractions corresponding to the desired molecular weight of the product +/- 1mu were collected. The final products that were all >90% pure are listed in the **Table 4.**

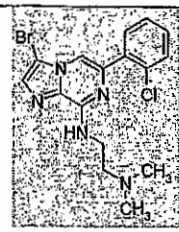
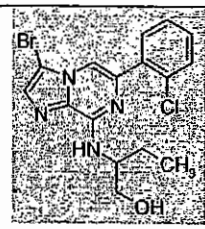
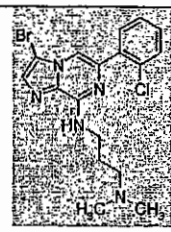
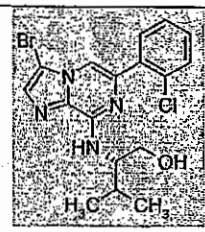
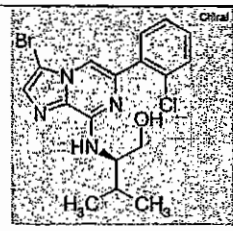
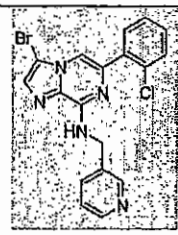
TABLE 4

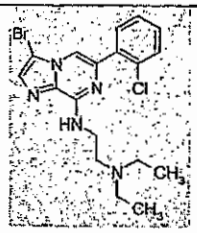
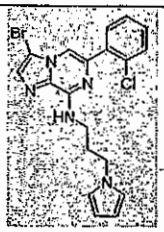
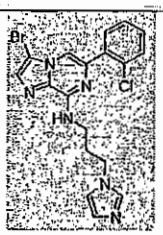
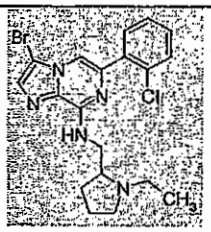
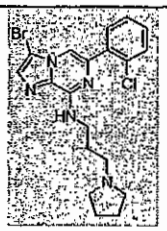
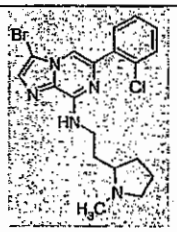
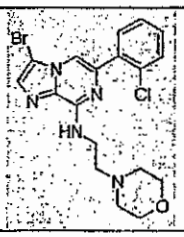
	STRUCTURE	MW	LCMS m/z	% PURITY
		377.7	379.2	97
		379.7	381.2	90
		391.7	393.2	93
		393.7	395.2	99
		395.7	397.1	98
		405.7	407.1	100

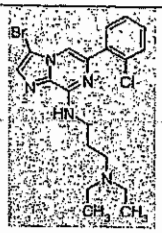
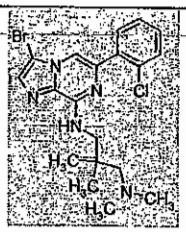
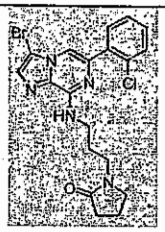
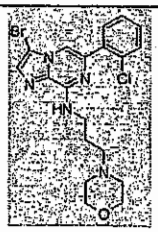
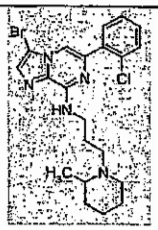
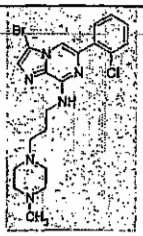
		407.7	409.2	93
		409.7	411.2	99
		419.7	421.1	100
		419.8	421.2	94
		423.7	425.2	100
		427.7	429.2	99
		427.7	429.2	91

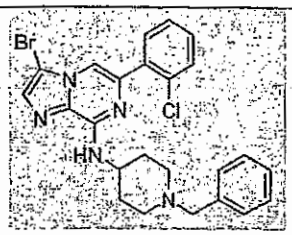
		437.8	439.2	95
		441.8	443.2	90
		441.8	443.2	94
		443.7	445.1	100
		448.2	449.1	91
		455.8	457.3	99

		462.2	463.1	99
		478.8	480.1	100
		481.7	483.3	97
		503.8	505.1	94
		517.9	519.1	100
		445.8	447.2	98
		381.7	383.1	99

		394.7	396.2	98
		395.7	397.1	92
		408.7	410.2	98
		409.7	411.1	100
		409.7	411.2	96
		414.7	416.1	97

		422.8	424.2	98
		430.7	432.2	94
		431.7	433.2	94
		434.8	436.1	100
		434.8	436.1	100
		434.8	436.2	95
		436.7	438.1	100

		436.8	438.2	98
		436.8	438.2	98
		448.8	450.2	95
		450.8	452.2	95
		462.8	464.3	99
		463.8	465.3	92

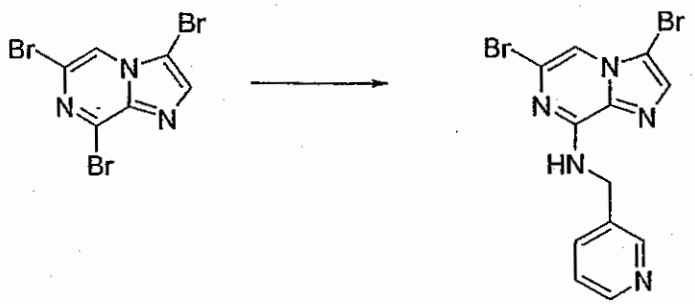
		496.8	498.1	99

PREPARATIVE EXAMPLE 51:



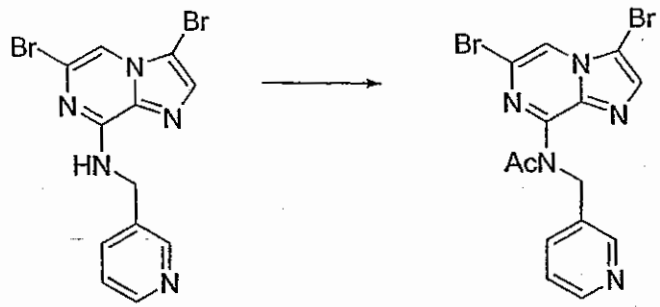
A solution of NBS (1 eq.) in anhydrous CH_3CN (2.0 mL) is added under N_2 to a stirred solution of the product from Preparative Example 29 in anhydrous CH_3CN and CH_2Cl_2. The mixture is stirred at 25°C for 48 hr and the solvent is then evaporated. Chromatography on silica gel with CH_2Cl_2/EtOAc affords the product.

EXAMPLE 52 :



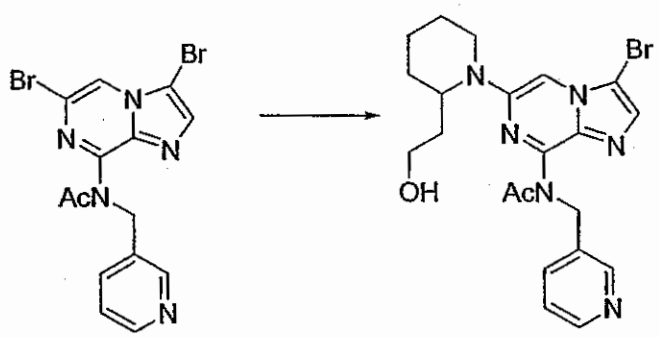
A mixture of the product from Preparative Example 51, 3-(aminomethyl) pyridine (1.1eq), diisopropylethylamine (3.0 eq), and anhydrous dioxane is stirred at 90°C under N_2 for 48 hr. The solvent is evaporated and the residue is purified by column chromatography on silica gel with CH_2Cl_2/MeOH/conc. aqueous NH_4OH to yield the product.

EXAMPLE 53:



A mixture of the product from Example 52, acetyl chloride (4.0 eq.), and pyridine (8.0 eq.) in 1,2-dichloroethane is stirred and refluxed for 72 hr. The mixture is poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The extracts are dried over Na_2SO_4, filtered and the solvent is evaporated. Chromatography on silica gel with EtOAc as eluent affords the product.

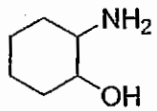
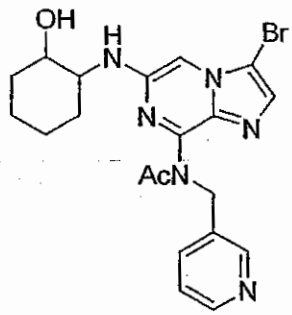
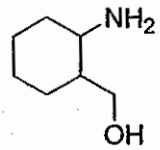
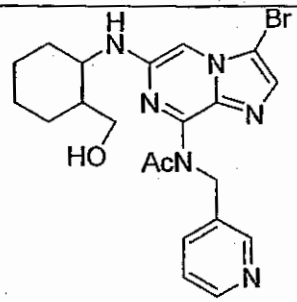
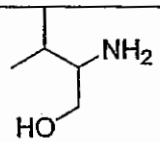
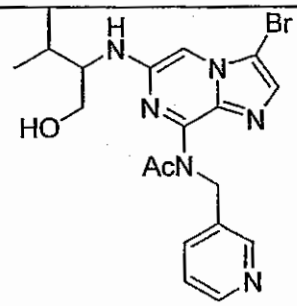
EXAMPLE 54:



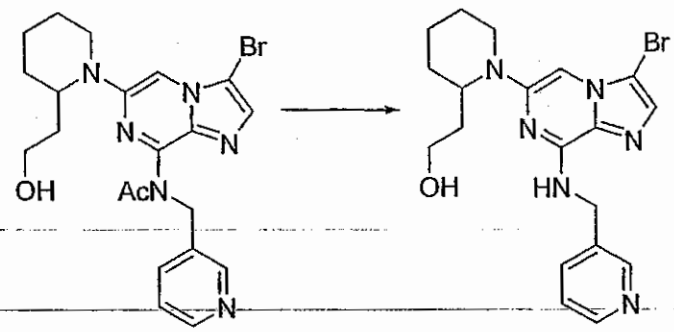
A mixture of the product from Example 53, the aminolacohol (1.5 eq.), and triethylamine (2.0 eq.) in dioxane is stirred and refluxed for 72 hr. The mixture is poured into 10% aqueous Na_2CO_3 and extracted with . The extracts are dried over Na_2SO_4, filtered and the solvent is evaporated. Chromatography on silica gel with CH_2Cl_2:MeOH as eluent affords the product.

TABLE 5

By essentially the same procedure given in Example 54, combining intermediates from Preparative Example 53 with the amines given in column 1, compounds given in column 2 can be prepared.

Example	Column 1	Column 2
55		
56		
57		

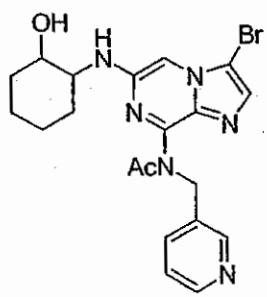
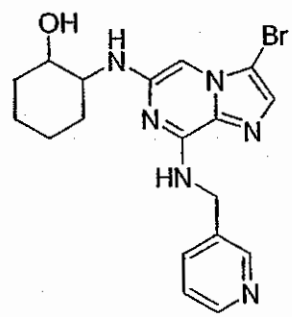
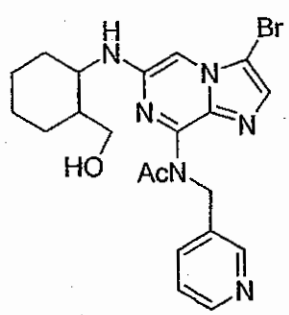
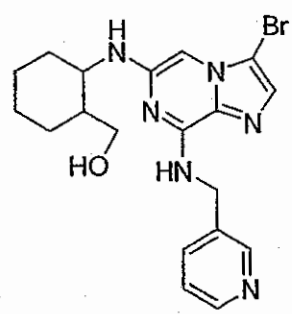
EXAMPLE 58:

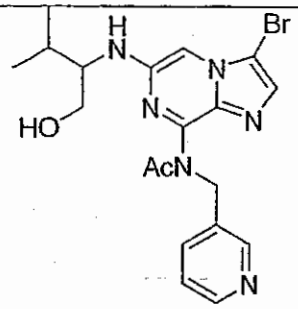
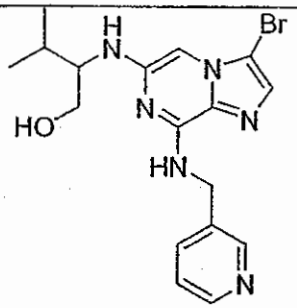


A mixture of the product from Example 54, and K_2CO_3 (2.0 eq.) in 1:1 EtOH :H_2O is stirred at 60°C for 2 hr. The mixture is poured into H_2O and extracted with CH_2Cl_2. The extracts are dried over Na_2SO_4, filtered and the solvent is evaporated. Chromatography on silica gel with CH_2Cl_2 :MeOH :conc.NH_4OH affords the product.

TABLE 6

By essentially the same procedure given in Example 58, starting form compounds given in Column 1, compounds given in column 2 can be prepared.

Example	Column 1	Column 2
59		
60		

61		

ASSAY:

BACULOVIRUS CONSTRUCTIONS: Cyclins A and E were cloned into pFASTBAC (Invitrogen) by PCR, with the addition of a GluTAG sequence (EYMPME) at the amino-terminal end to allow purification on anti-GluTAG affinity columns. The expressed proteins were approximately 46kDa (cyclin E) and 50kDa (cyclin A) in size. CDK2 was also cloned into pFASTBAC by PCR, with the addition of a haemaglutinin epitope tag at the carboxy-terminal end (YDVPDYAS). The expressed protein was approximately 34kDa in size.

ENZYME PRODUCTION: Recombinant baculoviruses expressing cyclins A, E and CDK2 were infected into SF9 cells at a multiplicity of infection (MOI) of 5, for 48 hrs. Cells were harvested by centrifugation at 1000 RPM for 10 minutes. Cyclin-containing (E or A) pellets were combined with CDK2 containing cell pellets and lysed on ice for 30 minutes in five times the pellet volume of lysis buffer containing 50mM Tris pH 8.0, 0.5% NP40, 1mM DTT and protease/phosphatase inhibitors (Roche Diagnostics GmbH, Mannheim, Germany). Mixtures were stirred for 30-60 minutes to promote cyclin-CDK2 complex formation. Mixed lysates were then spun down at 15000 RPM for 10 minutes and the supernatant retained. 5ml of anti-GluTAG beads (for one liter of SF9 cells) were then used to capture cyclin-CDK2 complexes. Bound beads were washed three times in lysis buffer. Proteins were competitively eluted with lysis buffer containing 100-200ug/mL of the GluTAG peptide. Eluate was dialyzed overnight in 2 liters of kinase buffer containing 50mM Tris pH 8.0, 1mM DTT,

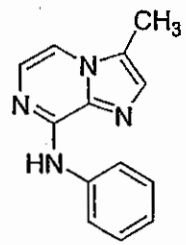
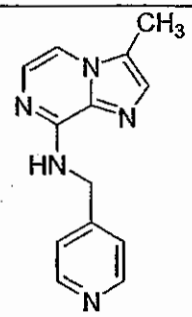
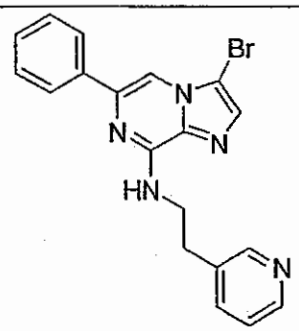
10mM MgCl2, 100uM sodium orthovanadate and 20% glycerol. Enzyme was stored in aliquots at -70°C.

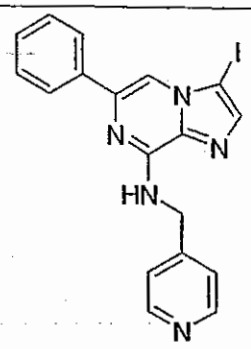
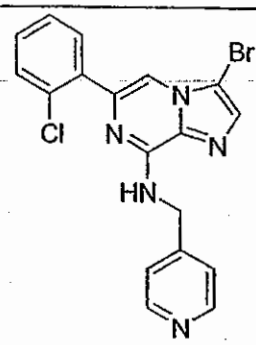
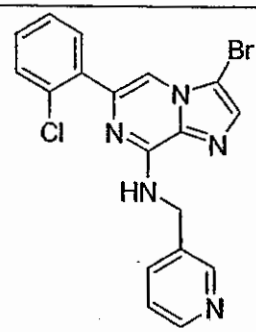
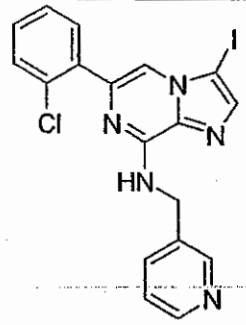
IN VITRO KINASE ASSAY: CDK2 kinase assays (either cyclin A or E-dependent) were performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme was diluted to a final concentration of 50 ug/ml in kinase buffer containing 50mM Tris pH 8.0, 10mM $MgCl_2$, 1mM DTT, and 0.1mM sodium orthovanadate. The substrate used in these reactions was a biotinylated peptide derived from Histone H1 (from Amersham, UK). The substrate was thawed on ice and diluted to 2 uM in kinase buffer. Compounds were diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 µl of the 50 ug/ml enzyme solution (1 µg of enzyme) and 20 µl of the 1 µM substrate solution were mixed, then combined with 10 µl of diluted compound in each well for testing. The kinase reaction was started by addition of 50 µl of 4 µM ATP and 1 µCi of 33P-ATP (from Amersham, UK). The reaction was allowed to run for 1 hour at room temperature. The reaction was stopped by adding 200 µl of stop buffer containing 0.1% Triton X-100, 1mM ATP, 5mM EDTA, and 5 mg/ml streptavidine coated SPA beads (from Amersham, UK) for 15 minutes. The SPA beads were then captured onto a 96-well GF/B filter plate (Packard/Perkin Elmer Life Sciences) using a Filtermate universal harvester (Packard/Perkin Elmer Life Sciences.). Non-specific signals were eliminated by washing the beads twice with 2M NaCl then twice with 2 M NaCl with 1% phosphoric acid. The radioactive signal was then measured using a TopCount 96 well liquid scintillation counter (from Packard/Perkin Elmer Life Sciences).

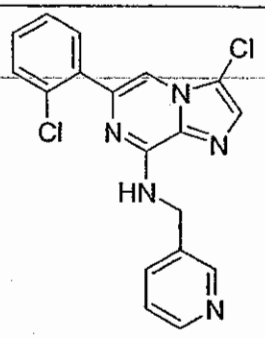
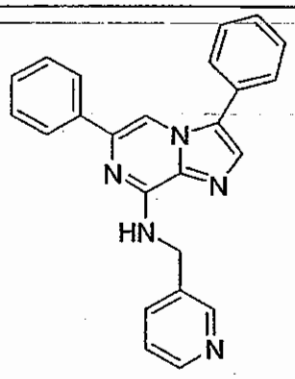
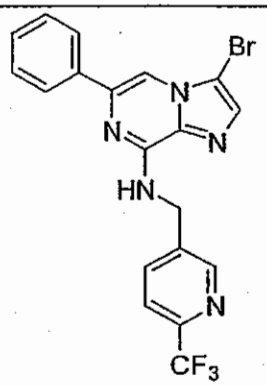
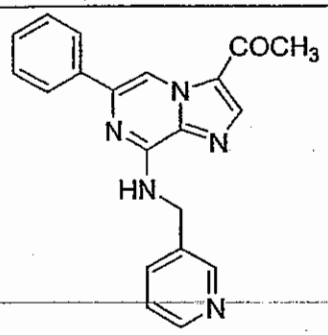
IC_{50} DETERMINATION: Dose-response curves were plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory compounds. Concentration of compound was plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated samples. To generate IC_{50} values, the dose-response curves were then fitted to a standard sigmoidal curve and IC_{50} values were derived by nonlinear regression analysis. The thus-obtained IC_{50} values for the compounds of the invention are shown in

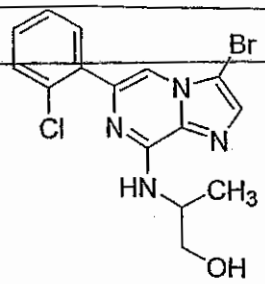
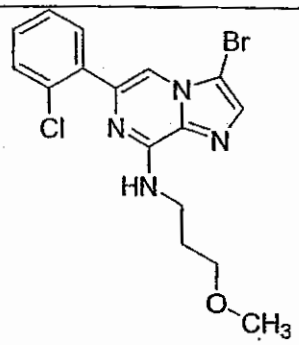
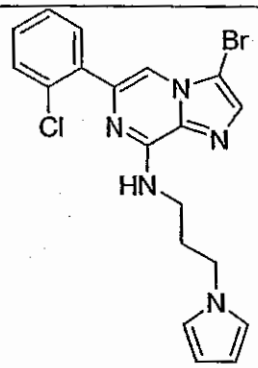
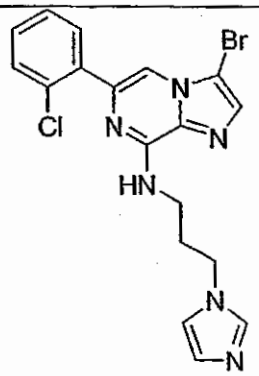
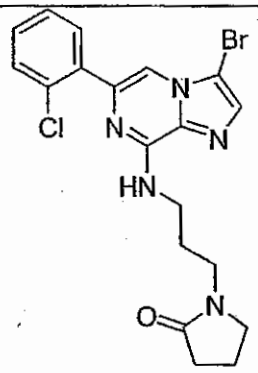
Table 7. These kinase activities were generated by using cyclin A or cyclin E using the above-described assay.

Table 7

CMPD	IC_{50} (μM)	% INH @ 0.05ug/mL	% INH @ 0.5ug/ mL
	15		
	22.5		
	4.18		

	0.53		
	0.49		
	0.24	47.4	88.6
	0.23		

	0.43		
	6.7		
	4.551		
	4.7		

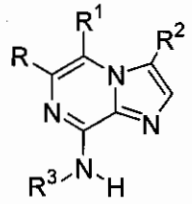
	0.2	63.0	92.7
		30.7	71.5
		42.2	48.8
		37.5	29.4
		30.7	67.8

As demonstrated above by the assay values, the compounds of the present invention exhibit excellent CDK inhibitory properties.

While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS

1. A compound represented by the structural formula:

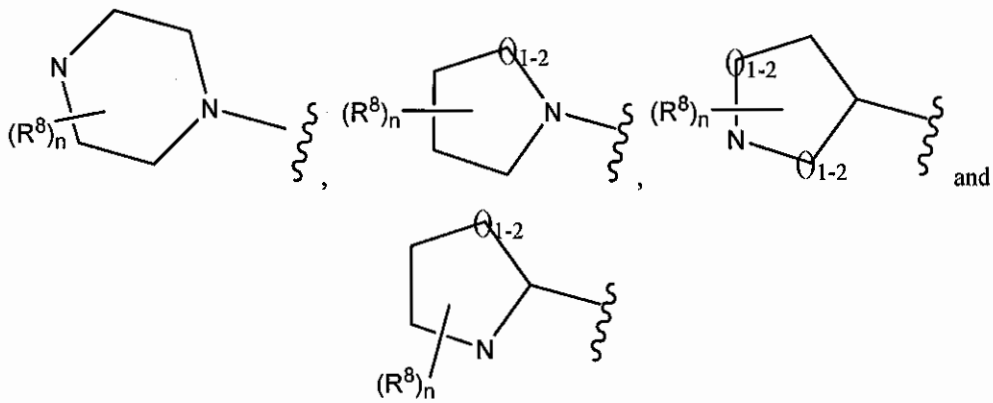


Formula III

or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R is selected from the group consisting of H, halogen, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, $-C(O)R^7$,

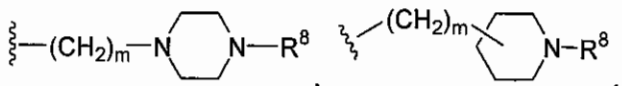


wherein each of said aryl, heteroaryl, cycloalkyl, arylalkyl, alkenyl, heterocyclyl and the heterocyclyl moieties whose structures are shown immediately above for R can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-(CHR^5)_nOR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

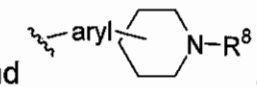
R^1 is H, halogen or alkyl;

R^2 is selected from the group consisting of halogen, R^9, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, alkenyl, alkynyl, cycloalkyl,

$-CF_3$, $-C(O)R^7$, alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected,

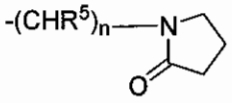


and

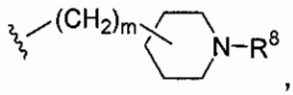


, wherein each of said aryl, heteroaryl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^6$, $-C(O)R^7$, $-NR^5R^6$, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^3 is selected from the group consisting of H, aryl, heteroaryl, heterocyclyl, $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n-OR^6$, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-(CH_2)_m-NR^8$, $-(CHR^5)_n-CH(aryl)_2$,



and



, wherein each of said aryl, heteroaryl and heterocyclyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$,

$-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^7 is selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^6$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^6$, $-S(O_2)NR^5R^6$, $-C(O)R^7$, $-C(O_2)R^6$, $-S(O_2)R^7$ and $-(CH_2)$-aryl;

R^9 is selected from the group consisting of halogen, CN, NR^5R^6, $-C(O_2)R^6$, $-C(O)NR^5R^6$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^6$;

m is 0 to 4;

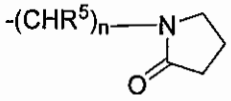
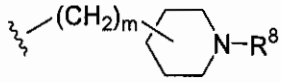
n is 1-4; and

p is 0-3.

2. The compound of claim 1, wherein R is selected from the group consisting of H, halogen, aryl, heteroaryl, alkenyl and $-C(O)R^7$, wherein each of said aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, CF_3, CN, $-OCF_3$, and $-OR^6$;

R^1 is H or lower alkyl;

R^2 is selected from the group consisting of halogen, aryl, heteroaryl, alkenyl and $-C(O)R^7$, wherein each of said aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, CF_3, CN, $-OCF_3$, and $-OR^6$;

R^3 is selected from the group consisting of H, aryl, heteroaryl, -$(CHR^5)_n$-aryl, - $(CHR^5)_n$-heteroaryl, -$(CHR^5)_n$-OR^6, -$C(O)R^6$, cycloalkyl, -$CH(aryl)_2$,  and , wherein each of said aryl and heteroaryl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, CF_3, CN, -$C(O_2)R^5$ and -$S(O_2)R^6$;

R^5 is H or lower alkyl;

m is 0 to 2; and

n is 1 or 2.

3. The compound of claim 2, wherein R is phenyl substituted with one or more moieties selected from the group consisting of F, Cl, Br and OCF_3.

4. The compound of claim 2, wherein R^2 is F, Cl, Br, I, ethenyl, or -$C(CH_3)_2$-OH.

5. The compound of claim 4, wherein R^2 is Br, or I.

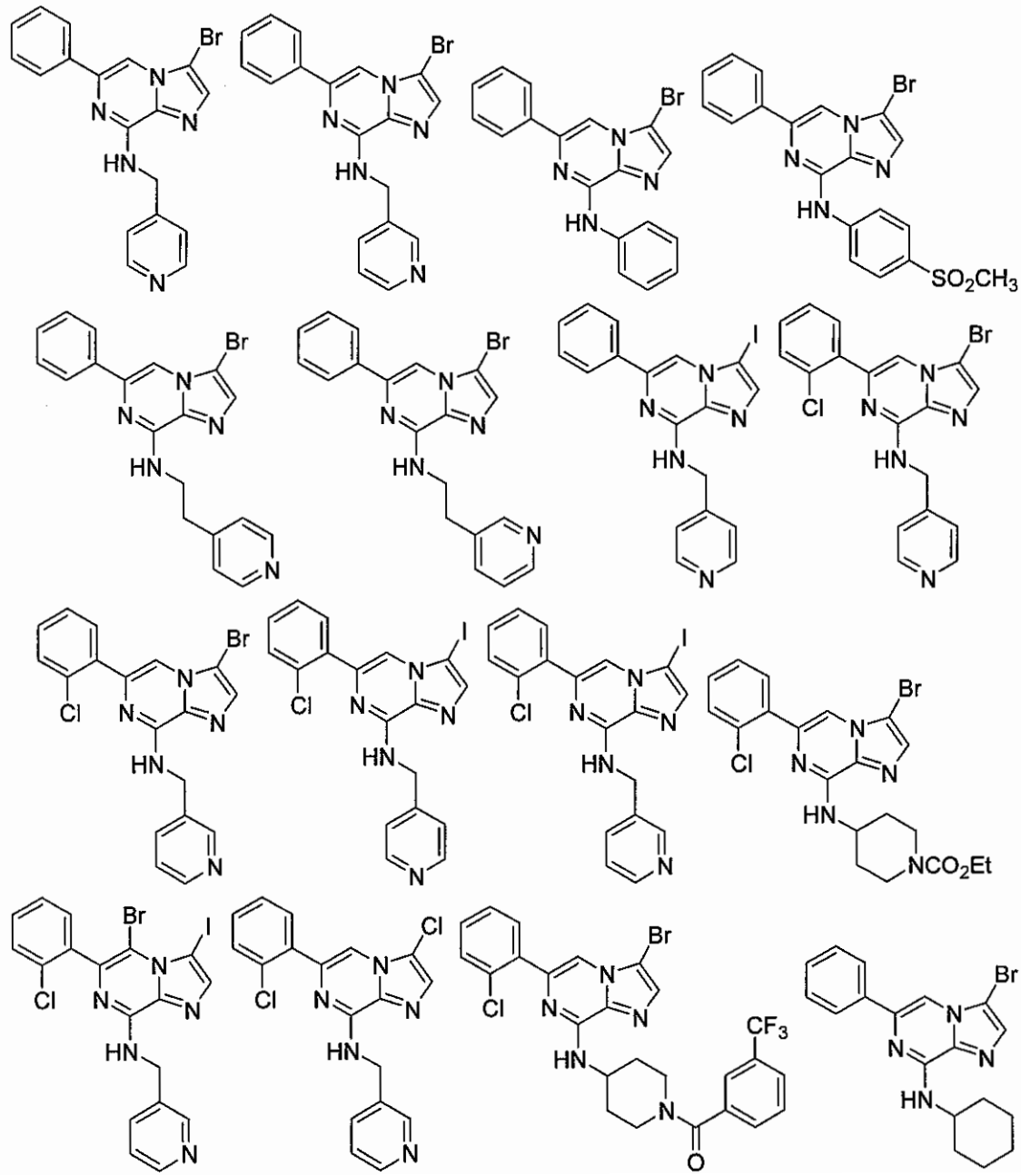
6. The compound of claim 2, wherein R^3 is H, propan-1-ol-2-yl, phenyl, benzyl, (pyrid-2-yl)methyl, (pyrid-3-yl)methyl, (pyrid-4-yl)methyl, 2-[(pyrid-3-yl)]ethyl and 2-[(pyrid-4-yl)]ethyl wherein each of said phenyl (including phenyl of said benzyl) and pyridyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Cl, Br, CF_3, lower alkyl, -$S(O_2)CH_3$, methoxy and CN.

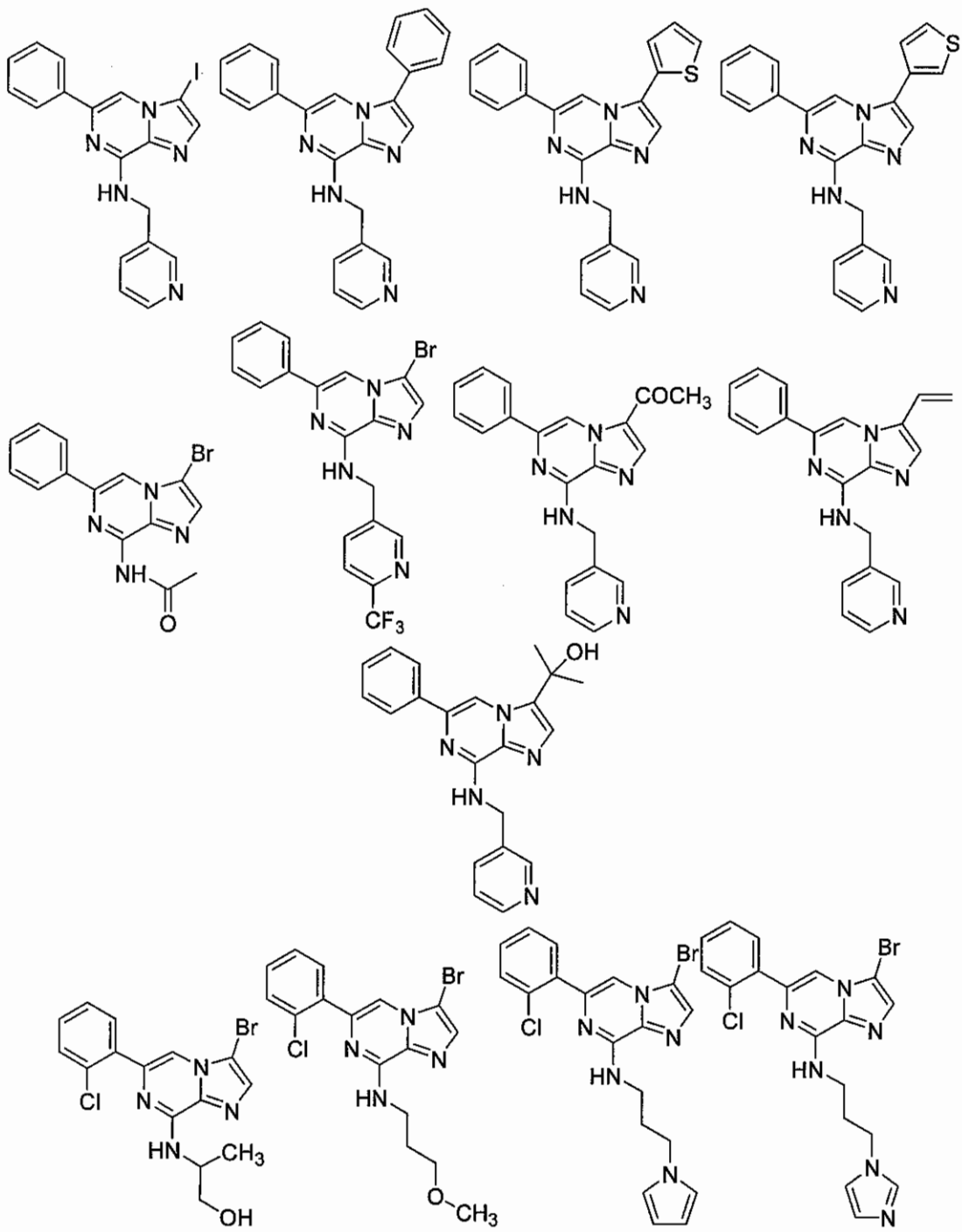
7. The compound of claim 6, wherein R^3 is (pyrid-2-yl)methyl.

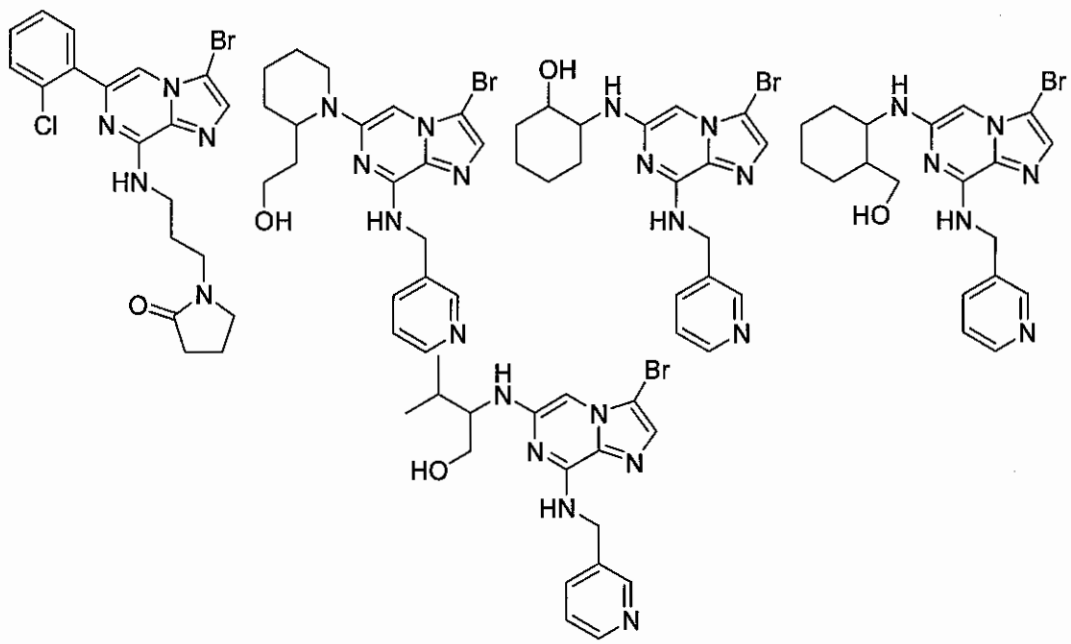
8. The compound of claim 6, wherein R^3 is (pyrid-3-yl)methyl.

9. The compound of claim 6, wherein R^3 is (pyrid-4-yl)methyl.

10. A compound of the formula:

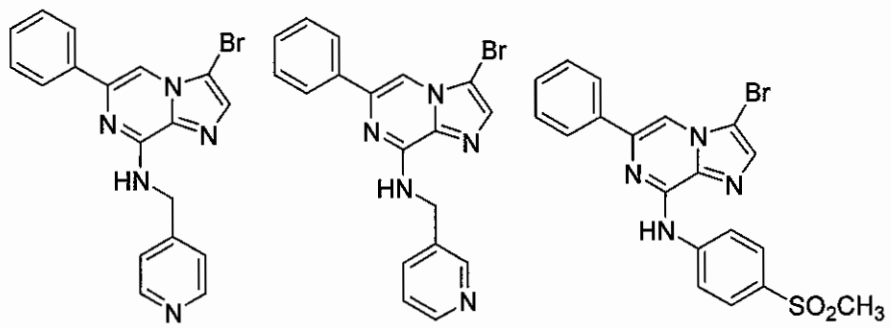


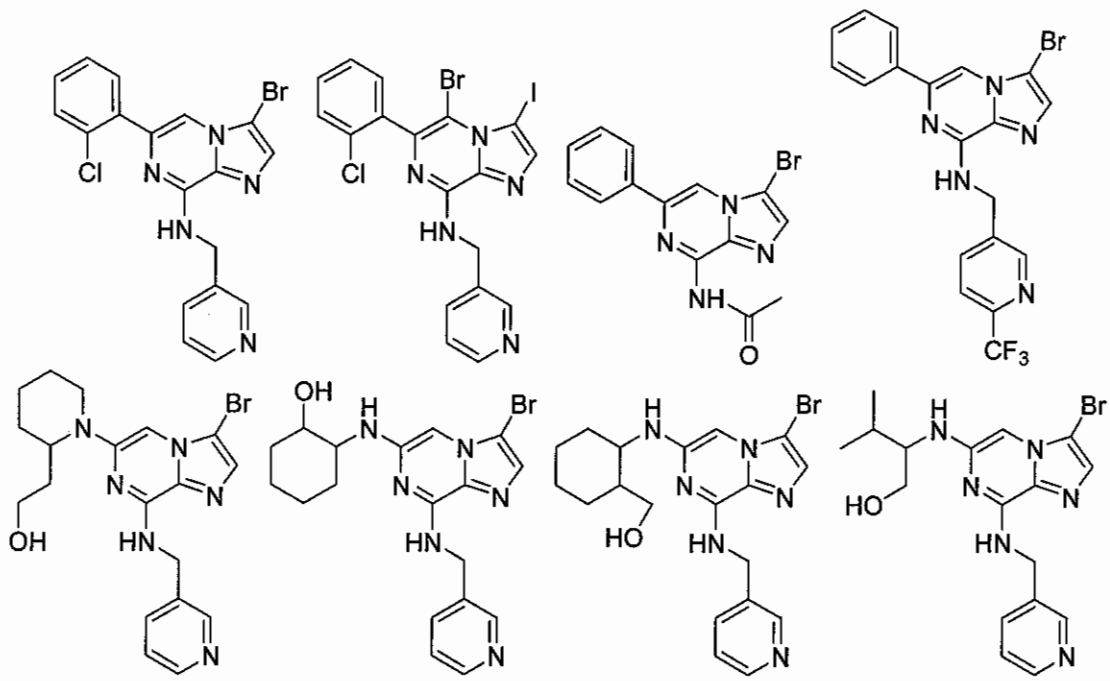




or a pharmaceutically acceptable salt or solvate thereof.

11. A compound of the formula:





or a pharmaceutically acceptable salt or solvate thereof.

12. The use of at least one compound of claim 1 for the manufacture of a medicament to inhibit cyclin dependent kinases ("CDK2").

13. The use of an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof; and an amount of at least one second compound, said second compound being an anti-cancer agent; for the manufacture of a medicament for treating one or more diseases associated with cyclin dependent kinase, wherein the amounts of the first compound and said second compound result in a therapeutic effect.

14. The method of claim 13, further comprising radiation therapy.

15. The method of claim 13, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, 5FU, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

16. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 in combination with at least one pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 13, additionally comprising one or more anti-cancer agents selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan,

camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, 5FU, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.