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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS OF USE

(57) Abstract: Heterocyclic compounds derived from benzotriazine, triazines, triazoles and oxadiazoles are disclosed. The methods of synthesis and of use of such heterocyclic compounds are also provided.

WO 2006/024034 A1

HETEROCYCLIC COMPOUNDS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of patent applications U.S. Serial Number 60/604,298 filed August 25, 2004, and 60/696,168 filed July 1, 2005, the entire content of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to the use of compounds to treat a variety of disorders, diseases and pathologic conditions and more specifically to the use of various heterocyclic compounds for therapeutic purposes.

BACKGROUND

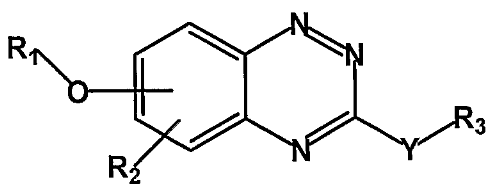
[0003] Kinases are a large family of cellular proteins involved in signal transduction of cascades which control cell growth and death, survival, migration, differentiation, gene expression, metabolism, protein synthesis and cell cycle regulation. A common mechanism by which these signals are transmitted is reversible phosphorylation, which induces conformational changes is these enzymes and alters their structure and function. The entire kinase genome discovered so far incorporates over 500 individual proteins and their isoforms. Different branches of this genomic tree have been characterized into groups specific for phosphorylating either serine/threonine residues or tyrosines. Some kinases exhibit dual specificity, capable of substrate phosphorylation of tyrosine as well as serine/threonines. Further differentiation can be made in terms of their location in cells. Transmembrane receptor protein kinases exhibit an extracellular domain, capable of ligand binding. These ligand binding mechanisms trigger activation of the kinase catalytic domain which initiates a cascade of signals that controls intracellular functions. Examples of a receptor protein kinase are growth factors such as EGF, FGF, PDGF and IGF. Nonreceptor protein kinases can be found in many compartments of a cell from inner-cell surface membranes to the cell nucleus. One example of a nonreceptor protein kinase is the mitogen activated protein kinase (MAPK) which regulates a pathway, which is important in cell signaling initiated on the exterior cell surfaces via growth factors, for example, VEGF, or hormones, and extending to the cell nucleus by activating transcription factors. These nuclear factors in turn control gene expression in the regulation of cell cycle progression and ultimately cell proliferation, and differentiation.

[0004] The MAPK cell signaling pathway is important for drug targeting as this path impinges on nearly all functional hallmarks of cancer cells such as immortalization, growth factor independent proliferation, insensitivity to growth inhibitory signals, metastasis, blood vessel attraction, evasion of apoptosis, and other functional hallmarks. Inappropriate activation though mutation of this molecule is associated with nearly 30% of all human cancers. In general, the inhibition of disregulated kinases such as Ras, PI3K and Raf is an important approach to discover novel treatments for cancer and other diseases. One approach is the discovery of small molecules capable of binding either to the kinase catalytic domain or a regulatory domain in order to modulate the function of protein kinases. Important in this respect is to discover molecules which inhibit a specific signaling path with a high degree of selectivity and a potency within a practical therapeutic window. While significant progress has been made in developing various compounds for the treatment of cancer and inflammatory diseases, there remains a need for specific chemical structures capable of modulating protein kinases, whose disregulated function has been implicated in these diseases.

SUMMARY OF THE INVENTION

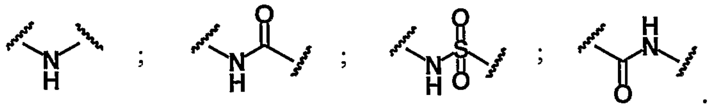
[0005] The present invention provides compounds which affect the MAPK pathway. The compounds of the invention are useful as pharmaceutical compositions, for example where modulation of the MAPK pathway is indicated for the treatment of various human diseases, such as cancer.

[0006] According to one embodiment of the invention, compounds having the structure (A) are provided, or an N-oxide, N,N'-dioxide, N,N',N''-trioxide, or a pharmaceutically acceptable salt thereof:

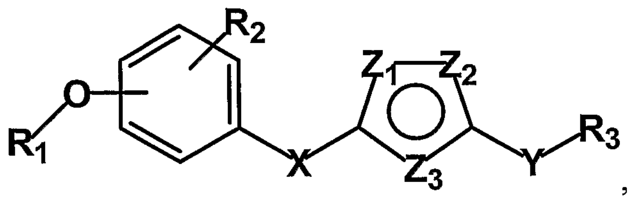


(A)

wherein Y can be absent or can be one of the following moieties:

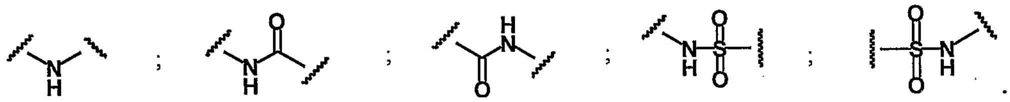


[0007] According to another embodiment of the invention, compounds having the structure (B) are provided, or an N-oxide, N,N'-dioxide, N,N',N''-trioxide, or a pharmaceutically acceptable salt thereof:



(B)

wherein X can be absent or can be NH, and Y can be absent or can be one of the following moieties:

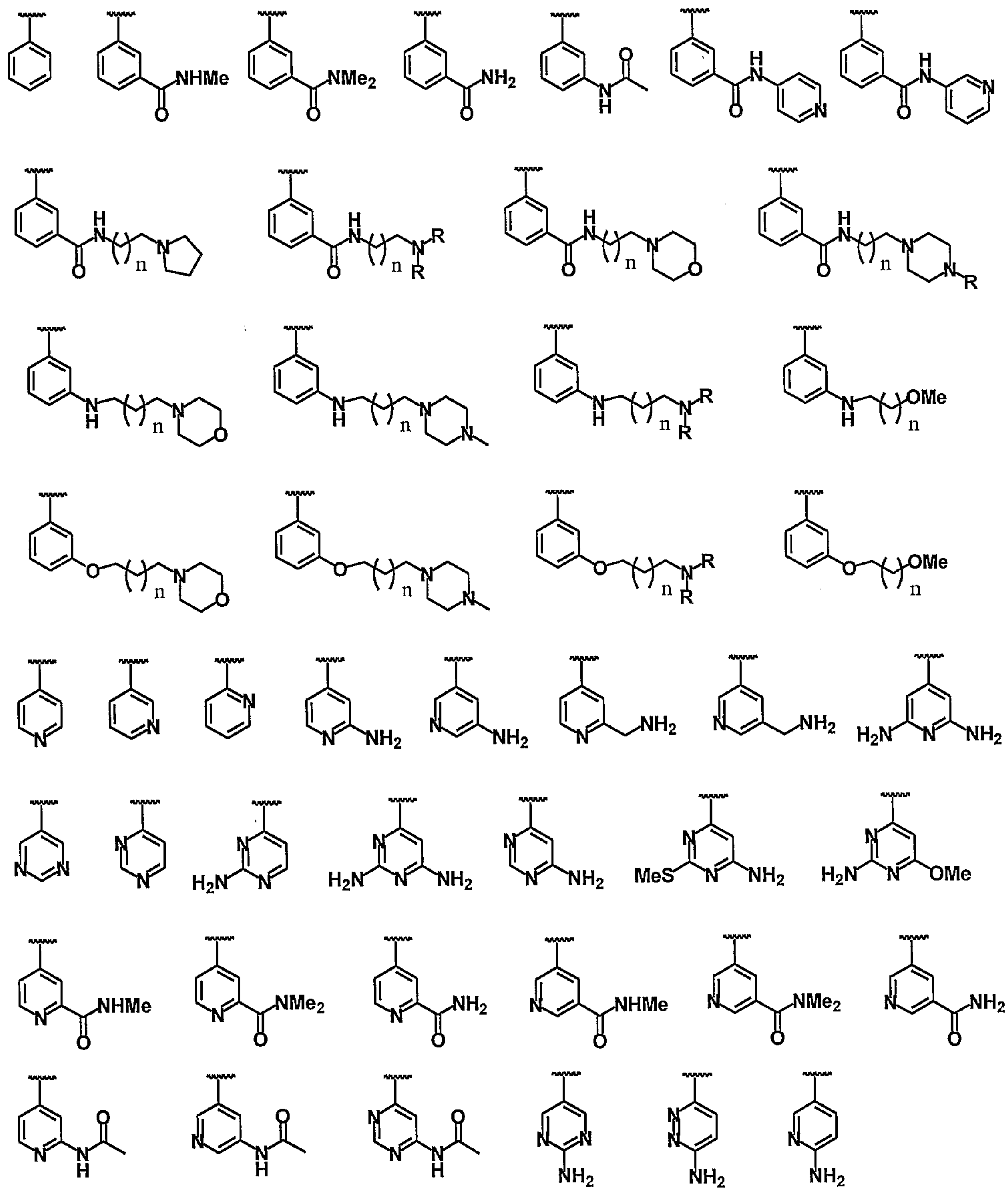


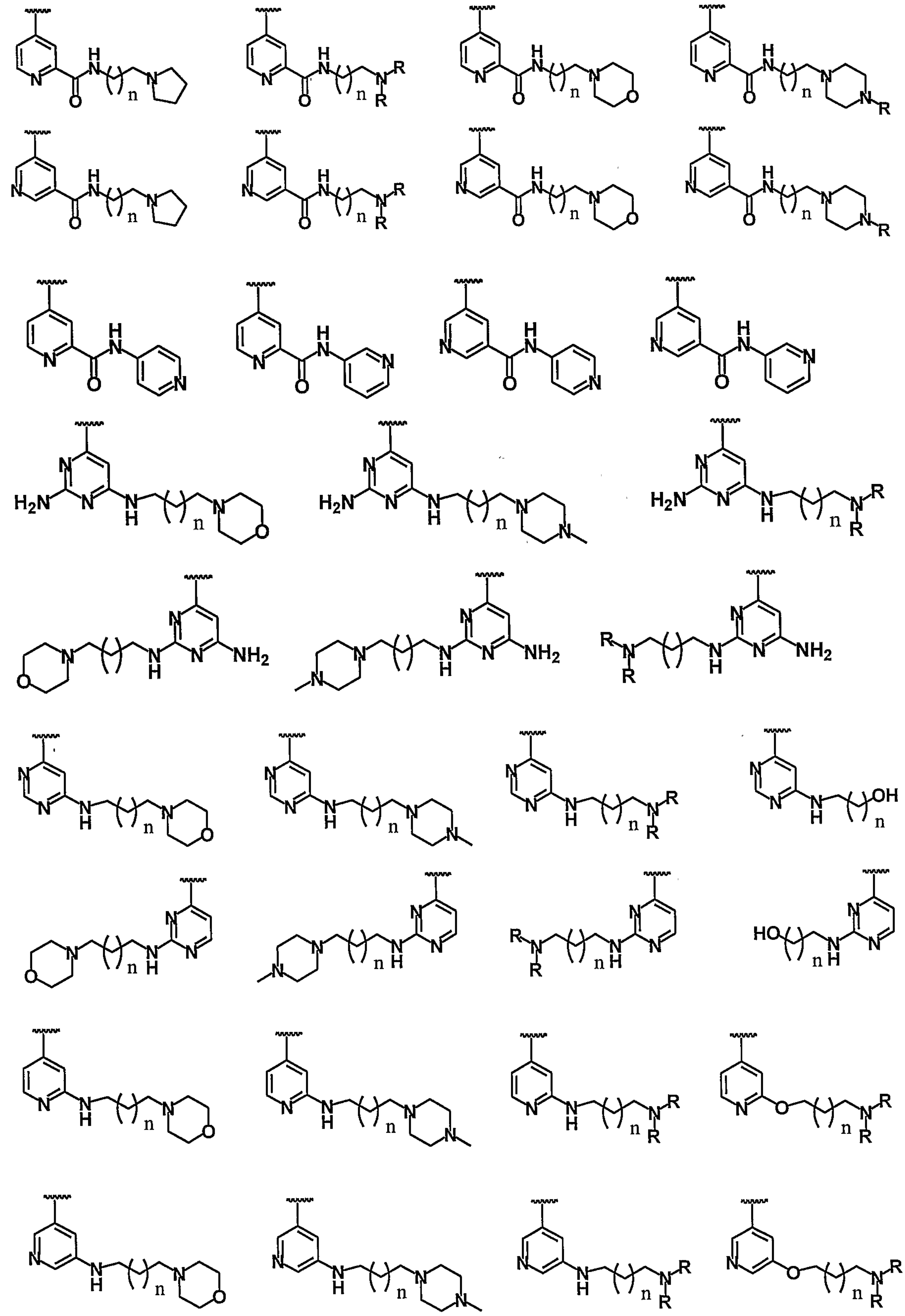
[0008] In compounds having structure (B), each of Z_1, Z_2 and Z_3 can be, independently, N, N=CH, CH, O, S or N-R^4, wherein R^4 is hydrogen or lower alkyl, with the further proviso that at least one of Z_1, Z_2 and Z_3 is not CH.

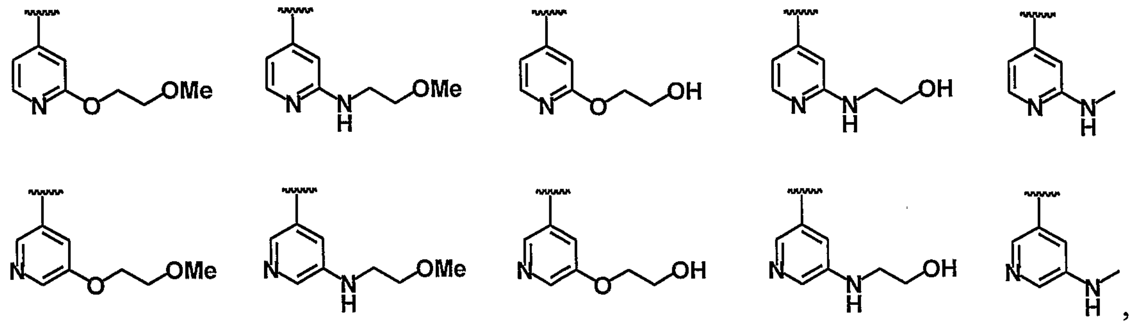
[0009] In compounds having structure (A), the substitutent R_1 can be an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl. For example, R_1 can be one of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms such as N, S, and O; substituted C_6-C_{12} aryl; substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl.

[0010] In compounds having structure (B), the substitutent R_1 can be, independently of the substitutent R_1 present in the structure (A), an unsubstituted or a substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S or O. The substituent R_1 that can be present in compounds having structure (B), can include a substituted pyridyl group. The substituents in the substituted pyridyl group can include an amido moiety, an aminoalkyl group (e.g., aminomethyl), or a carboxyl group, or a carboxylate group. The amido moiety attached to the pyridyl group can be in turn also substituted by attaching to the nitrogen in the amido moiety a substitutent selected from an alkyl (e.g., methyl), an alkylaminoalkyl (e.g., diethylamino alkyl), a pyridyl, an alkyl pyrrolidine, an alkyl morpholine, and an alkyl piperazine groups.

[0011] Some examples of the substituent R_1 that can be present in compounds having either structure (A) or structure (B), can be selected from one of the following moieties:







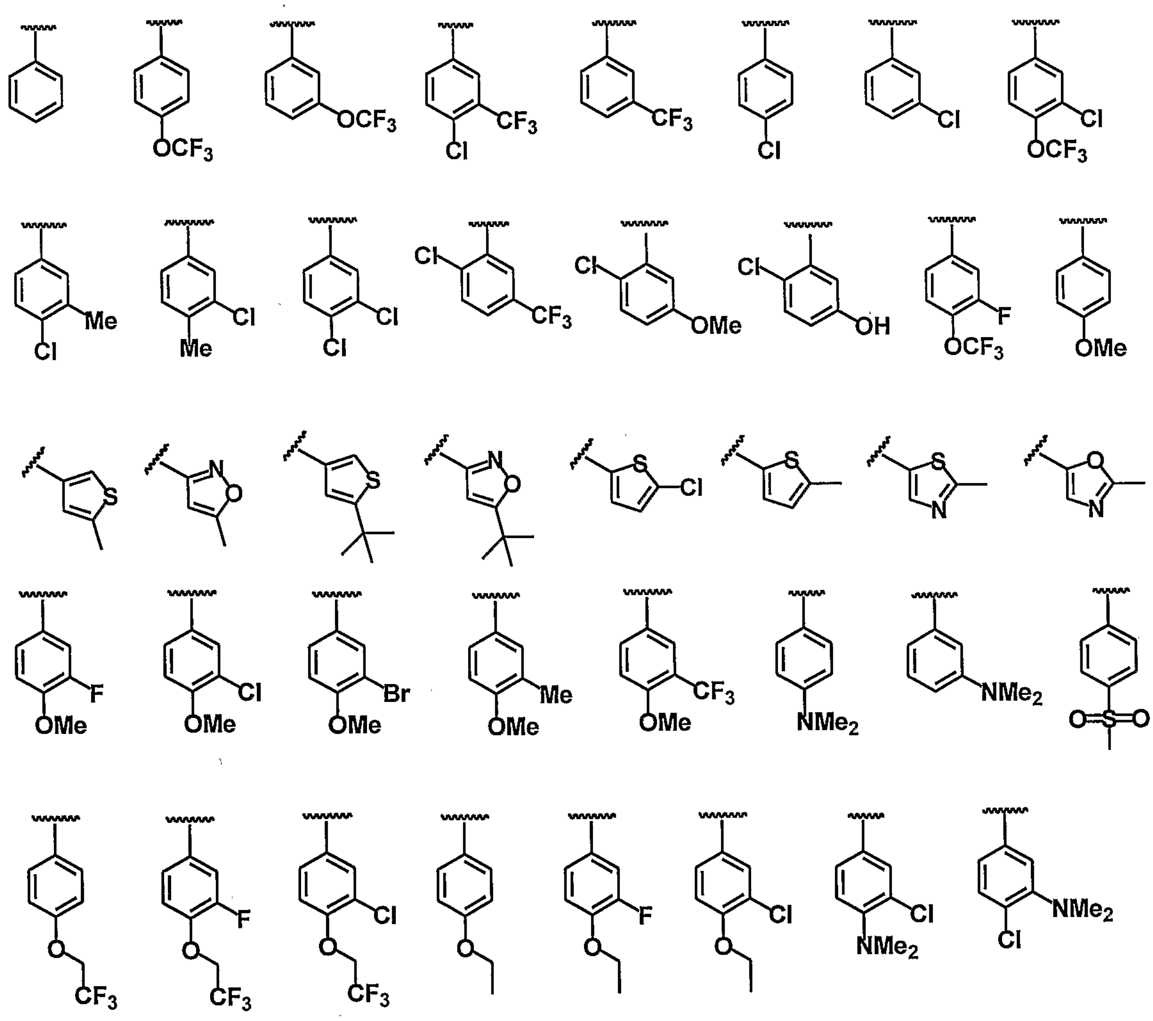
where n can be an integer selected from a group consisting of 0, 1, 2, and 3.

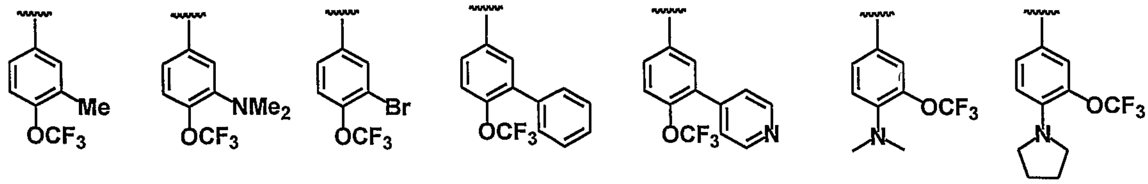
[0012] In compounds having structure (A) or (B), R_2 can be, independently, any one of hydrogen, halogen, C_1-C_{18} alkyl (e.g., methyl), -OH, $-NO_2$, -CN, C_1-C_{18} alkoxy (e.g., methoxy), $-NHSO_2R^5$, $-SO_2NHR^5$, $-NHCOR^5$, $-NH_2$, $-NR^5R^6$, $-S(O)R^5$, $-S(O)_2R^5$, $-CO_2R^5$, $-CONR^5R^6$, and where R^5 and R^6 are independently selected from hydrogen, a C_1-C_{12} alkyl and a substituted C_1-C_{12} alkyl.

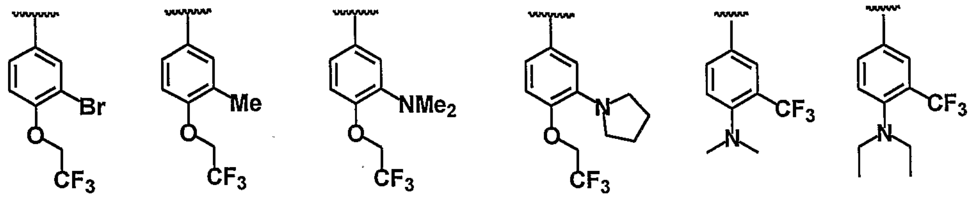
[0013] In compounds having structure (A), the substituent R_3 can be an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl. For example, R_3 can be one of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms such as N, S, and O; substituted C_6-C_{12} aryl; substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl.

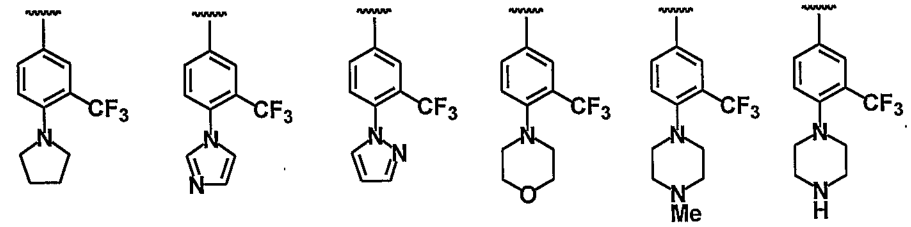
[0014] In compounds having structure (B), the substitutent R_3 can be, independently of the substitutent R_3 present in the structure (A), hydrogen, a C_1-C_{18} alkyl, a substituted C_1-C_{18} alkyl, a C_1-C_{12} cycloalkyl, a substituted C_1-C_{12} cycloalkyl, a substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms such as N, S, or O, an aryl such as a C_6-C_{12} aryl, a substituted aryl such as a substituted C_6-C_{12} aryl, a heterocycle, a substituted heterocycle, a heteroaryl such as a C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S or O, a substituted heteroaryl such as substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S or O, a C_7-C_{24} aralkyl, a substituted C_7-C_{24} aralkyl, a C_7-C_{24} alkylaryl, and a substituted C_7-C_{24} alkaryl. Some particular examples of the substituent R_3 than can be used include *tert*-butyl phenyl, trifluoromethoxyphenyl, methoxyphenyl, dimethylaminophenyl, aminophenyl, trifluoroethoxyphenyl, trifluoromethoxychlorophenyl, trifluoromethoxybromophenyl, trifluoroethoxychlorophenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchlorophenyl, chlorotoluyl, N-phenylacetamide, N,N-alkyl-benzamide, isopropoxyphenyl, alkoxyphenyl, dialkoxyphenyl, or acetylphenyl.

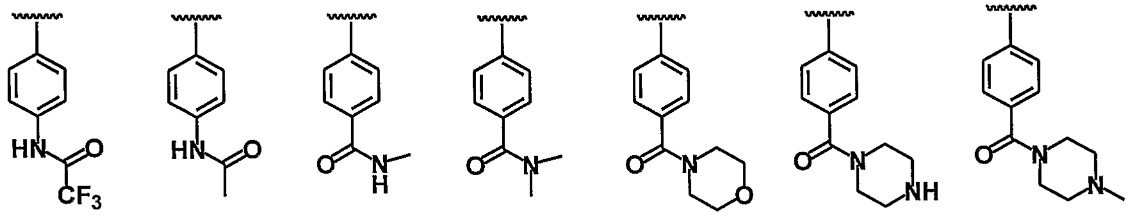
[0015] To summarize, some examples of the substituent R_3 that can be present in compounds having either structure (A) or structure (B), can be selected from one of the following moieties:

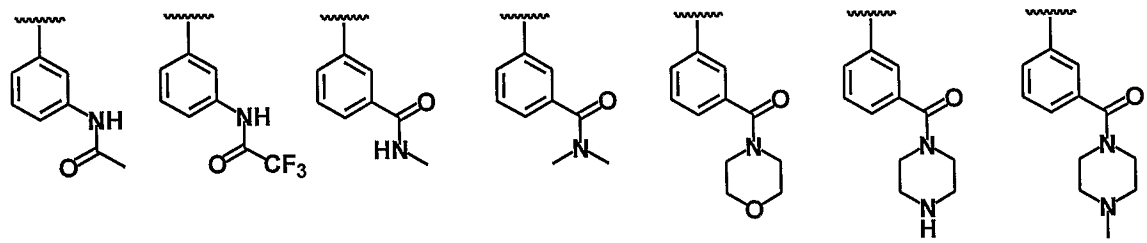


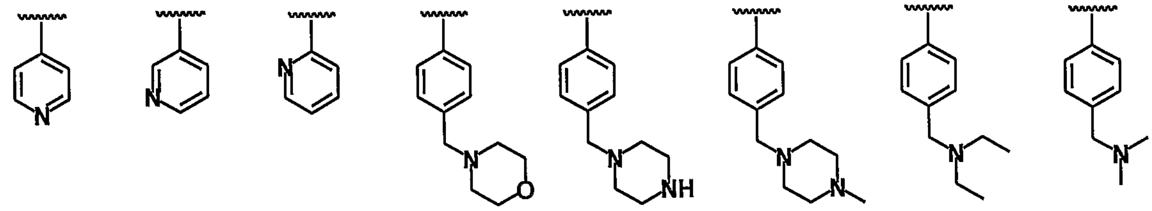


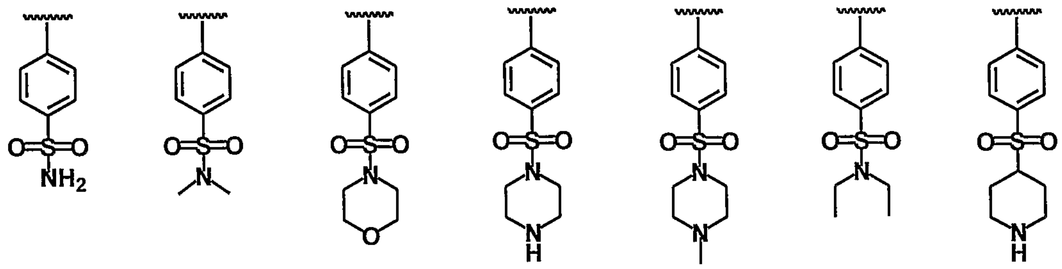


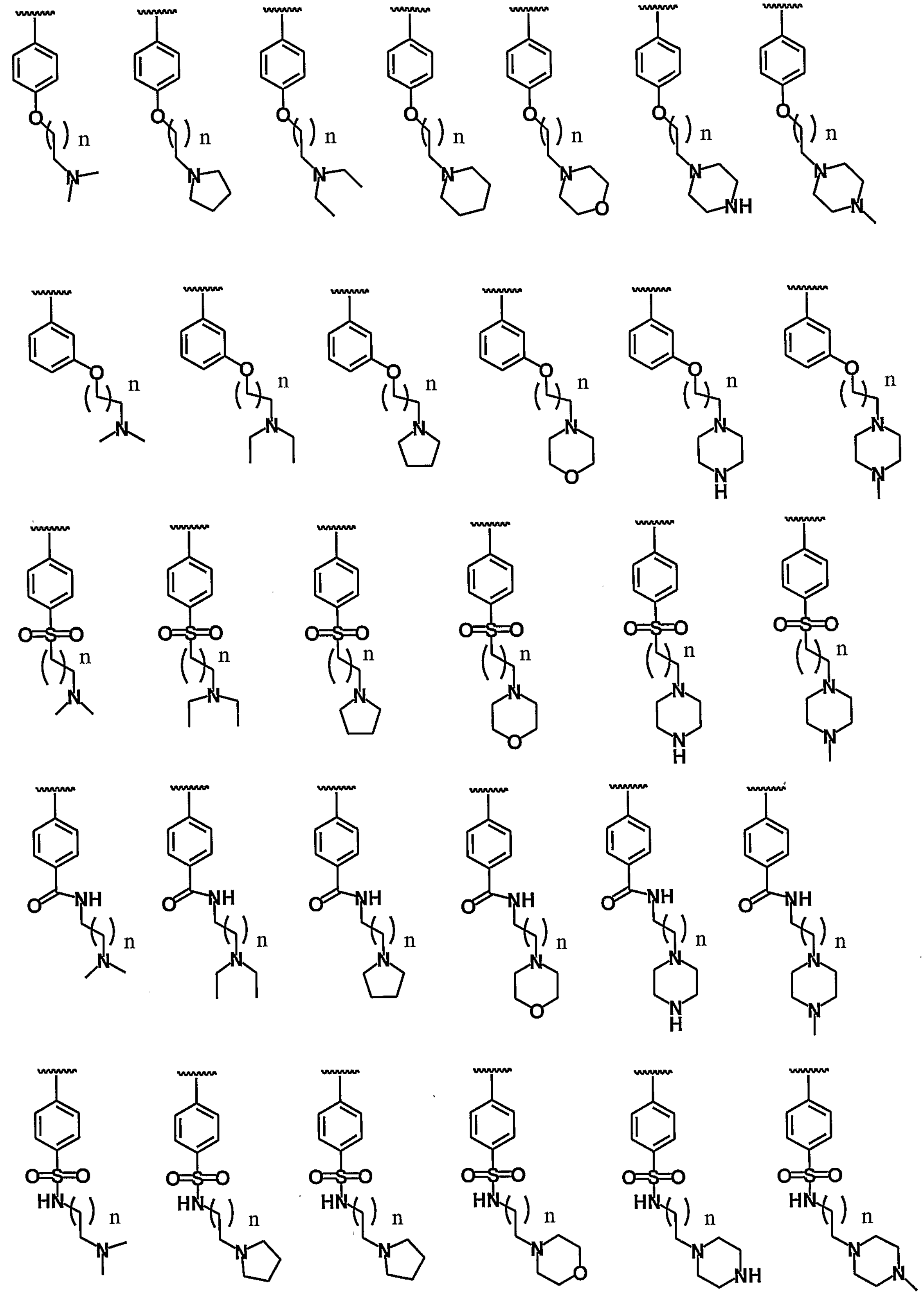


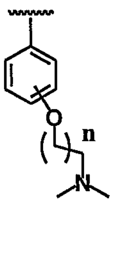
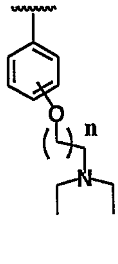
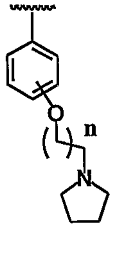
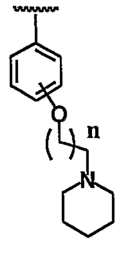
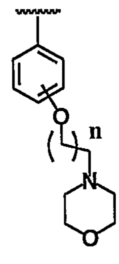
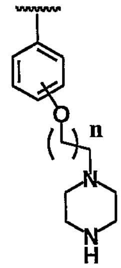
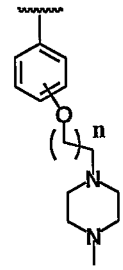


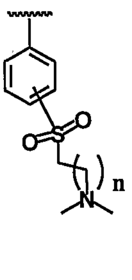
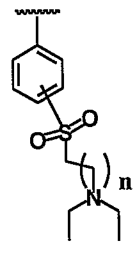
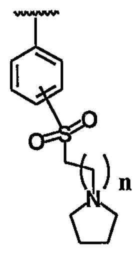
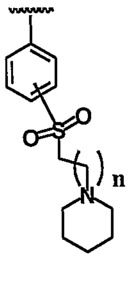
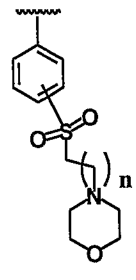
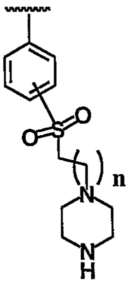
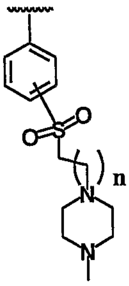


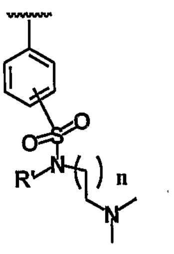
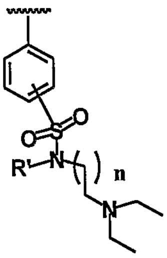
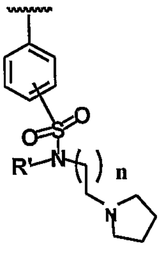
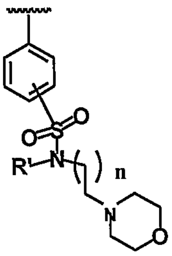
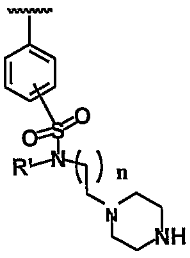
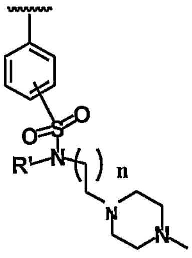


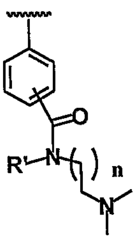
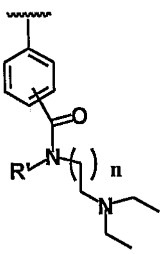
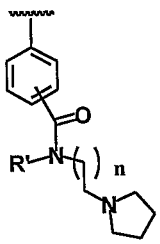
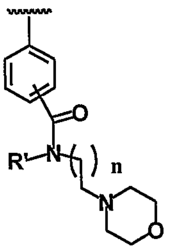
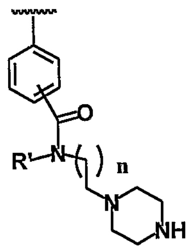
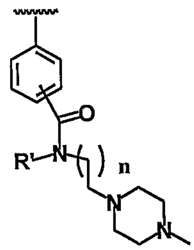


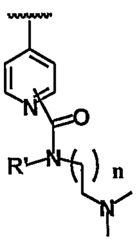
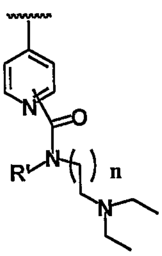
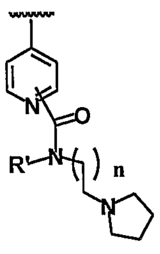
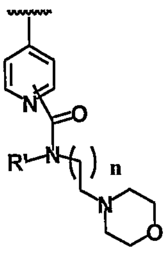
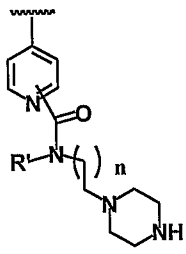
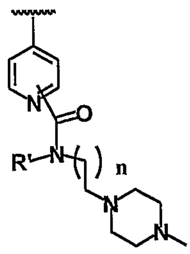


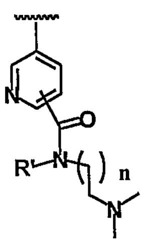
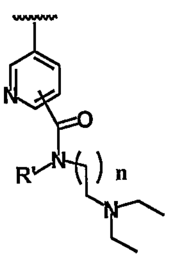
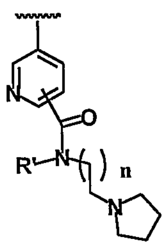
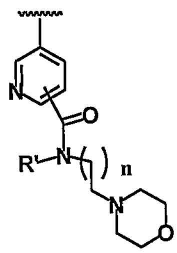
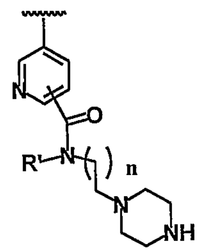
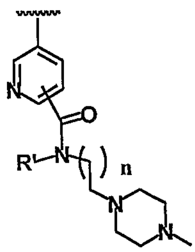








[0016] According to another embodiment of the invention, compounds that are derivatives of benzotriazine are provided, the compounds including a benzotriazine moiety having at least a first substituent attached to the benzene ring of benzotriazine and a second substituent attached to the triazine ring of the benzotriazine, where the first substituent includes a substituted pyridyl group, and the second substituent includes a secondary amino group, a substituted amide group, or a substituted sulfonylamino group.

[0017] According to yet another embodiment of the invention, compounds including a benzene-derived moiety bridged to a heterocyclic moiety are provided, where the benzene-derived moiety includes a molecule of benzene substituted with either a sulfonyl group or a pyridyl group connected to the benzene molecule via an oxygen link, and the heterocyclic moiety includes triazole, oxadiazole, oxazole, pyrazol, imidazole, thiadiazole and triazine.

[0018] According to yet another embodiment, articles of manufacture are provided, the articles including packaging material and a pharmaceutical composition contained within the packaging material, wherein the packaging material includes a label which indicates that the pharmaceutical composition can be used for treatment of disorders associated with cancer. The pharmaceutical composition can include at least one compound set forth in Structures (A) and (B) or any combination thereof.

[0019] According to another embodiment, a method for treating a disorder including administering to a subject in need thereof an effective amount of a compound, wherein the compound is set forth in Structures (A) and (B) or any combination thereof.

[0020] In one aspect, the disorder is cancer, eye disease, inflammation, psoriasis, or a viral infection, for example. More particularly, the cancer is an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

[0021] According to yet another embodiment, a pharmaceutical composition is provided, at least one compound set forth in structures (A) and (B) or any combination thereof, in a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1 shows the results of the Raf1 direct assay of invention compounds

[0023] FIG. 2 shows the results of XTT cell viability assay of invention compounds

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention is directed to heterocyclic compounds, such as heterocyclic compounds derived from benzotriazine, triazines, triazoles, oxadiazoles, imidazoles and thiadiazole and to use of the heterocyclic compounds for therapeutic purposes.

[0025] The following terminology and definitions apply as used in the present application, generally in conformity with the terminology recommended by the International Union of Pure and Applied Chemistry (IUPAC).

[0026] The term "heterocyclic," when used to describe an aromatic ring, means that the aromatic ring contains at least one heteroatom. The abbreviation "Het" is sometimes used to signify a heterocyclic structure.

[0027] The term "heteroatom" is defined to include any atom other than carbon, for example, N, O, or S.

[0028] The term "aromatic" or "aryl" is defined to include a cyclically conjugated molecular entity with a stability, due to delocalization, significantly greater than that of a hypothetical localized structure, such as the Kekulé structure.

[0029] The term "heterocyclic," when not used to describe an aromatic ring, is defined to include cyclic (i.e., ring-containing) groups other than aromatic groups, the cyclic group being formed by between 3 and about 14 carbon atoms and at least one heteroatom described above.

[0030] The term "substituted heterocyclic" is defined to include both aromatic and non-aromatic structures to heterocyclic groups further bearing one or more substituents described above.

[0031] The term "alkyl" is defined to include a monovalent straight or branched chain hydrocarbon group having from one to about 12 carbon atoms, for example, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl (also known as *n*-amyl), *n*-hexyl, and the like. The abbreviations “Me” and “Et” stand for the methyl and ethyl groups, respectively.

[0032] The term “aralkyl” refers to an aryl or heteroaryl group, as defined herein, attached through a C1-C6 alkyl linker. Examples of “aralkyl” include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 2-imidazolylethyl.

[0033] The term “methoxy” is defined as the group $-OCH_3$.

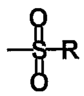
[0034] The term “halogen” is defined to include an atom of fluorine, chlorine, bromine or iodine.

[0035] The term “carboxyl” or “carboxyl group” is defined as an acid moiety having the structure —COOH.

[0036] The term “amino” or “amino group” is defined to include moieties —NRR', where each of R and R' is hydrogen (“primary amino”), or one of them is an organic radical (“secondary amino”), or each is an organic radical (“tertiary amino”).

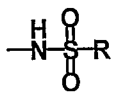
[0037] The term “aminoalkyl” or “aminoalkyl group” is defined to include moieties —R—N(R'R"), wherein R is an organic radical and each of R' and R" is hydrogen or an organic radical. If at least one of R' and R" is an organic radical, the moiety is defined as “alkylaminoalkyl” or “alkylaminoalkyl group.”

[0038] The term “sulfonyl” or “sulfonyl group” is defined to include moieties that comprise structure (S), in which R is an organic radical:



(S)

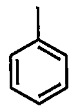
[0039] The term “sulfonylamino” or “sulfonylamino group” is defined to include moieties that comprise structure (SA), in which R is an organic radical:



(Sa)

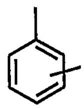
[0040] The term "amide," or "amido," or "amide group," or "amido group" is defined to include moieties containing at least one acyl group >C=O attached to nitrogen. The term "substituted amide" is defined to include moieties containing a structure RNH—CO—, in which R is an organic radical.

[0041] The term "phenyl" is defined to include moieties having structure (Ph):



(Ph)

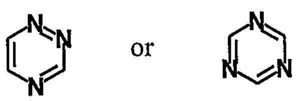
[0042] The term "toluyl" is defined to include moieties having structure (Tl):



(Tl)

[0043] The term "heteroaryl" is defined to include aromatic rings, where the ring structure is formed by between 3 and about 14 carbon atoms and by at least one heteroatom described above, and the term "substituted heteroaryl" refers to heteroaryl groups further bearing one or more substituents described above.

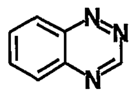
[0044] The term "triazine" is defined to include moieties containing the aromatic 6-member heterocycle having three atoms of nitrogen in the ring. Two examples of such heterocycle are shown as the following structures (Tr):



(Tr)

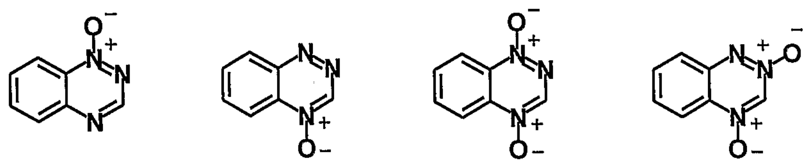
[0045] The term "benzotriazine" is defined to include moieties containing a heterocyclic structure in which the triazine ring is fused with the benzene ring, as shown by structure (BTr):

[0046]

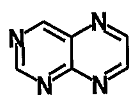


(BTr)

[0047] The terms "N-oxide," "N,N'-dioxide," and "N,N',N''-trioxide" are defined to include nitrogen-containing heterocyclic moieties in which at least one nitrogen atom is associated with oxygen to form the structures N→O. The heterocyclic moiety can be any nitrogen-containing heterocycle, for example, benzotriazine, triazine, pyridine, pyrimidine, etc. Where the heterocyclic structure is benzotriazine, for example, some N-oxides or dioxides can be described as the following structures:

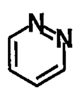


[0048] The term "pteridine" is defined to include moieties containing a heterocyclic structure having two fused 6-member rings, each ring containing two atoms of nitrogen, as shown by structure (PTr):



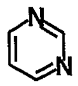
(PTr)

[0049] The term "pyridazine" is defined to include moieties containing the aromatic 6-member heterocycle having two atoms of nitrogen in the ring in *ortho* position, as shown by the structure (PAz):



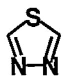
(PAz)

[0050] The term "pyrimidine" is defined to include moieties containing the aromatic 6-member heterocycle having two atoms of nitrogen in the ring in *meta* position, as shown by the structure (PRm):



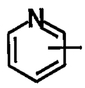
(PRm)

[0051] The term “thiadiazole” is defined to include moieties containing the aromatic 5-member thiophene-based heterocycle, having two atoms of nitrogen and one atom of sulfur, as shown by the structure (TDa):



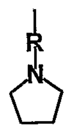
(TDa)

[0052] The term “pyridyl” is defined to include moieties containing a radical derived from pyridine. One structure of pyridyl is shown as the structure (Py):



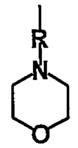
(Py)

[0053] The term “alkyl pyrrolidine” is defined to include moieties containing a radical derived from pyrrolidine (a 5-member saturated heterocycle having one nitrogen atom), where an alkylene group R is attached to the nitrogen atom of the pyrrolidine ring. One structure of alkyl pyrrolidine is shown as the structure (APy):



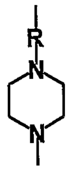
(APy)

[0054] The term “alkyl morpholine” is defined to include moieties containing a radical derived from morholine, (a 6-member saturated heterocycle having one nitrogen atom and one oxygen atom), where an alkylene group R is attached to the nitrogen atom of the morpholine ring. One structure of alkyl morpholine is shown as the structure (AMr):



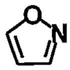
(AMr)

[0055] The term "alkyl piperazine" is defined to include moieties containing a radical derived from piperazine (a 6-member saturated heterocycle having two nitrogen atoms), where an alkylene group R is attached to one nitrogen atom of the piperazine ring. One structure of alkyl piperazine is shown as the structure (APi):



(APi)

[0056] The term "isoxazole" is defined to include moieties containing the aromatic 5-member heterocycle, having one atoms of nitrogen and one atom of oxygen, as shown by the structure (ISo):



(Iso)

[0057] The term "hydrophobic" is defined as a group or structure free of strongly polar groups such as –OH, –COOH, $–NH_2$, –NH–CO–, halogens, or the like.

[0058] The term "kinase" is defined to include any enzyme that catalyzes the addition of phosphate groups to a protein residue; for example, serine and threonine kinases catalyze the addition of phosphate groups to serine and threonine residues.

[0059] The term "therapeutically effective amount" is defined as the amount of the compound or pharmaceutical composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, e.g., restoration or maintenance of vasculostasis or prevention of the compromise or loss or vasculostasis; reduction of tumor burden; reduction of morbidity and/or mortality.

[0060] The term "pharmaceutically acceptable" is defined as a carrier, whether diluent or excipient, that is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0061] The terms "administration of a compound" or "administering a compound" is defined to include an act of providing a compound of the invention or pharmaceutical composition to the subject in need of treatment.

[0062] According to embodiments of the present invention, two types of heterocyclic compounds are provided for treatment of various diseases, disorders, and pathologies, including cancer. The heterocyclic compounds of the invention can inhibit the activity of a kinase, such as any kinase in the MAPK signaling pathway.

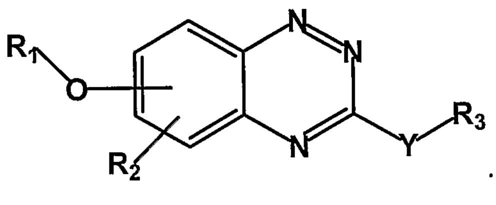
[0063] According to an embodiment of the invention, a first type of compounds is provided for treatment of various diseases, disorders, and pathologies, including cancer. The first type of compounds can include derivatives of benzotriazine. The derivatives of benzotriazine that can be used can comprise the compounds that include a benzotriazine moiety having at least one substituent attached to the benzene ring of benzotriazine and a at least one substituent attached to the triazine ring of the benzotriazine, and an N-oxide, N,N'-dioxide, N,N',N"-trioxide, or pharmaceutically acceptable salts thereof.

[0064] A substituent attached to the benzene ring of benzotriazine can include a substituted pyridyl group. The substituents in the substituted pyridyl group can include an amido moiety, an aminoalkyl group (e.g., aminomethyl), or a carboxyl group, or a carboxylate group. The amido moiety attached to the pyridyl group can be in turn also substituted by attaching to the nitrogen in the amido moiety a substituent selected from an alkyl (e.g., methyl), an alkylaminoalkyl (e.g., diethylamino alkyl), a pyridyl, an alkyl pyrrolidine, an alkyl morpholine, and an alkyl piperazine groups.

[0065] Optionally, the benzene ring of the compounds of the first type can contain a second substituent located in any available position of the ring, for example, methyl, halogen or methoxy. Some particular examples of benzene-ring containing moieties that can be used include *tert*-butyl phenyl, trifluoromethoxyphenyl, methoxyphenyl, dimethylamino, dimethylaminophenyl, aminophenyl, trifluoroethoxyphenyl, trifluoromethoxychlorophenyl, trifluoromethoxybromophenyl, trifluoroethoxychlorophenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchloro phenyl, chlorotoluyl, N-phenylacetamide, N,N-alkyl-benzamide, isopropoxyphenyl, alkoxyphenyl, dialkoxyphenyl, acetylphenyl.

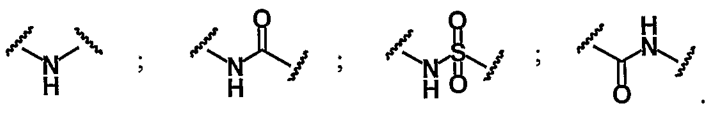
[0066] A substituent attached to the triazine ring of benzotriazine in the compounds of the first type can include a secondary amino group, a substituted amide group, or a substituted sulfonylamino group; each of these groups can further contain a moiety derived from benzene, thiophene, or isoxazole. If the substituent attached to the triazine ring of benzotriazine in the compounds of the first type is a secondary amino group, the moiety derived from benzene, thiophene, or isoxazole can be attached to the nitrogen of the secondary amino group. If the substituent in the triazine ring is a substituted amide group or the substituted sulfonylamino group, the moiety derived from benzene, thiophene, or isoxazole can be attached via the acyl group or the sulfonyl group, respectively. Moieties derived from benzene, thiophene, or isoxazole can further include alkyls, e.g., *t*-butyl phenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchloro phenyl, and chlorotoluyl.

[0067] Compounds of the first type can be described as compounds having the general structure (A), and an N-oxide, N,N'-dioxide, N,N',N''-trioxide, or a pharmaceutically acceptable salt thereof. The general structure (A) is as follows:

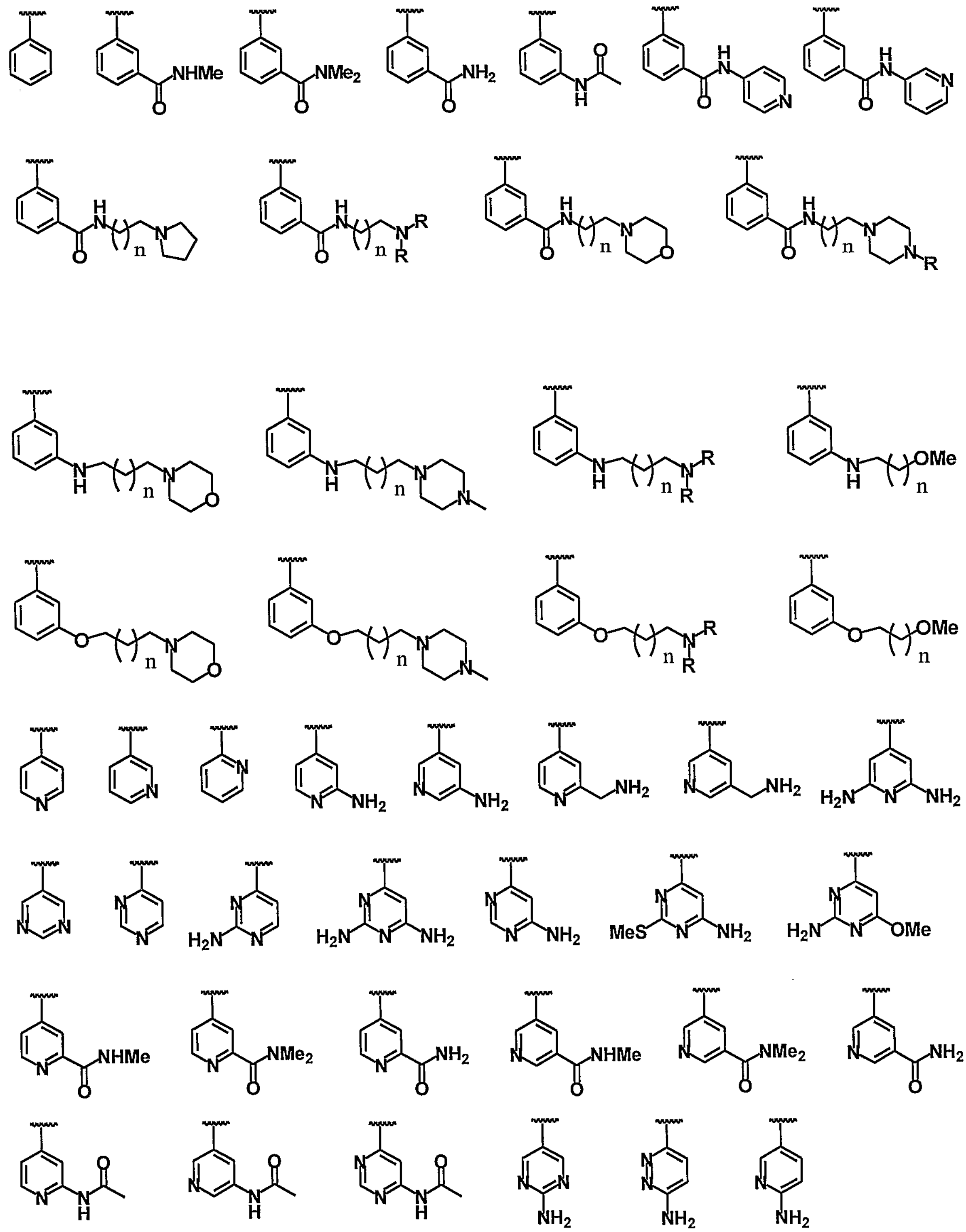


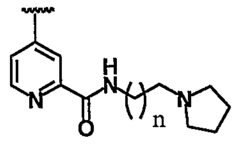
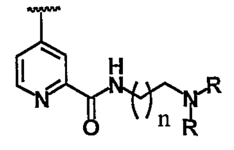
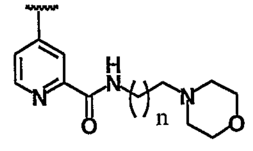
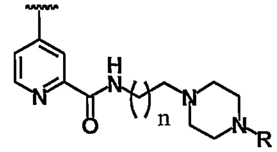
(A)

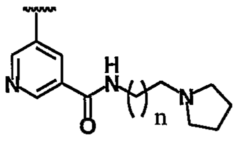
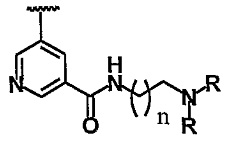
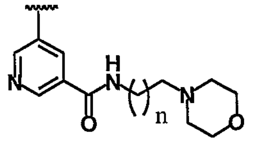
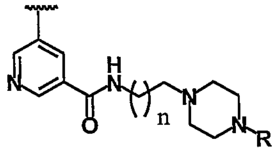
wherein Y can be absent or can be one of the following moieties:

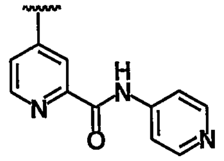
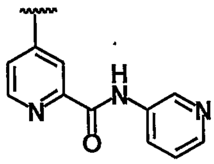
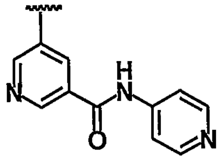
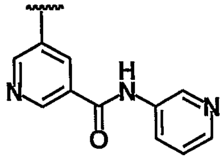


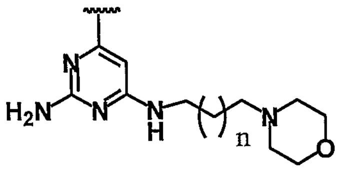
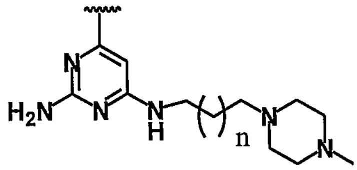
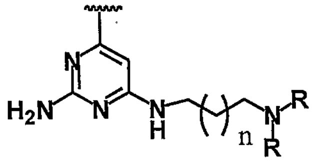
[0068] In structure (A), R_1 can be an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl, such as C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms such as N, S, and O; substituted C_6-C_{12} aryl; substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl. In particular, R_1 can be any one of the following moieties:

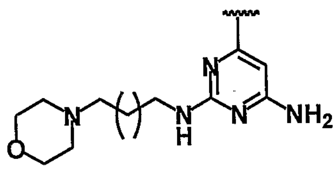
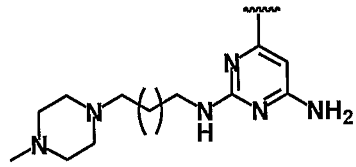
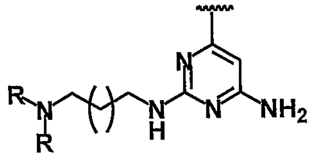


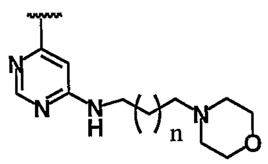
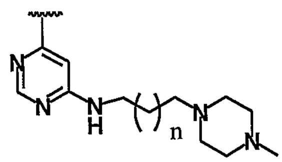
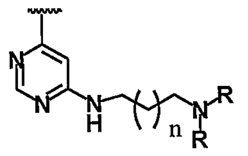
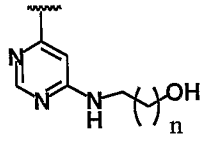
   

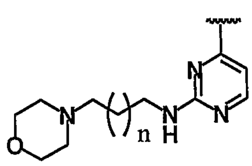
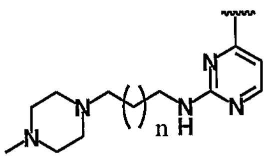
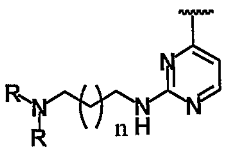
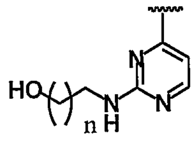
   

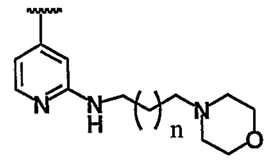
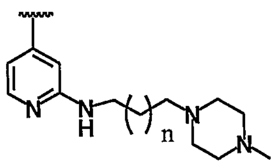
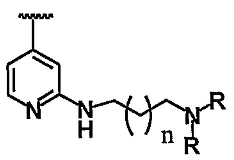
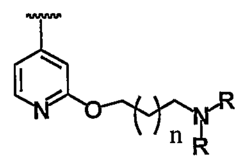
   

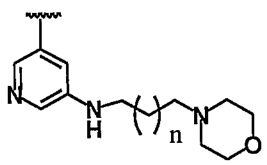
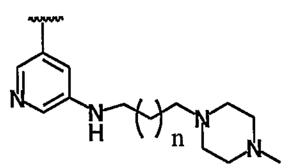
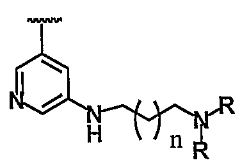
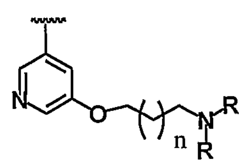
  

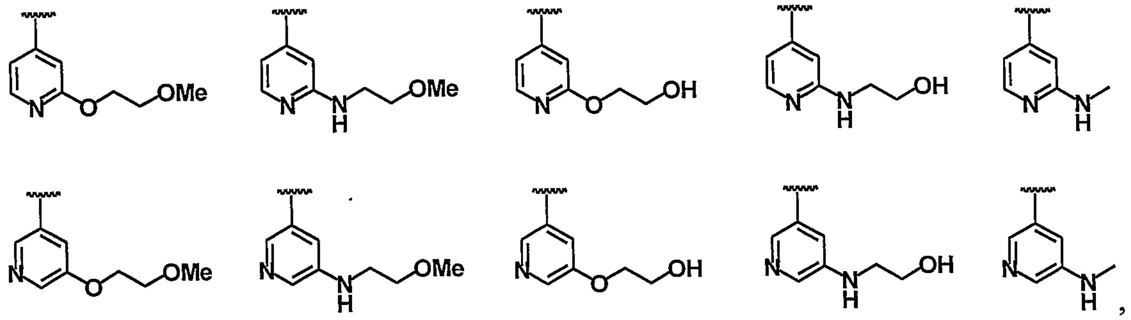
  

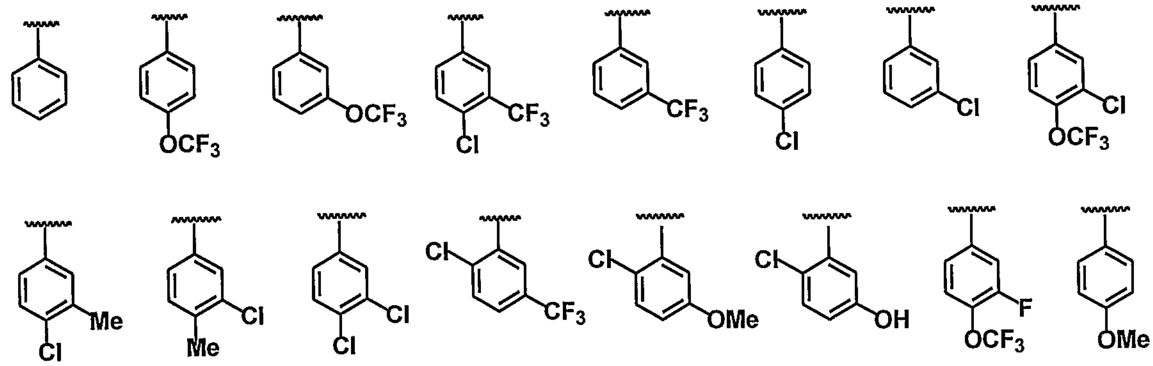
   

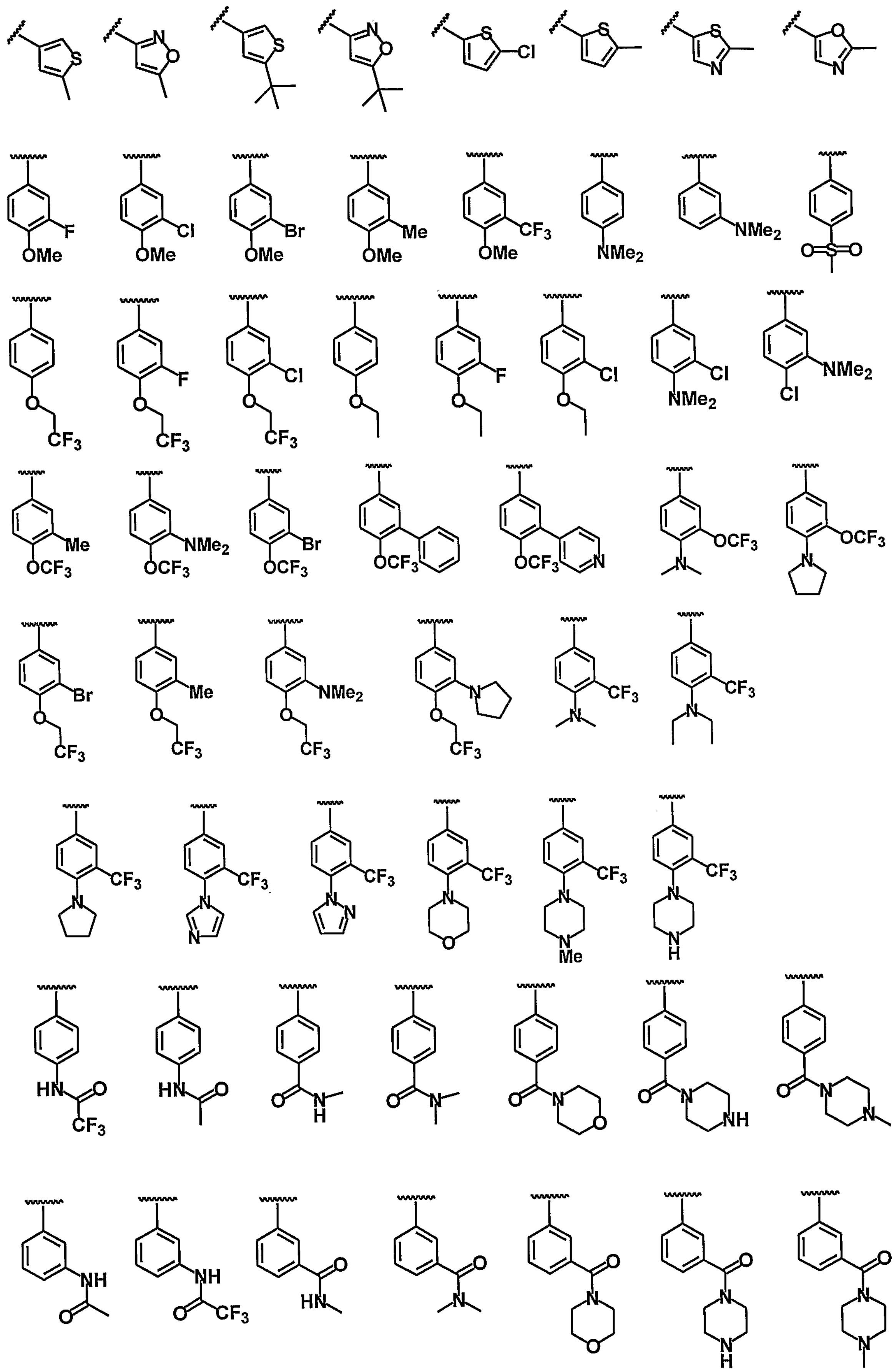


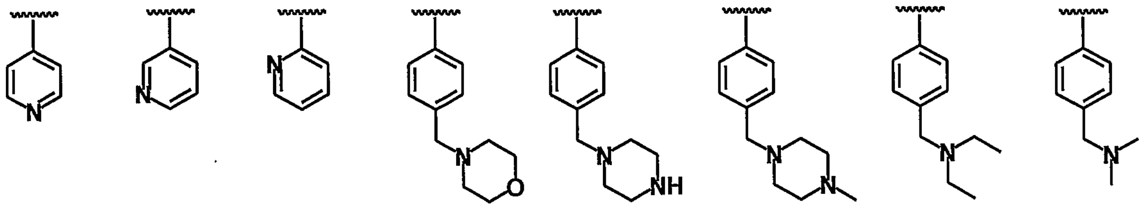
where n can be an integer selected from a group consisting of 0, 1, 2, and 3.

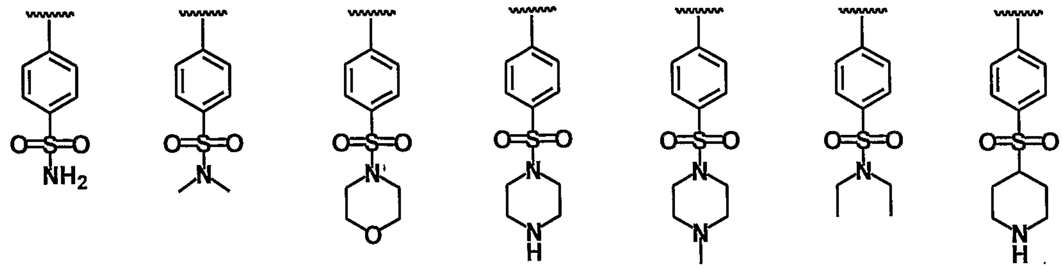
[0069] In structure (A), the substituent R_2 can be any one of hydrogen, halogen, C_1-C_{18} alkyl (e.g., methyl), -OH, $-NO_2$, -CN, C_1-C_{18} alkoxy (e.g., methoxy), $-NHSO_2R^5$, $-SO_2NHR^5$, $-NHCOR^5$, $-NH_2$, $-NR^5R^6$, $-S(O)R^5$, $-S(O)_2R^5$, $-CO_2R^5$, $-CONR^5R^6$, and where R^5 and R^6 are independently selected from hydrogen, a C_1-C_{12} alkyl and a substituted C_1-C_{12} alkyl.

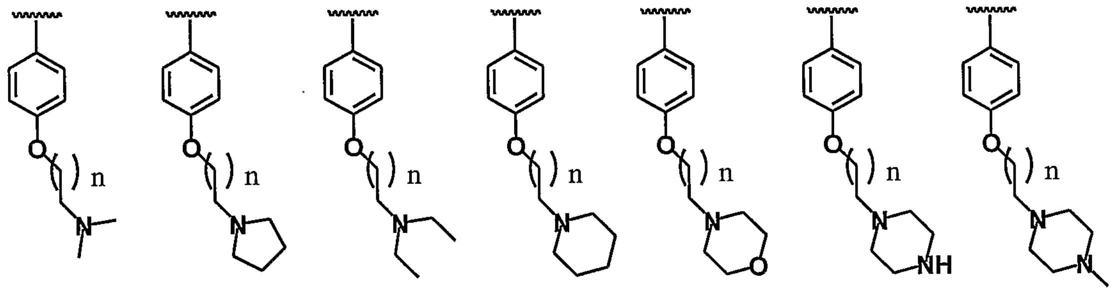
[0070] In structure (A), group R_3 can be an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl. For example, R_3 can be one of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms such as N, S, and O; substituted C_6-C_{12} aryl; substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S and O; C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl. In particular, the substitutent R_3 can be one of the following:

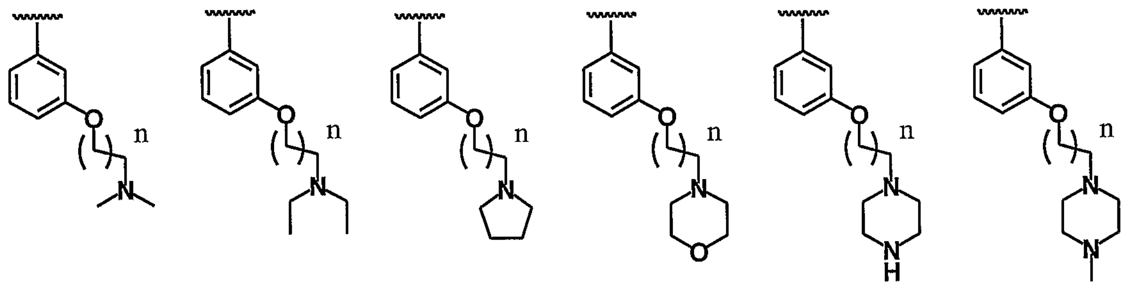


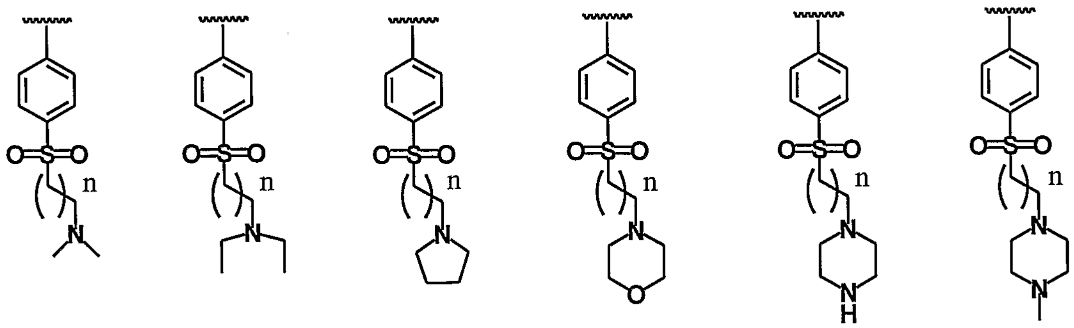


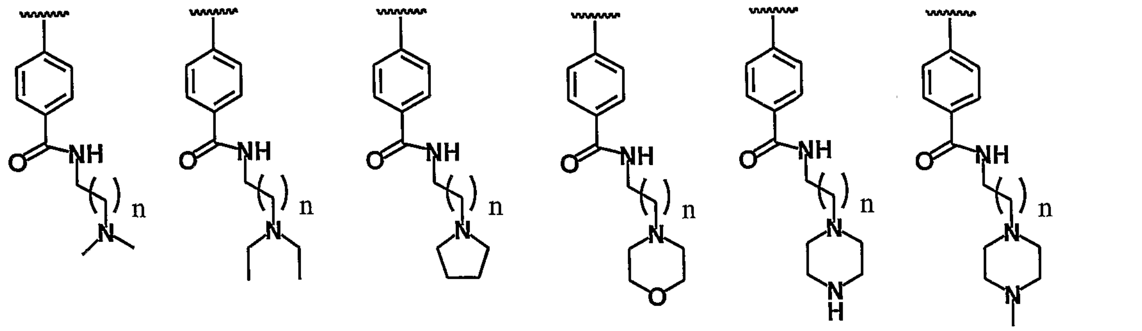


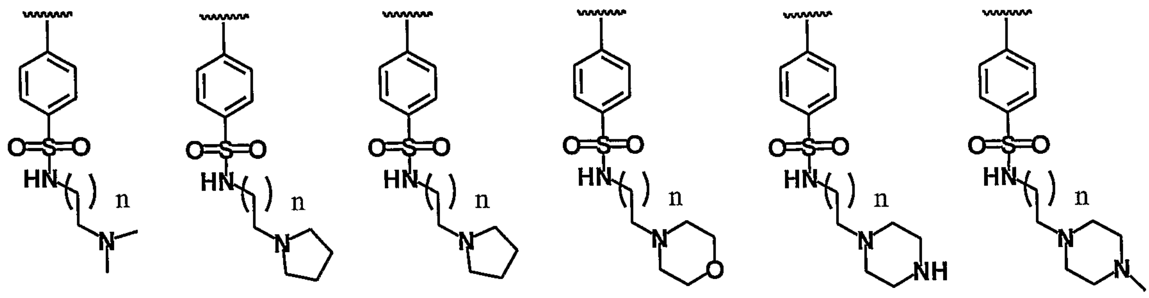


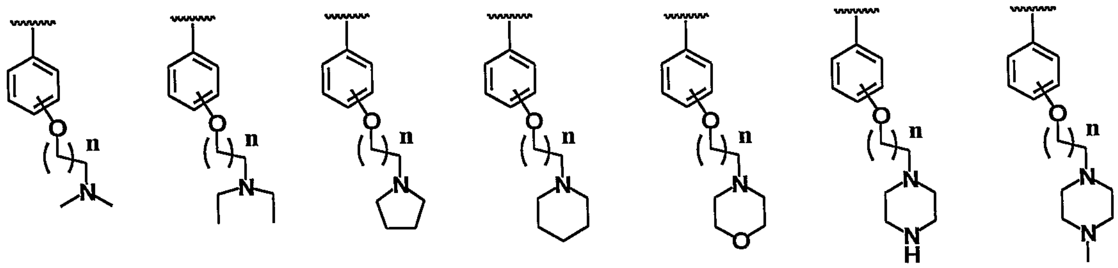


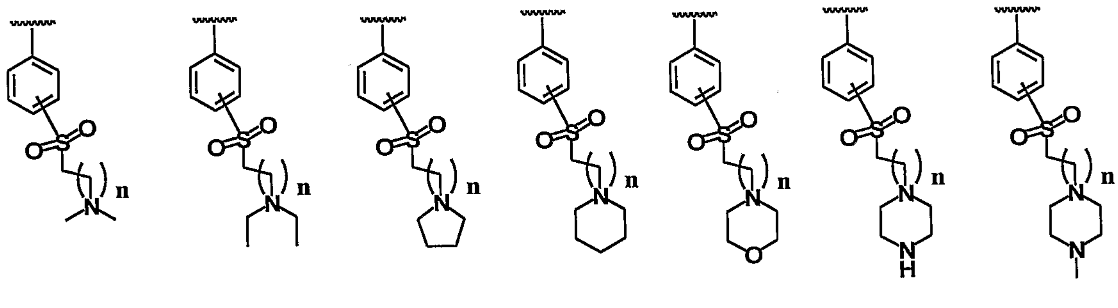


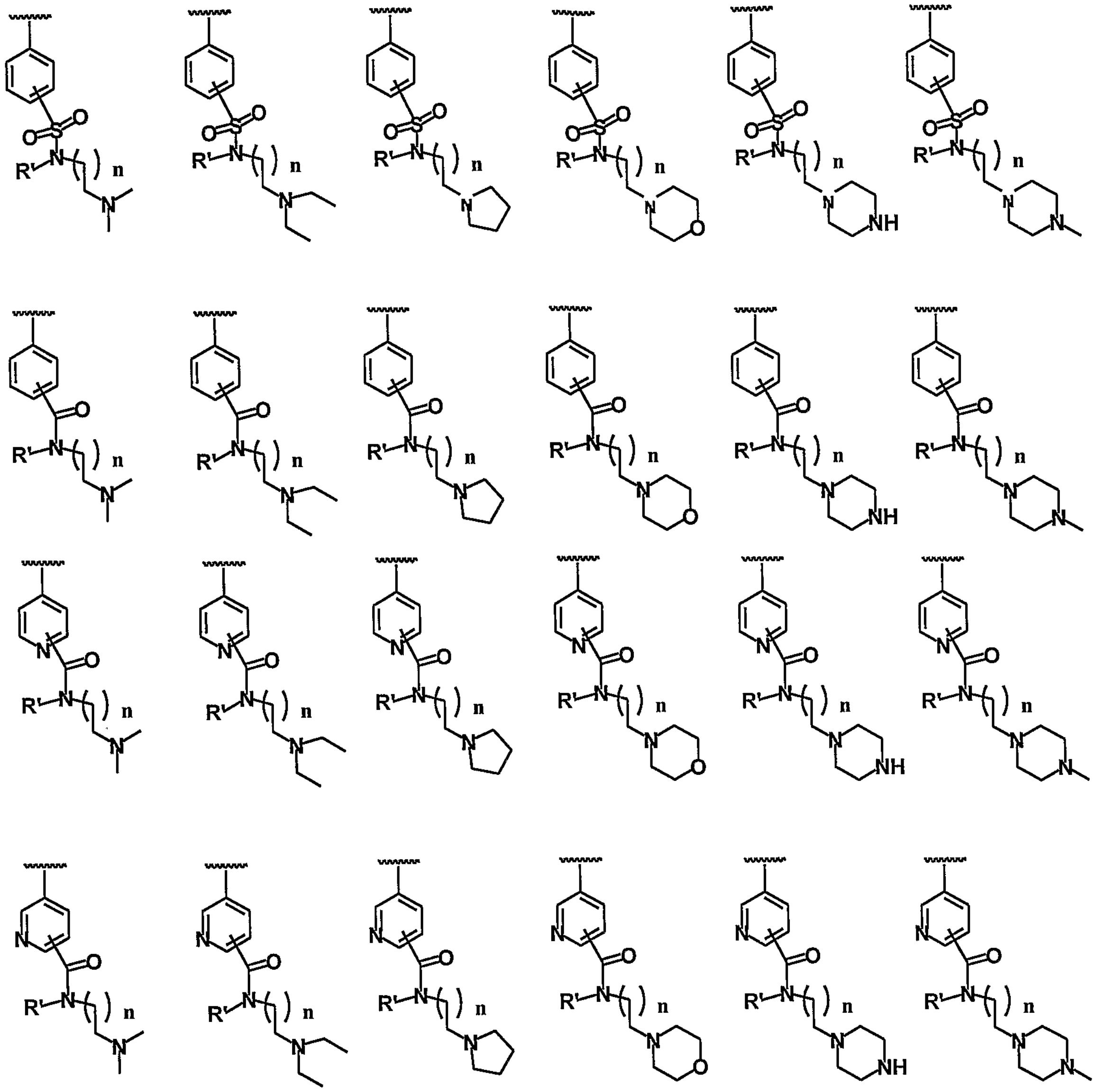




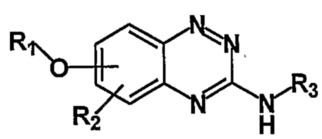




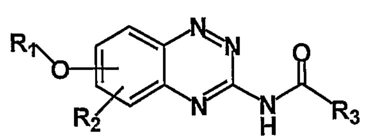




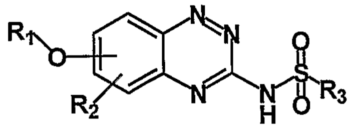
[0071] Some general examples of compounds described by the general structure (A). include a compound having the general structure (I), a compound having the general structure (II), a compound having the general structure (III) or a compound having the general structure (IV):



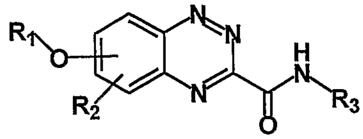
(I)



(II)

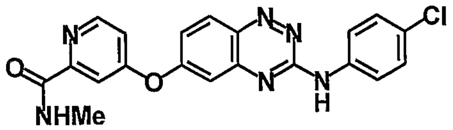


(III)

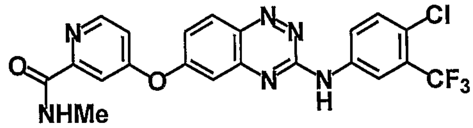


(IV)

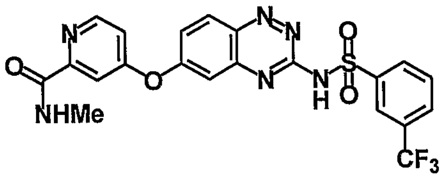
[0072] Some non-limiting examples of particular compounds described by the general structure (A) that can be used include compounds having formulae (1)-(33):



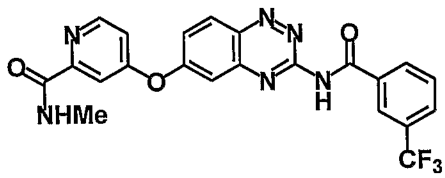
(1)



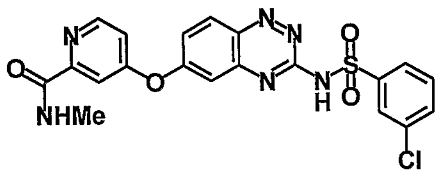
(2)



(3)



(4)



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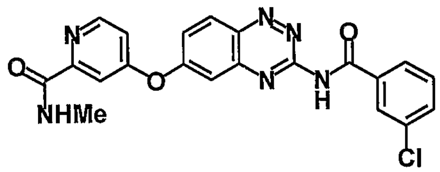

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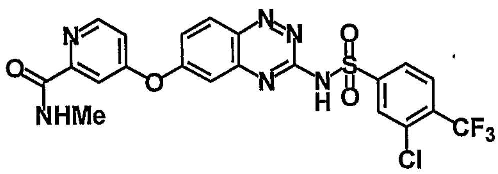

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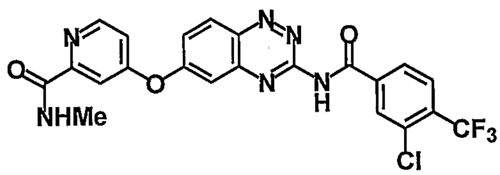

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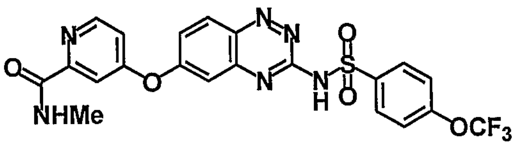

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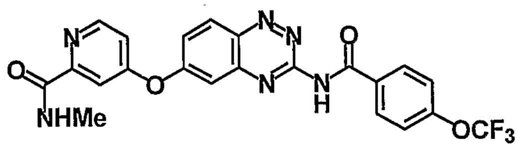

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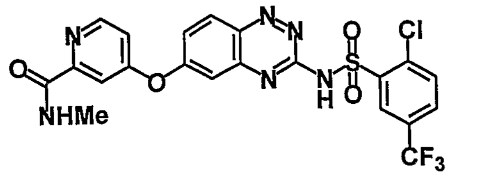

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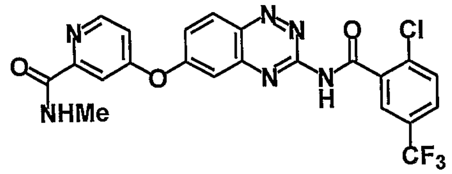

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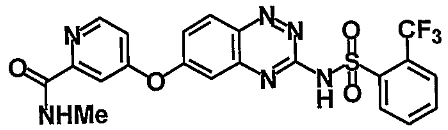

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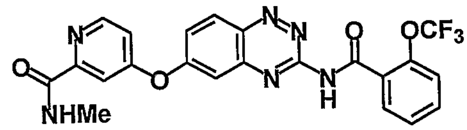

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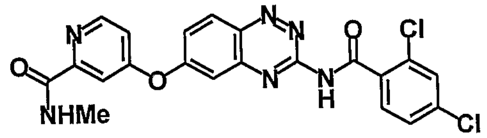

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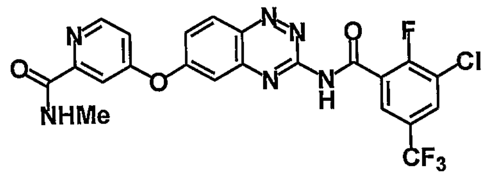

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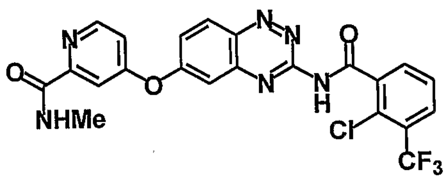

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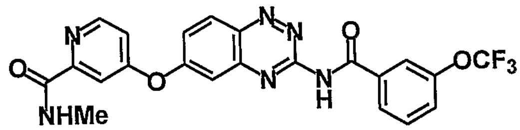

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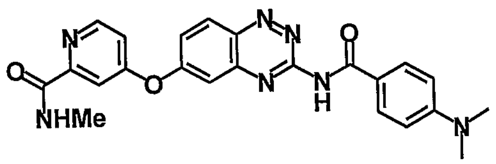

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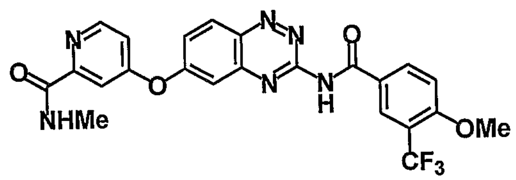

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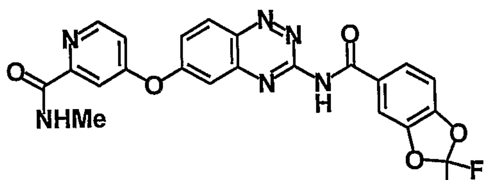

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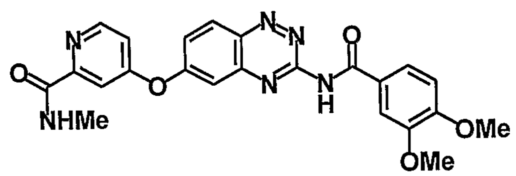

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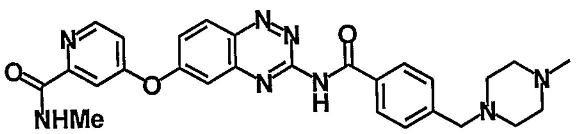

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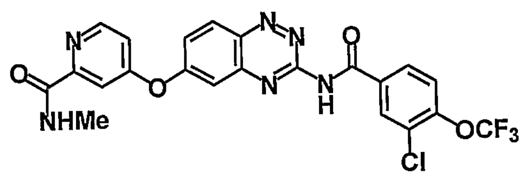

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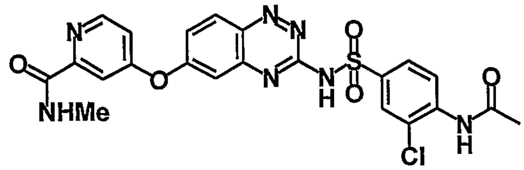

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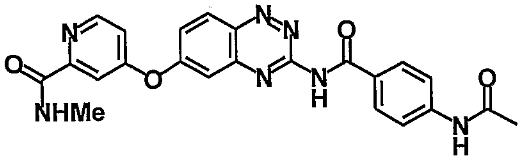

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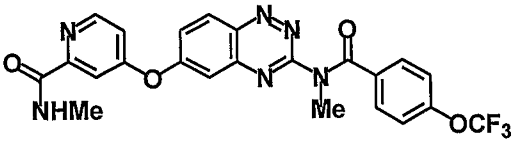

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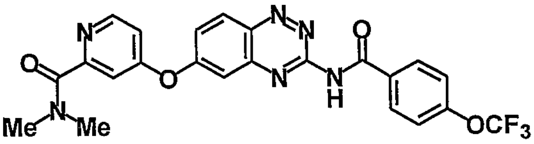

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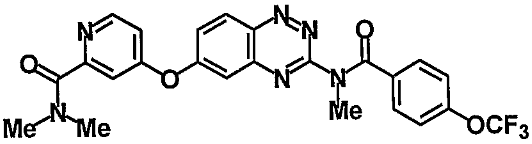

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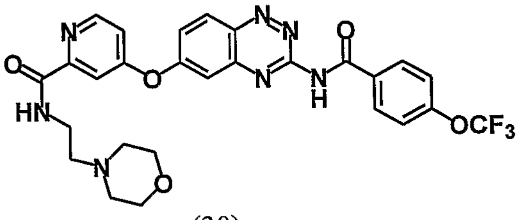

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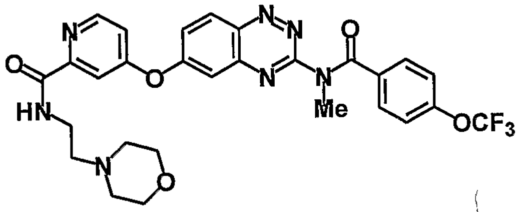

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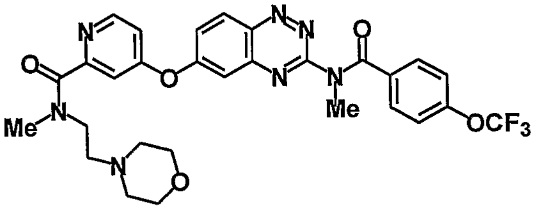

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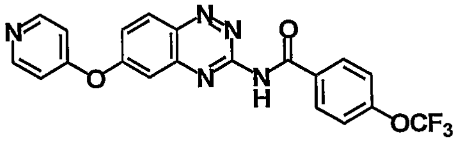
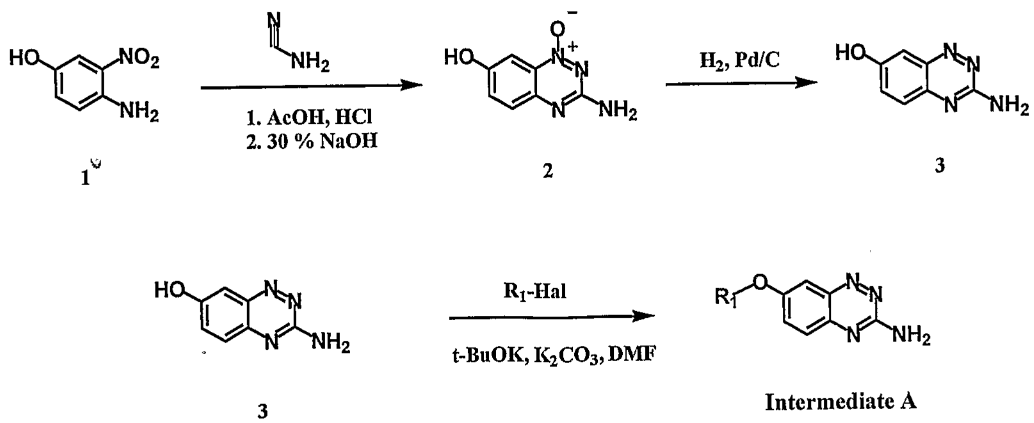
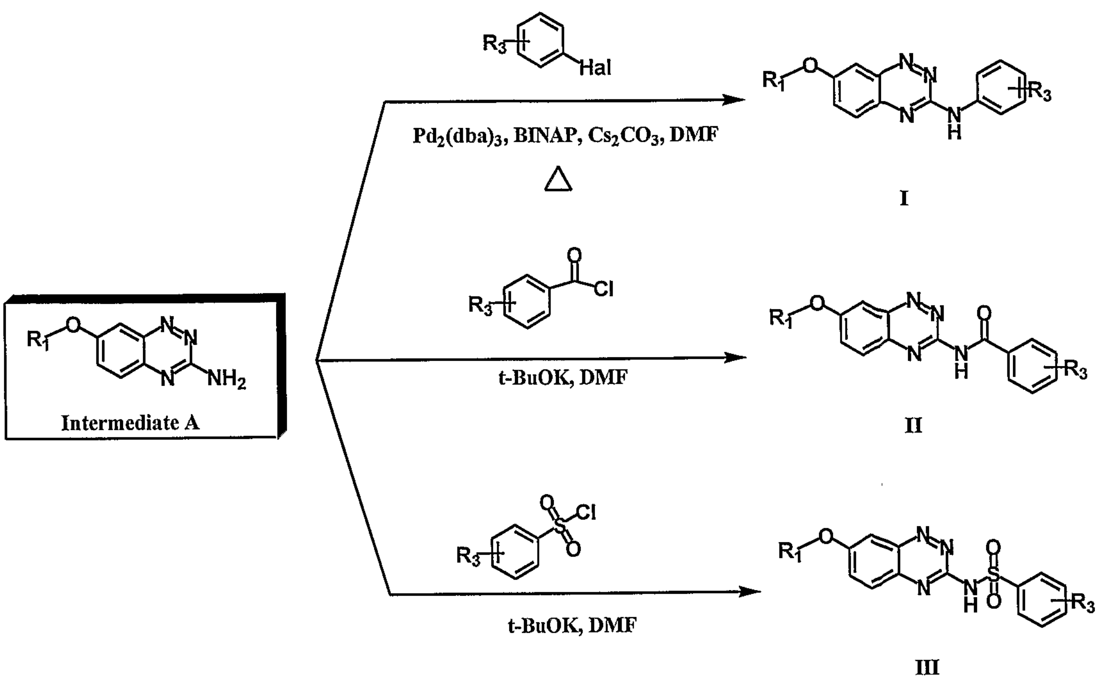


(33)

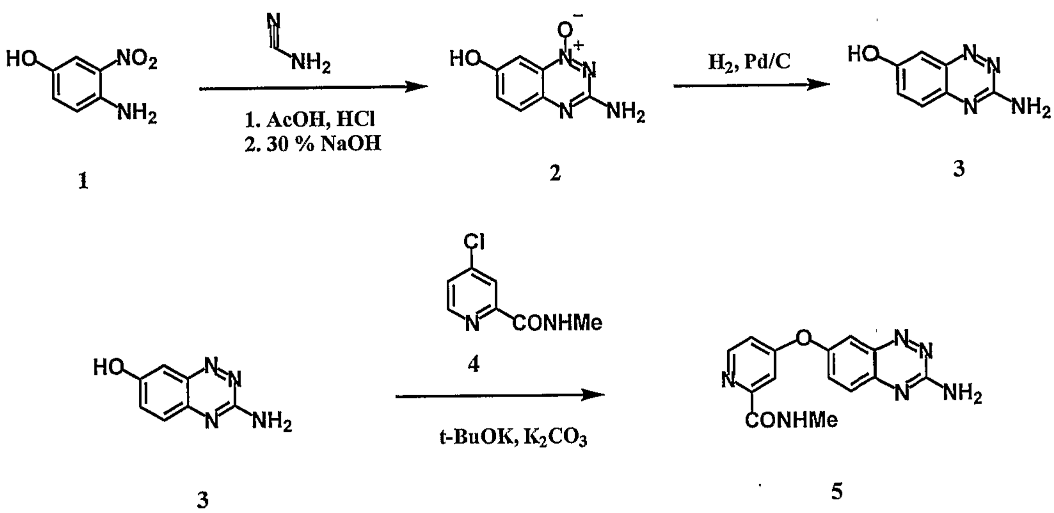
[0073] The benzotriazine derivatives described above and illustrated by the general structure (A) can be prepared as shown by Scheme I:





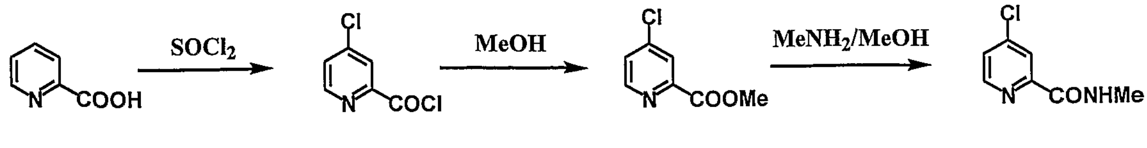
Scheme I

[0074] To prepare the intermediate A, where R_1 is, for example, 2-pyridine carboxamide, the synthetic route shown by Scheme II can be used:



Scheme II

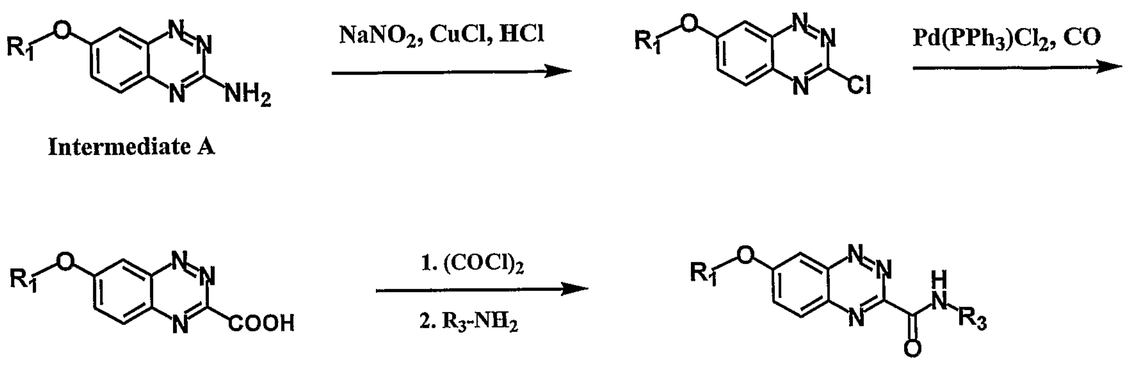
[0075] As seen from Scheme II, the synthesis of the intermediate A requires using 4-chloro-2-pyridinecarboxamide 4, which can be separately preliminarily synthesized as shown by Scheme III:



6 7 8 4

Scheme III

The benzotriazine derivatives described in the formula (IV) and illustrated by the general structure (A) can be prepared as shown by Scheme IV:



IV

Scheme IV.

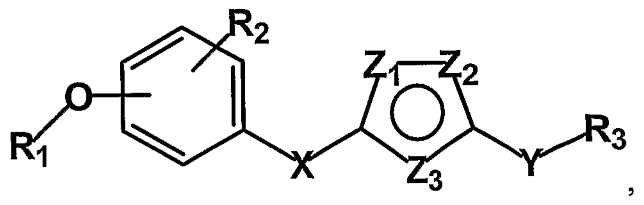
[0076] According to an embodiment of the invention, a second type of compounds is provided for treatment of various diseases, disorders, and pathologies, including cancer. The second type of compounds can include a benzene derived moiety bridged to a heterocyclic moiety, or pharmaceutically acceptable salts thereof. The bridge between the benzene-derived moiety and the heterocyclic moiety can include a single bond or a nitrogen atom. If the heterocyclic moiety contains at least one nitrogen, the second type of compounds can be an N-oxide, or N,N'-dioxide, or N,N',N"-trioxide.

[0077] Whether the compound can be an N-oxide, or N,N'-dioxide, or N,N',N"-trioxide, depends on the number of nitrogen atoms contained in the heterocyclic moiety. For example, if the heterocyclic moiety has only one nitrogen, the second type of compounds can be an N-oxide. If the heterocyclic moiety has two atoms of nitrogen, the second type of compounds can be an N-oxide or N,N'-dioxide. If the heterocyclic moiety has three atoms of nitrogen, the second type of compounds can be any of an N-oxide, an N,N'-dioxide, an N,N',N"-trioxide.

[0078] The benzene-derived moiety can include a substituent such as a pyridyl group connected to the benzene molecule via an oxygen link, or a sulfonyl group. The pyridyl group connected to the benzene molecule can be further substituted. The substituents in the pyridyl group can include the same moieties as described above for the first type of compounds of the present invention. The sulfonyl group connected to the benzene molecule can be also further substituted. The substituents in the sulfonyl group can include the substituted pyridyl group described above for the first type of compounds of the present invention.

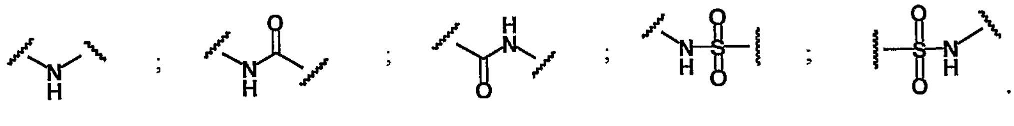
[0079] Optionally, the benzene-derived moiety of the compounds of the second type can contain a second substituent, e.g., methyl, halogen or methoxy, which can be located in any position of the benzene ring. Some exemplary benzene-derived moieties that can be included in the second type of compounds can include *tert*-butyl phenyl, trifluoromethoxyphenyl, methoxyphenyl, dimethylamino, dimethylaminophenyl, aminophenyl, trifluoroethoxyphenyl, trifluoromethoxychlorophenyl, trifluoromethoxybromophenyl, trifluoroethoxychlorophenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchloro phenyl, chlorotoluyl, N-phenylacetamide, N,N-alkyl-benzamide, isopropoxyphenyl, alkoxyphenyl, dialkoxyphenyl, acetylphenyl.

[0080] The compounds of the second type include heterocyclic compounds having the general structure (B), or an N-oxide, or N,N'-dioxide, N,N',N''-trioxide, or a pharmaceutically acceptable salt thereof, and can inhibit the activity of a kinase, such as any kinase in the MAPK signaling pathway. The general structure (B) can be represented as follows:



(B)

[0081] In structure (B), each of Z_1, Z_2 and Z_3 can be, independently, N, CH, N=CH, O, S or N-R^4, wherein R^4 is hydrogen or lower alkyl, with the further proviso that at least one of Z_1, Z_2 and Z_3 is not CH; X can be absent or be NH; Y can be absent or can be one of the following moieties:



[0082] Further, in structure (B), the substitutents R_1, R_2, and R_3 can be as follows:

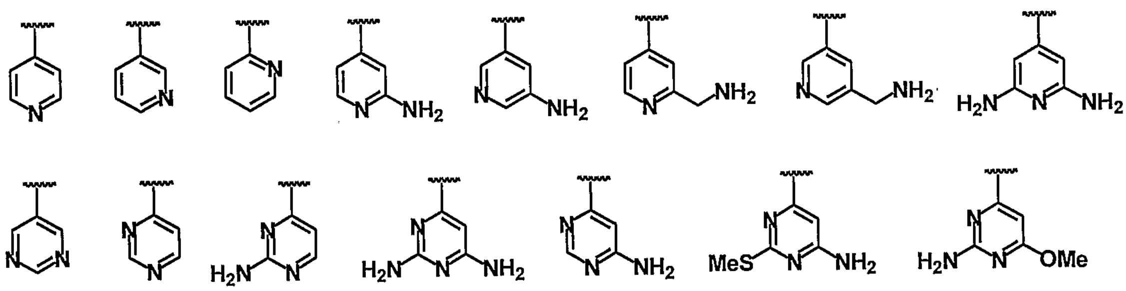
[0083] R_1 can be an unsubstituted or a substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S or O;

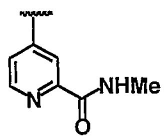
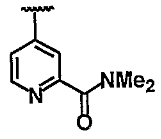
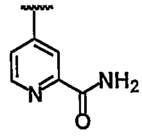
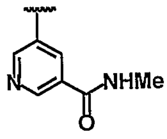
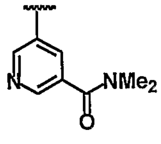
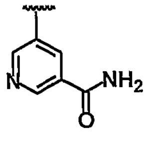
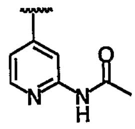
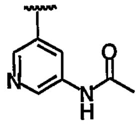
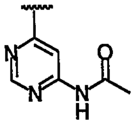
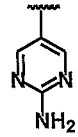
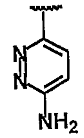
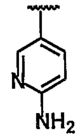
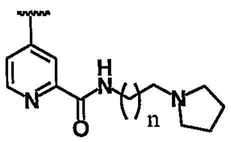
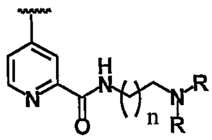
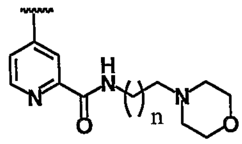
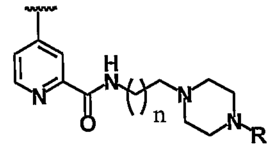
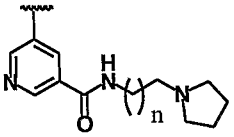
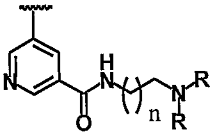
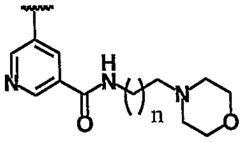
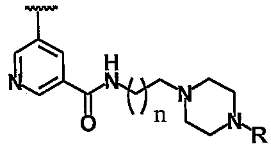
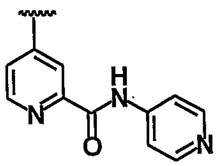
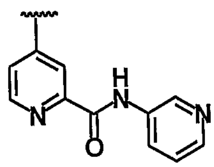
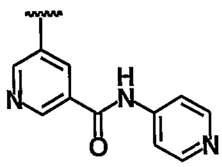
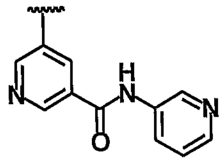
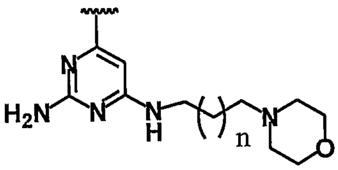
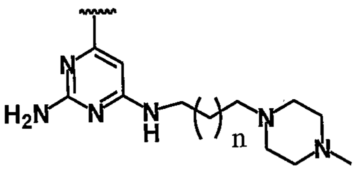
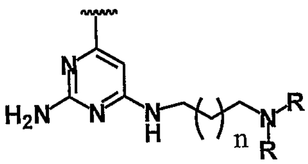
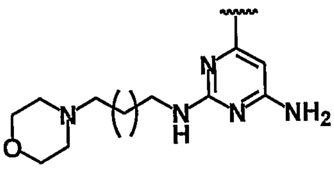
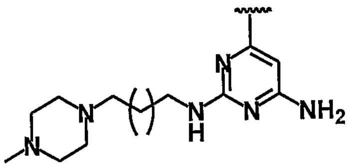
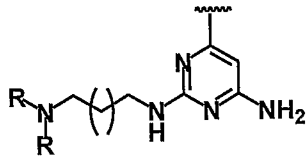
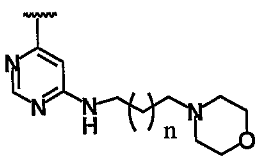
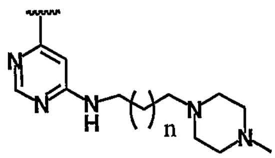
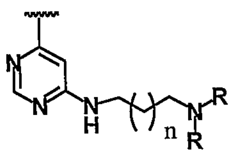
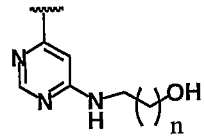
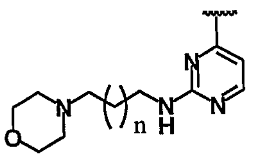
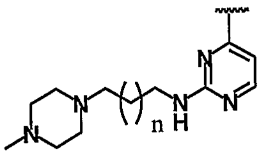
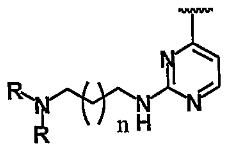
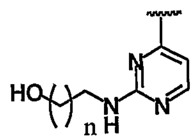
[0084] R_2 can be any one of hydrogen, halogen, C_1-C_{18} alkyl (e.g., methyl), -OH, $-NO_2$, -CN, C_1-C_{18} alkoxy (e.g., methoxy), $-NHSO_2R^5$, $-SO_2NHR^5$, $-NHCOR^5$, $-NH_2$, $-NR^5R^6$, $-S(O)R^5$, $-S(O)_2R^5$, $-CO_2R^5$, $-CONR^5R^6$, and where R^5 and R^6 are independently selected from hydrogen, a C_1-C_{18} alkyl and a substituted C_1-C_{12} alkyl; and

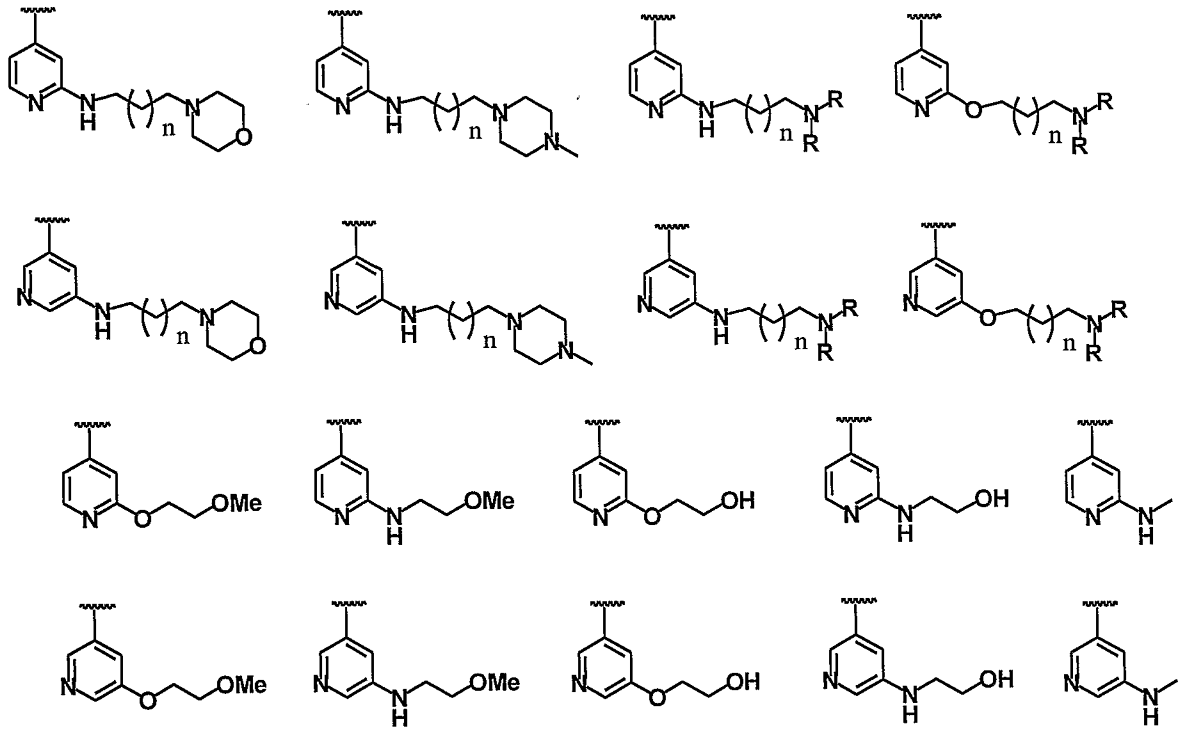
[0085] R_3 can be hydrogen, a C_1-C_{18} alkyl, a substituted C_1-C_{12} alkyl, a C_1-C_{12} cycloalkyl, a substituted C_1-C_{12} cycloalkyl, a substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms such as N, S, or O, an aryl such as a C_6-C_{12} aryl, a substituted aryl such as a substituted C_6-C_{12} aryl, a heterocycle, a substituted heterocycle, a heteroaryl such as a C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S or O, a substituted heteroaryl such as substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms such as N, S or O, a C_7-C_{24} aralkyl, a substituted C_7-C_{24} aralkyl, a C_7-C_{24} alkylaryl, and a substituted C_7-C_{24} alkaryl.

[0086] The substituent R_1 can include a substituted pyridyl or a substituted pyrimidyl group. The substituents in the substituted pyridyl or substituted pyrimidyl group can include an amido moiety, an aminoalkyl group (e.g., aminomethyl), or a carboxyl group, or a carboxylate group. The amido moiety attached to the pyridyl/pyrimidyl group can be in turn also substituted by attaching to the nitrogen in the amido moiety a substitutent selected from an alkyl (e.g., methyl), an alkylaminoalkyl (e.g., diethylamino alkyl), a pyridyl, an alkyl pyrrolidine, an alkyl morpholine, and an alkyl piperazine groups.

[0087] Particular, non-limiting examples of R_1 that can be used in compounds having the structure (B) include any of the following moieties:

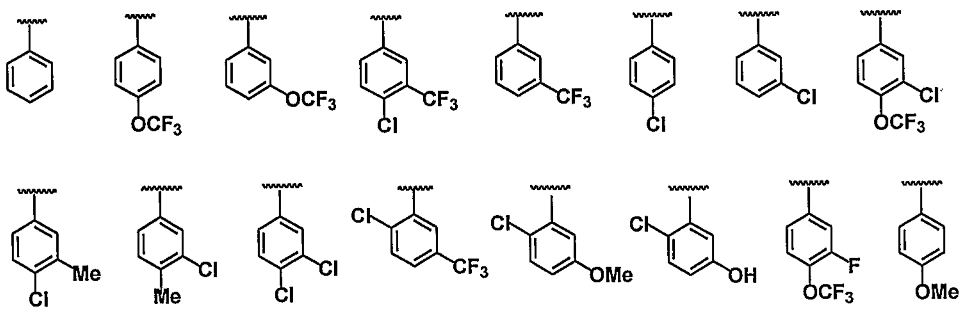


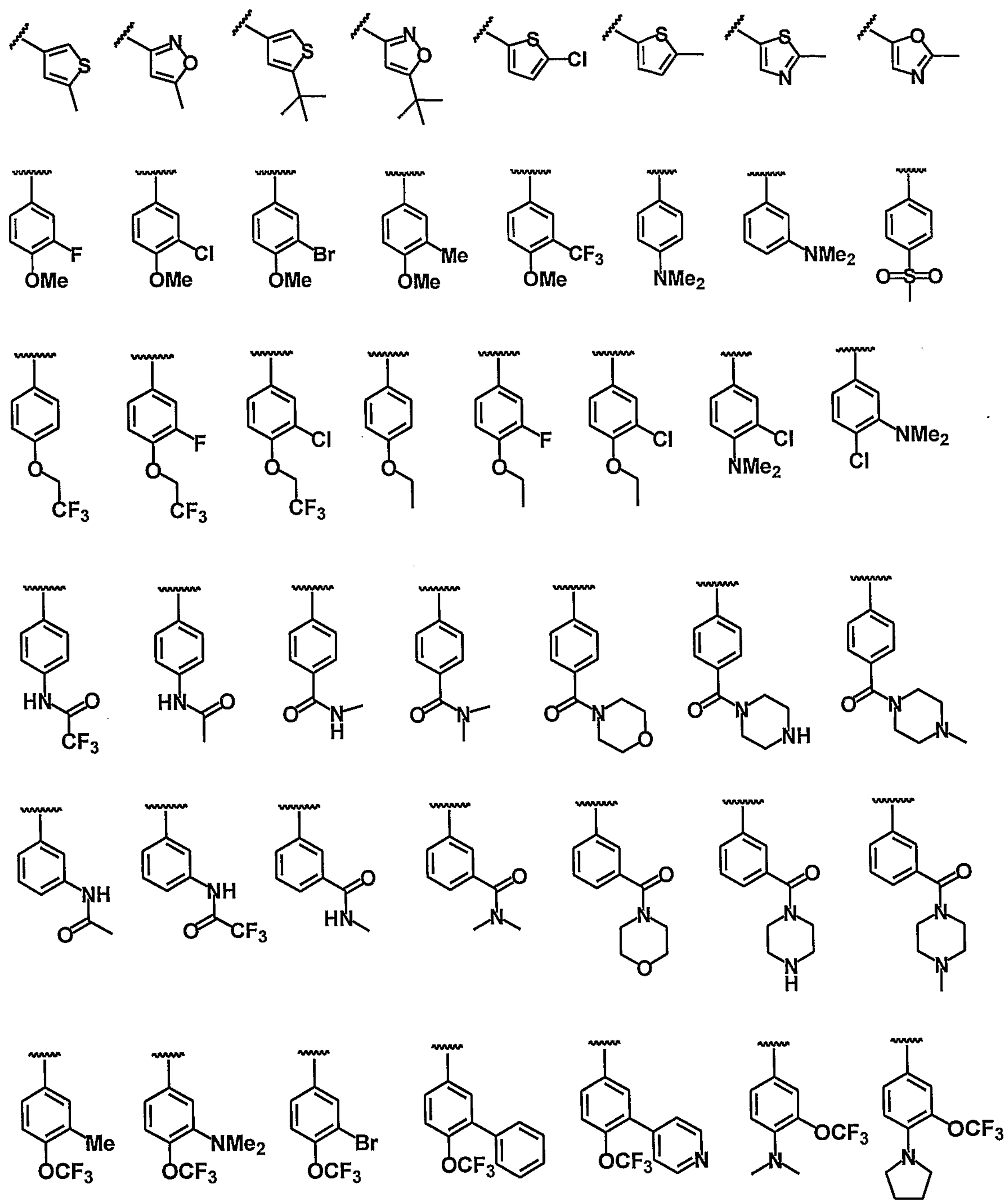







































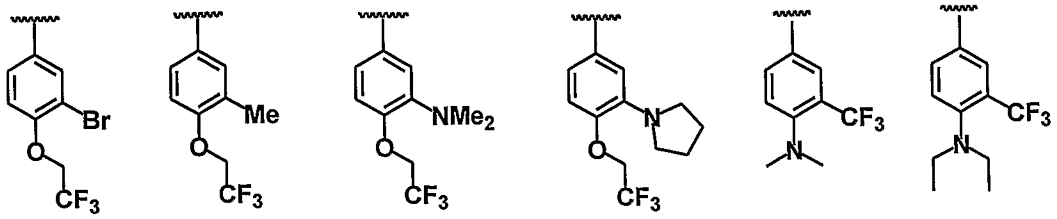


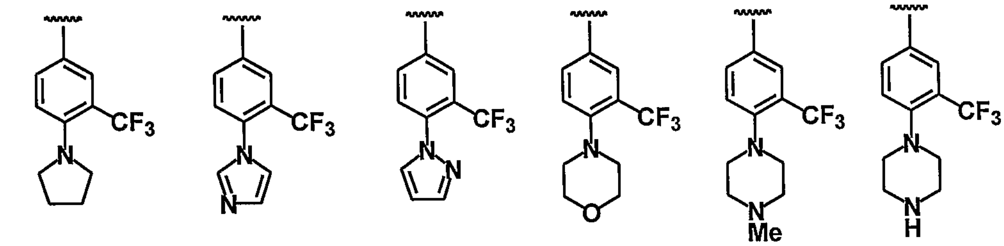
where n can be an integer selected from a group consisting of 0, 1, 2, and 3.

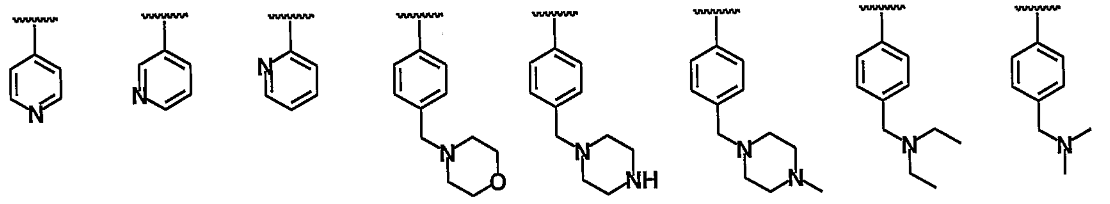
[0088] Some particular non-limiting examples of the substituent R_3 that can be used in compounds having the structure (B) include *tert*-butyl phenyl, trifluoromethoxyphenyl, methoxyphenyl, dimethylaminophenyl, aminophenyl, trifluoroethoxyphenyl, trifluoromethoxychlorophenyl, trifluoromethoxybromophenyl, trifluoroethoxychlorophenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchlorophenyl, chlorotoluyl, N-phenylacetamide, N,N-alkyl-benzamide, isopropoxyphenyl, alkoxyphenyl, dialkoxyphenyl, and acetylphenyl. These and yet other moieties that can be used as the substituent R_3 can be illustrated as follows:

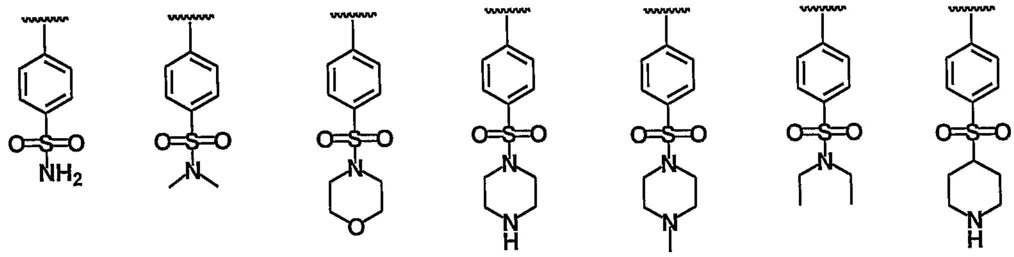


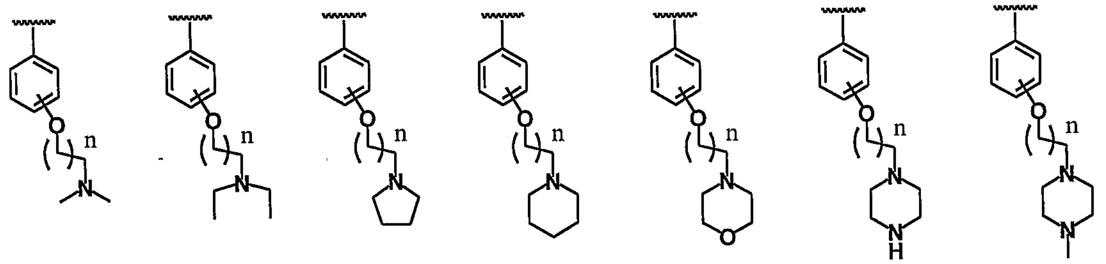


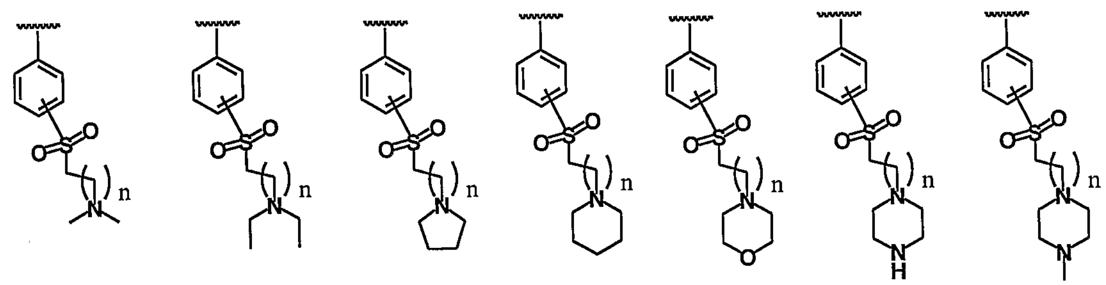


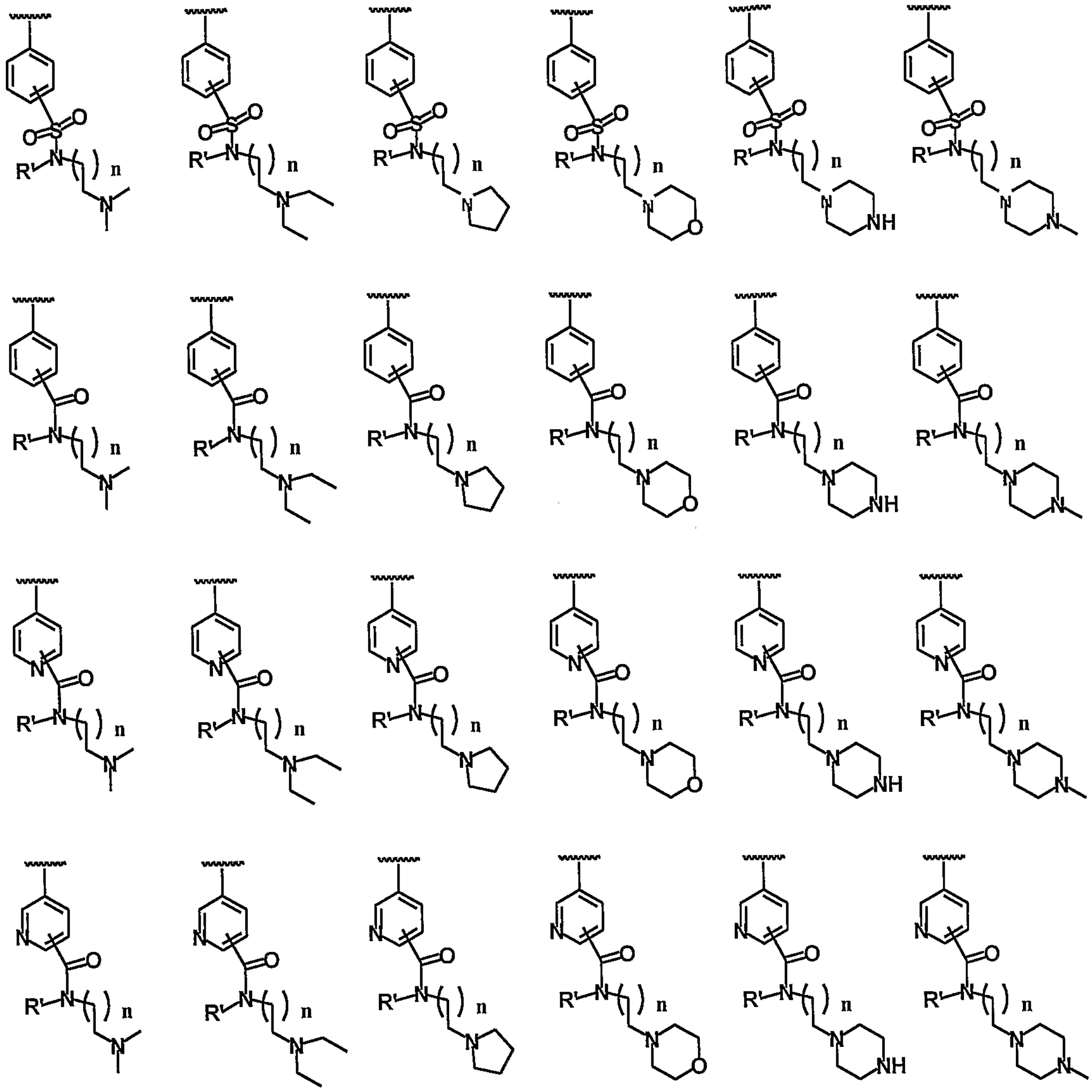






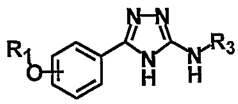




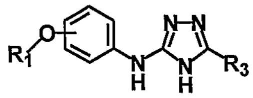


where n can be an integer selected from a group consisting of 0, 1, 2, and 3, and R′ is hydrogen, a C_1-C_{18} alkyl, or a substituted C_1-C_{18} alkyl.

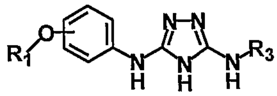
[0089] Some general examples of compounds described by the general structure (B) include a compound having the general structures (V)-(XXVIII):



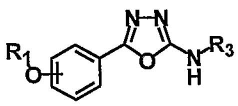
V



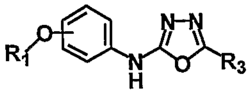
VI



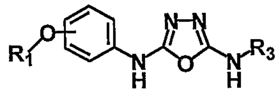
VII



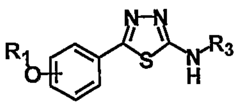
VIII



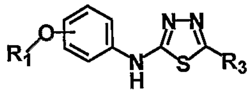
IX



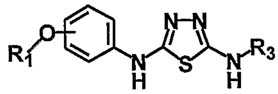
X



XI



XII



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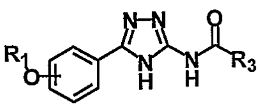

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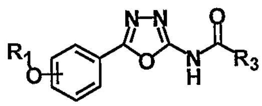

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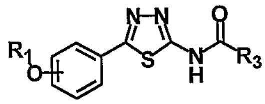

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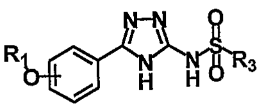

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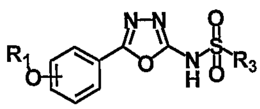

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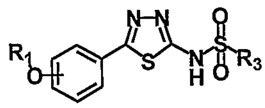

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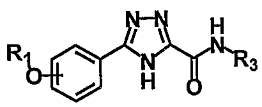
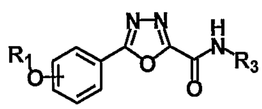
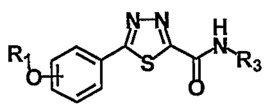


XX



XXI



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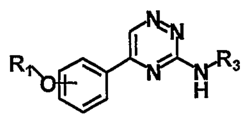
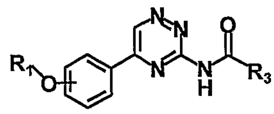
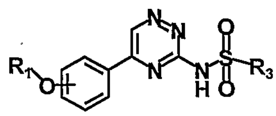


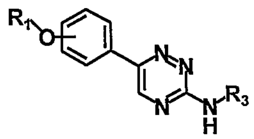
XXIII



XXIV



XXV



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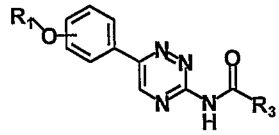
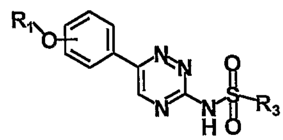
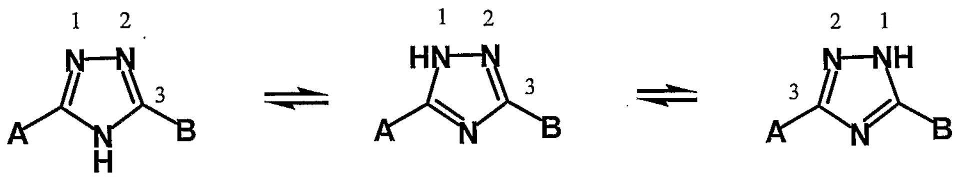


XXVII



XXVIII

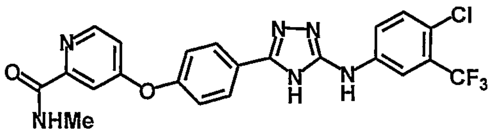
[0090] In the case of 1,2,4-triazoles, there exist three tautomeric structures, as shown below:



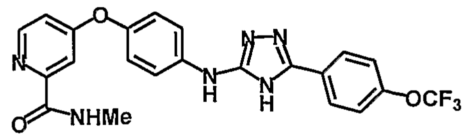
4*H*-1,2,4-triazole **1*H*-1,2,4-triazole** **1*H*-1,2,4-triazole**

[0091] Which tautomeric structure is prevailing depends on the substituents on the triazole moiety and on the reaction conditions. As known to those having ordinary skill in the art, typically, 1*H*-1,2,4-triazole is the most common tautomeric form, especially if an amino substituent is attached to the ring. Even though all three tautomeric structures can be present, all the generic structures and all the examples having 1,2,4-triazole moiety are shown herein in one tautomeric form, such as 4*H*-1,2,4-triazole, for simplicity and for the comparison with its direct analogues, such as examples containing 1,3,4-oxadiazole moiety. Using only 4*H*-tautomeric form to draw the structures for the sake of simplicity, does not imply that the compounds of the examples (30)-(74) shown below exist in that particular tautomeric form.

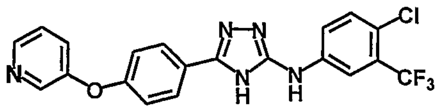
[0092] Some examples of particular compounds described by the general structure (B) include compounds having formulae (34)-(83):



(34)



(35)



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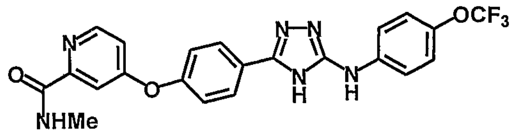

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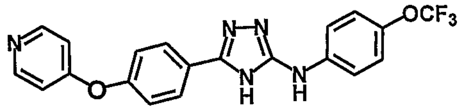

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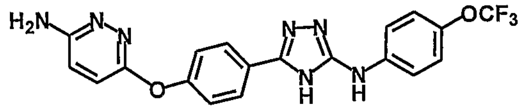

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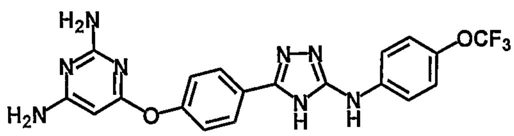

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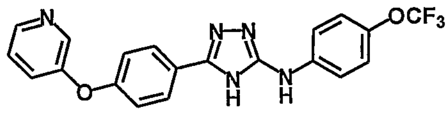

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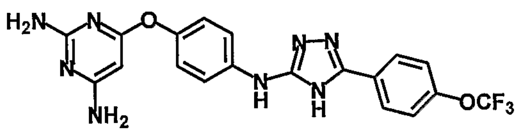

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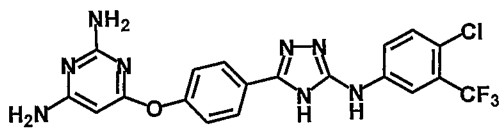

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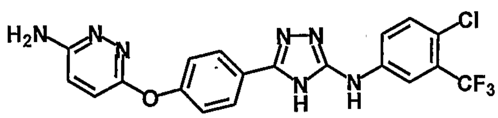

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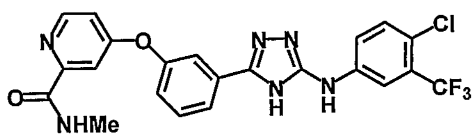

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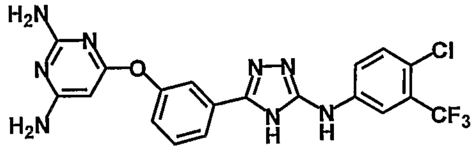

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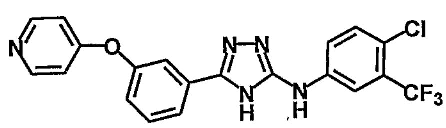

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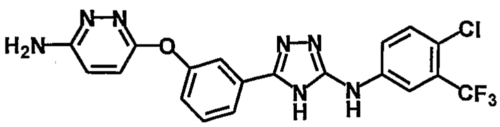

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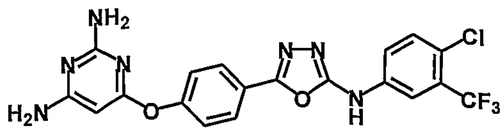

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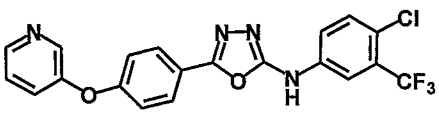

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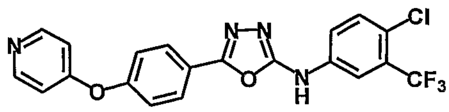

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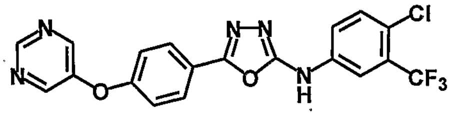

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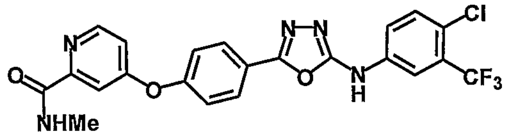

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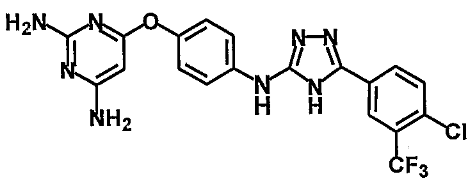

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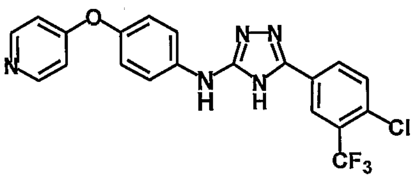

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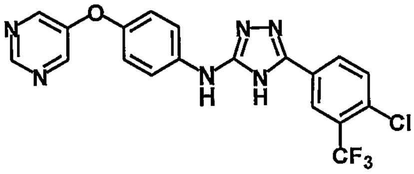

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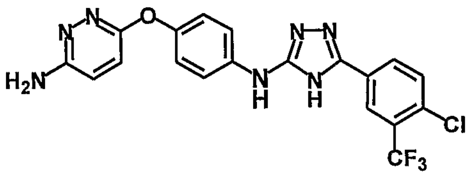

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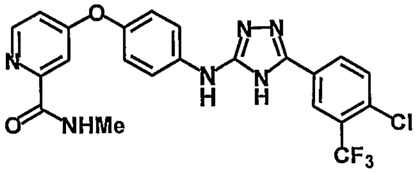

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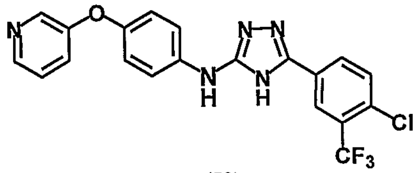

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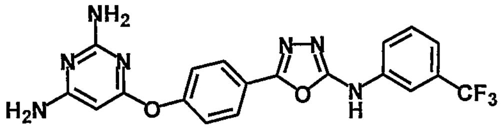

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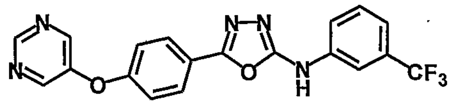

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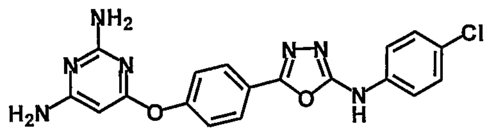

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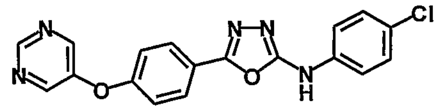

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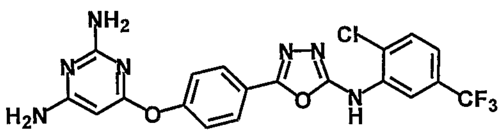

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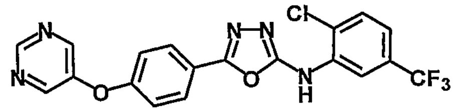

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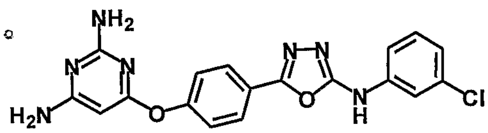

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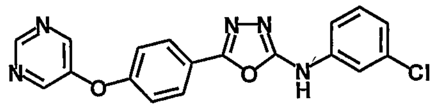

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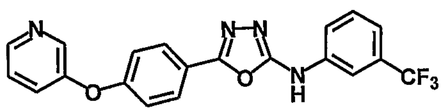

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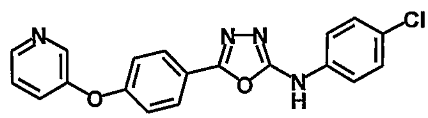

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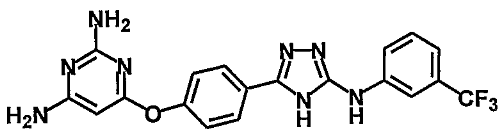

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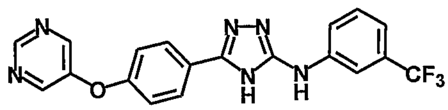

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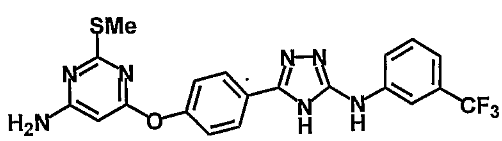

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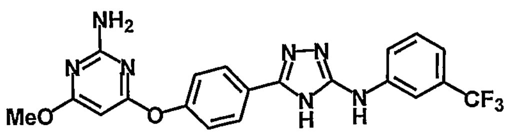

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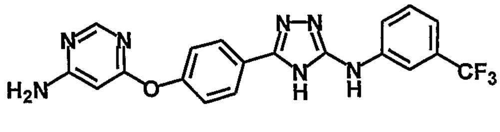

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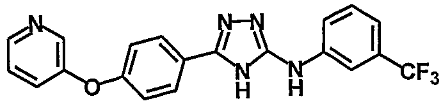

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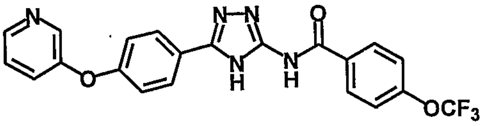

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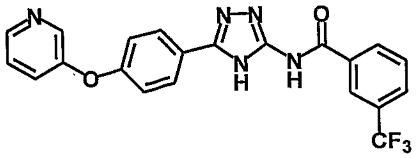

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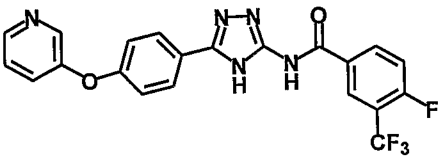

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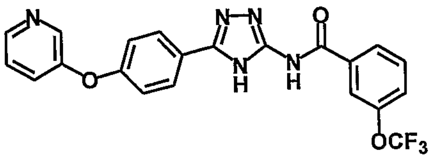

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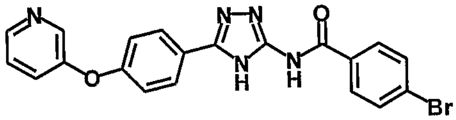

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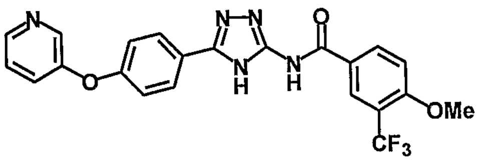

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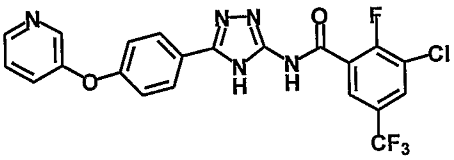

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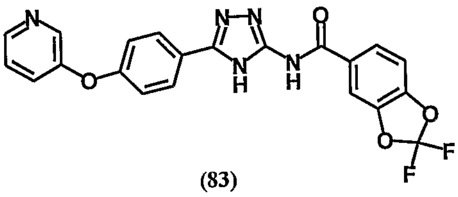
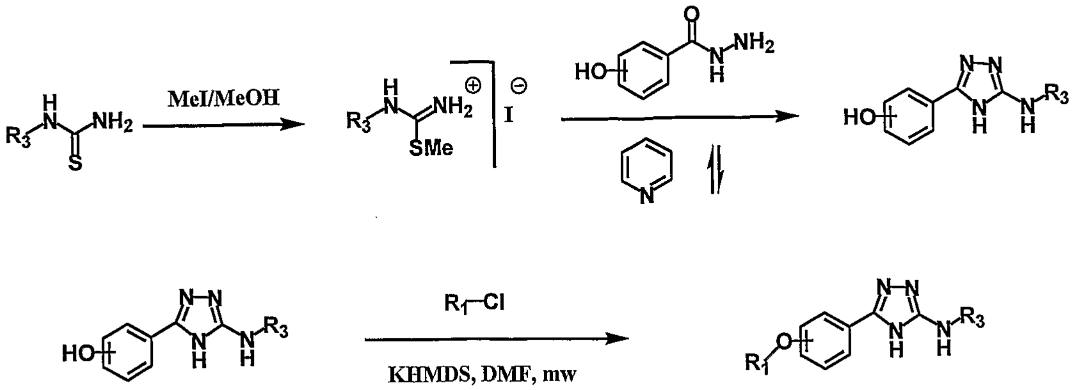
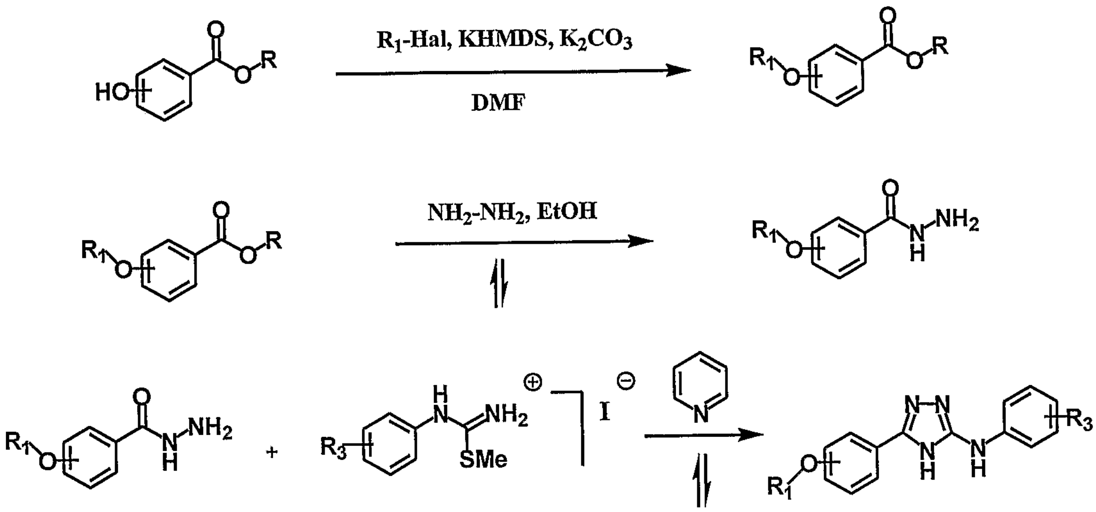


(83)

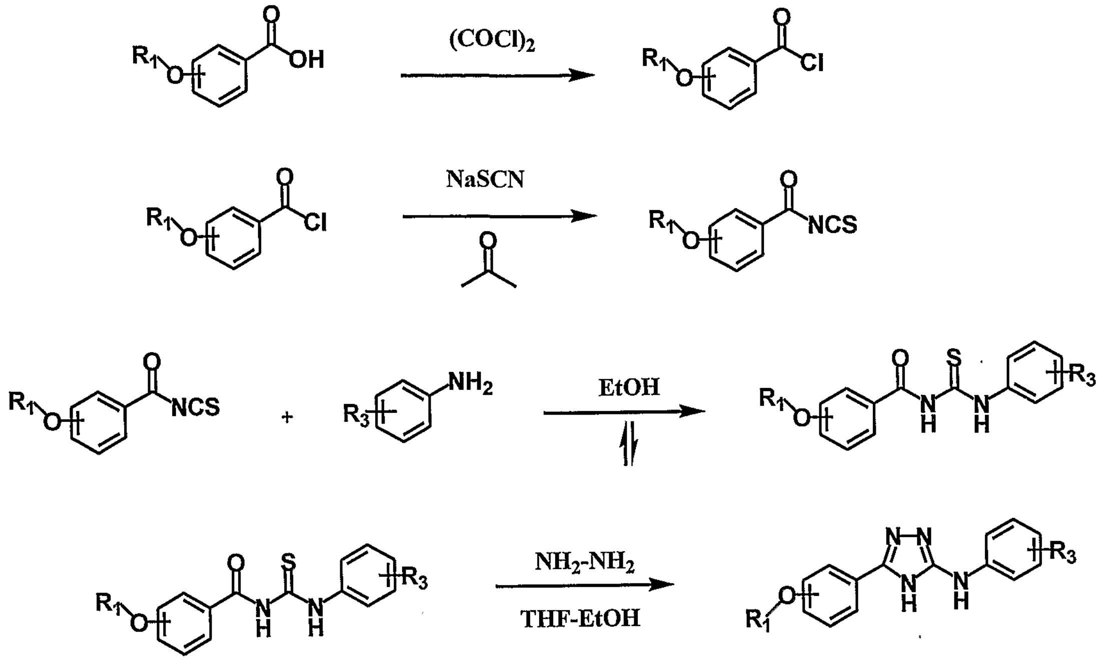
[0093] Appropriately substituted 1,2,4-triazoles of the type (V) described above and illustrated by the general structure (B) can be synthesized using one of several reaction schemes, for example as shown in Schemes V, VI and VII below. The appropriate method can be chosen based on the required substitution, availability of the starting materials and the ease of synthesis.



Scheme V

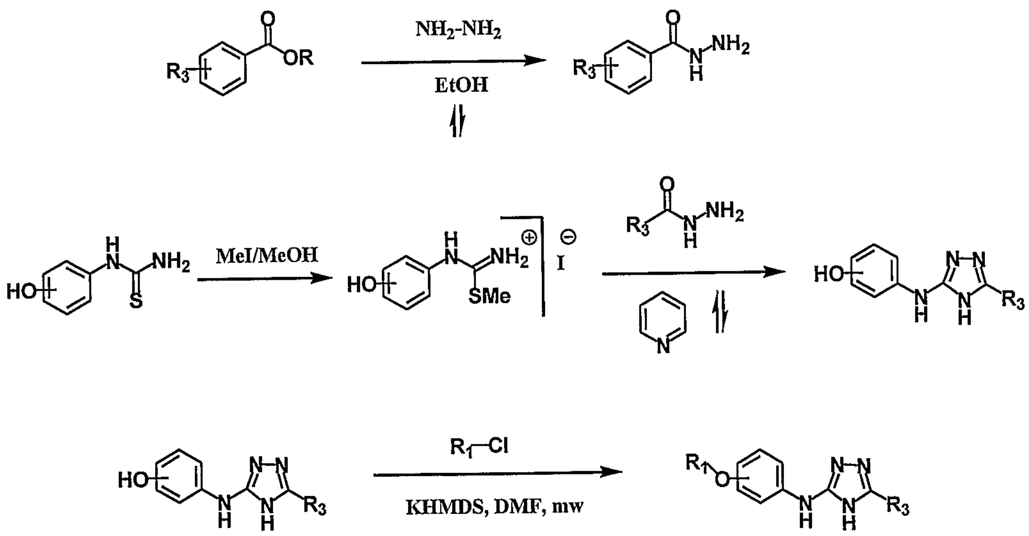


Scheme VI

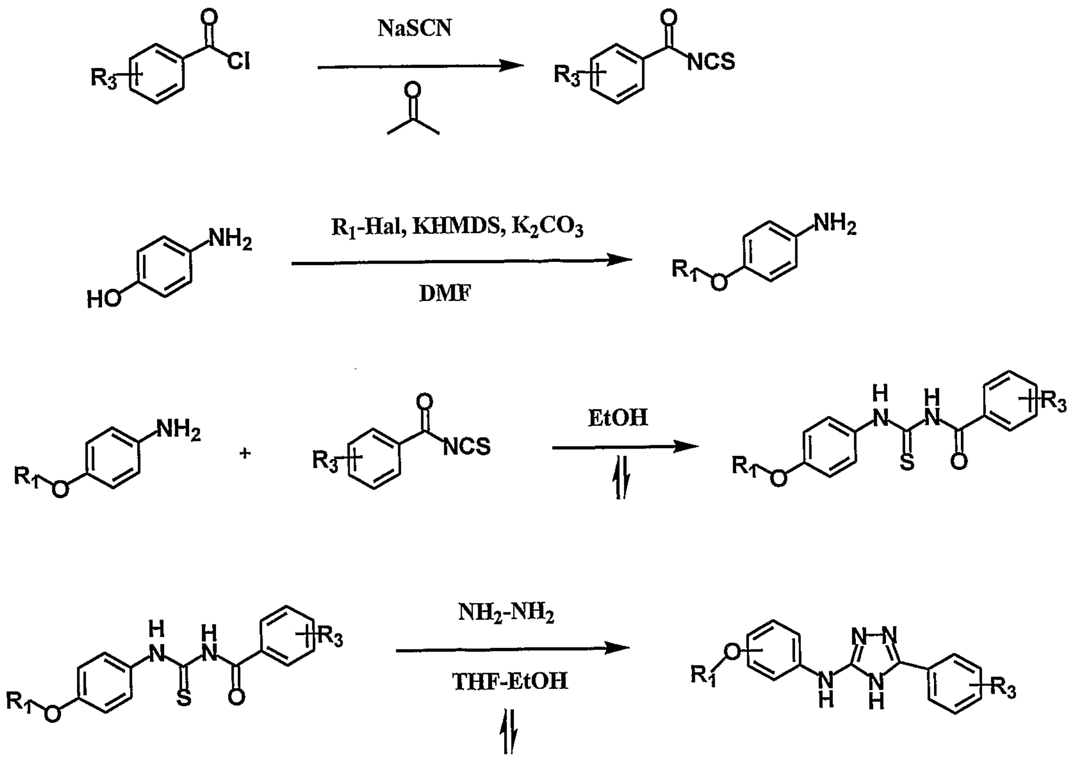


Scheme VII

[0094] 1,2,4-triazoles of the type (VI) described above, can be made as shown in Scheme VIII or by an alternative route as outlined in Scheme IX.

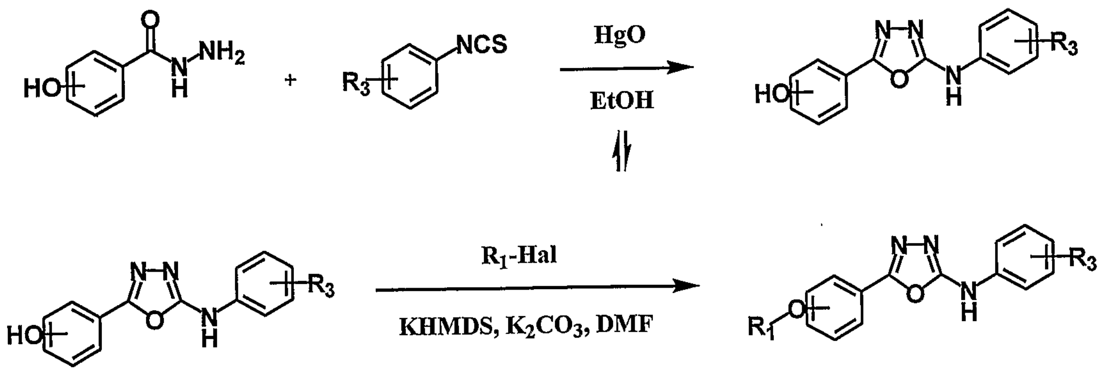


Scheme VIII

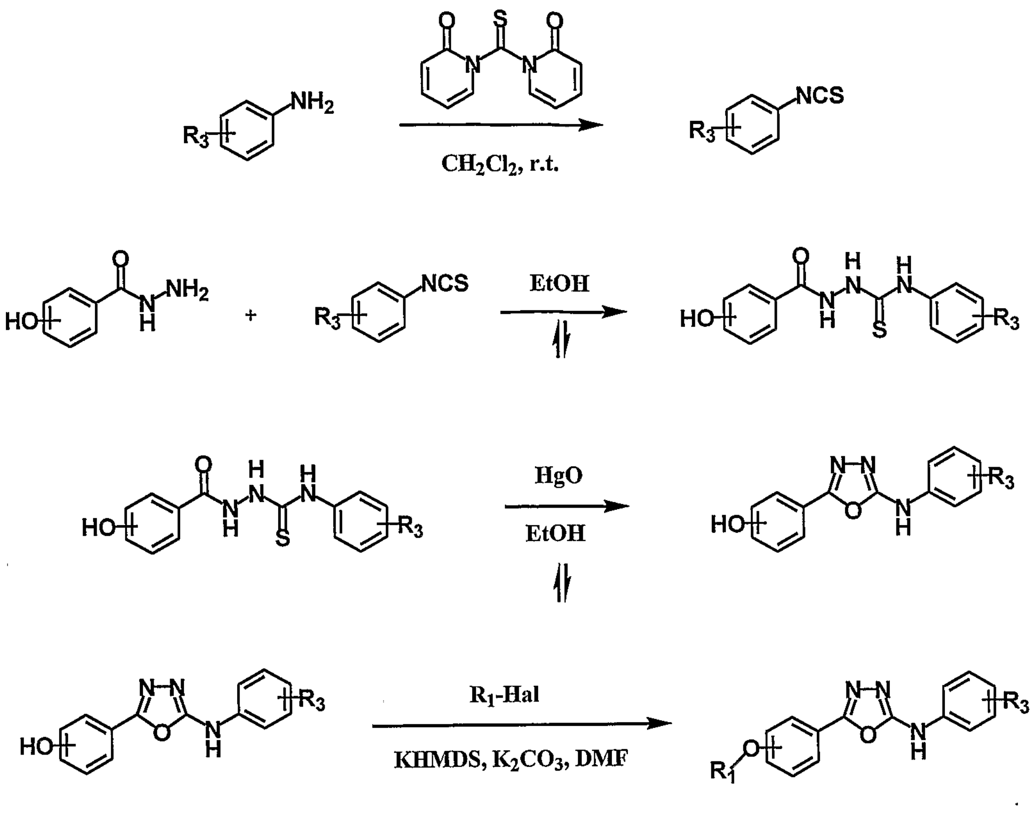


Scheme IX

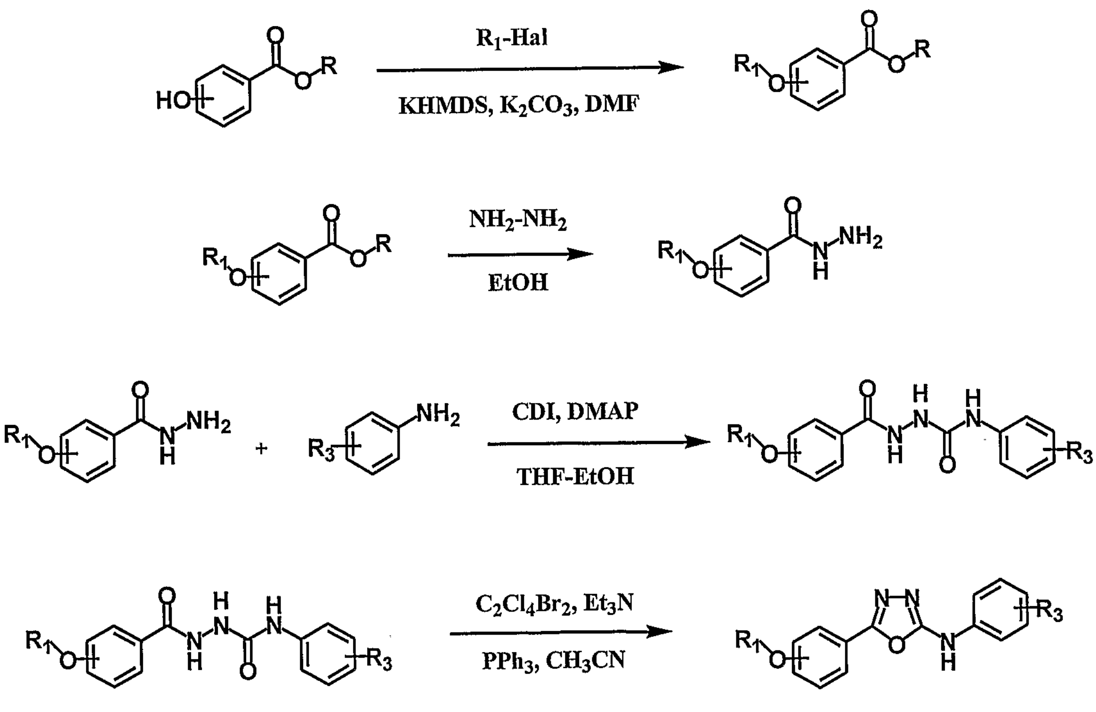
[0095] Appropriately substituted 2-amino-1,3,4-oxadoazoles of type (VIII), can be synthesized using one of several reaction schemes, for example, as shown by Schemes X, XI and XII.



Scheme X

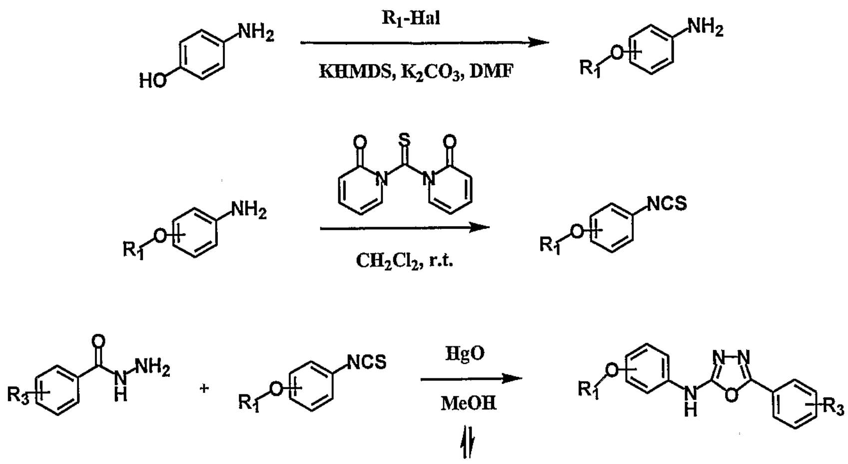


Scheme XI

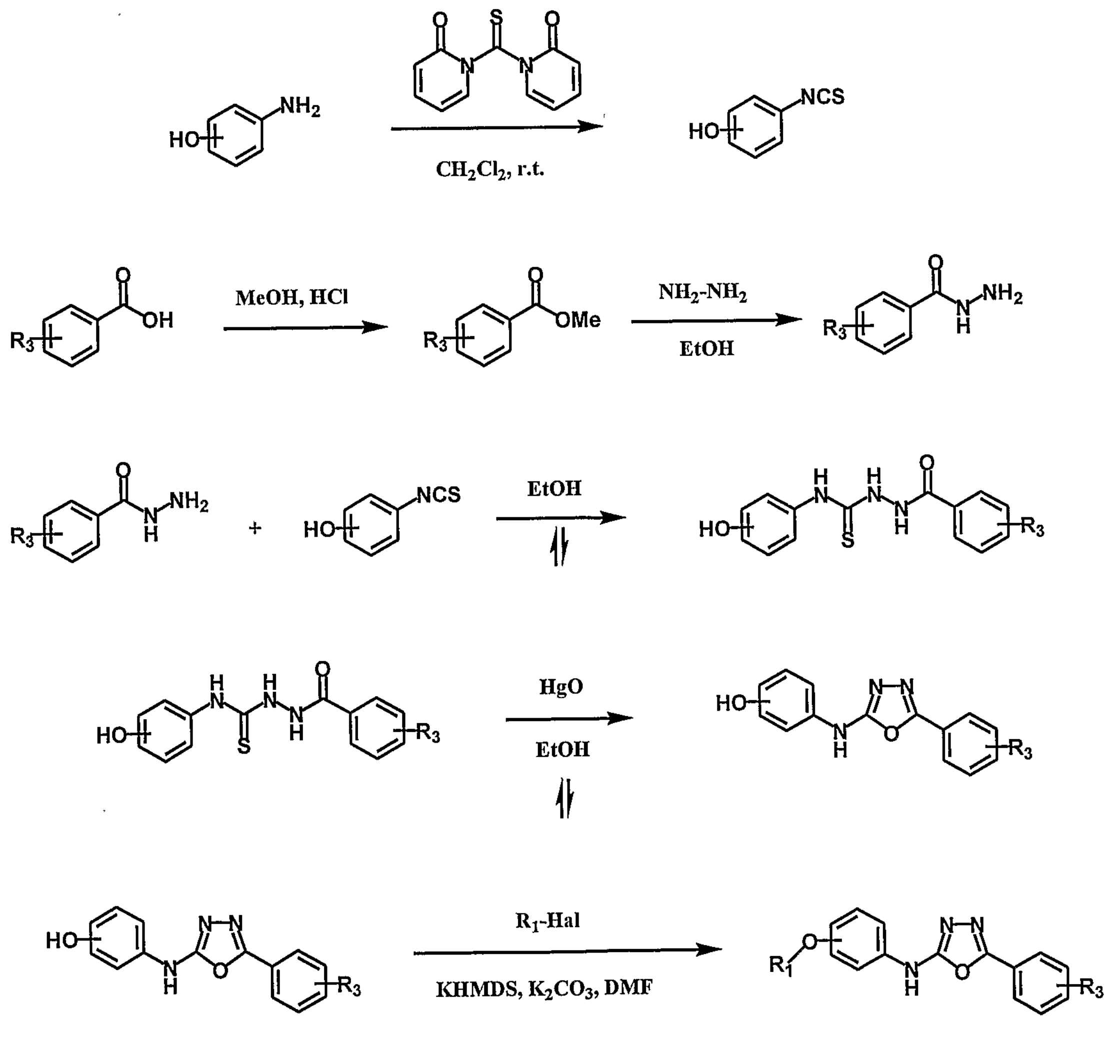


Scheme XII

[0096] Appropriately substituted 2-amino-1,3,4-oxadiazoles of type (IX), can be synthesized using one of several reaction schemes, for example, as shown by Schemes XIII and XIV.

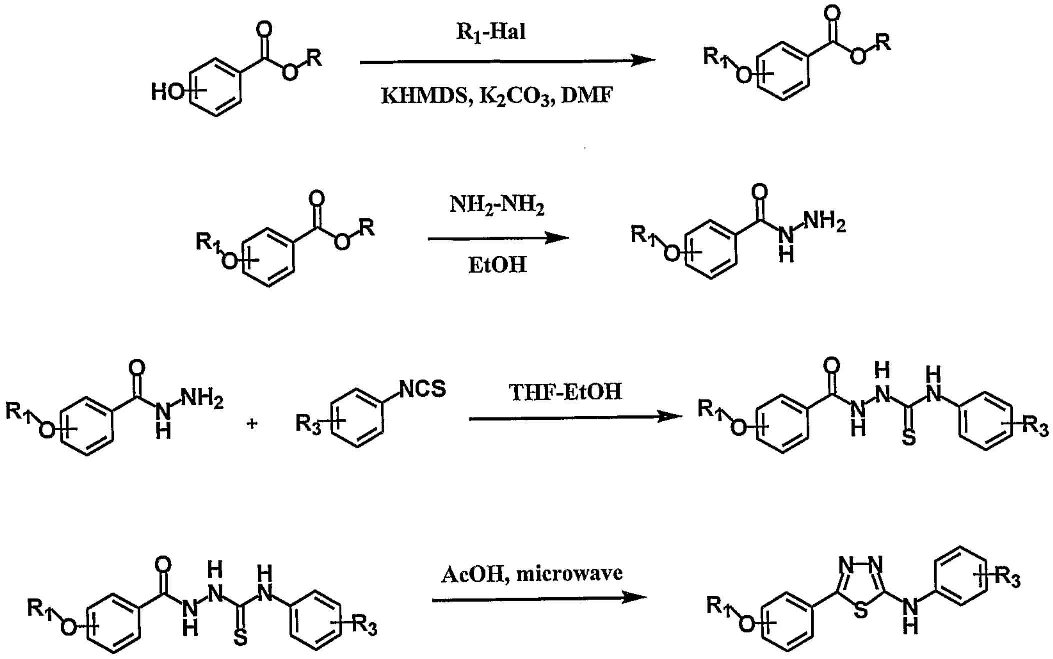


Scheme XIII



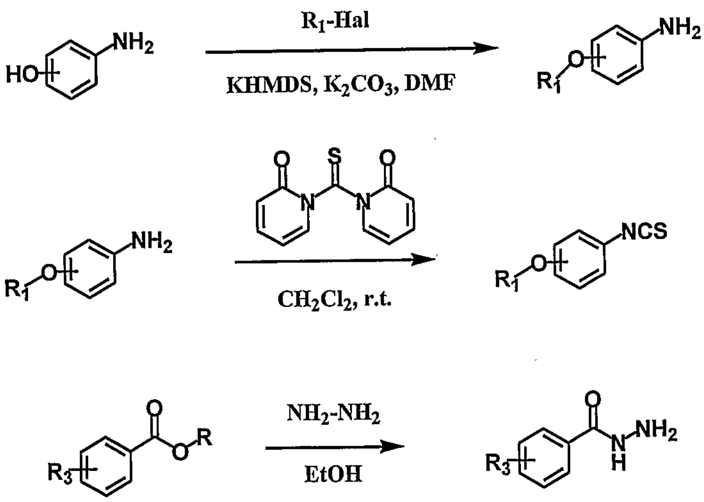
Scheme XIV

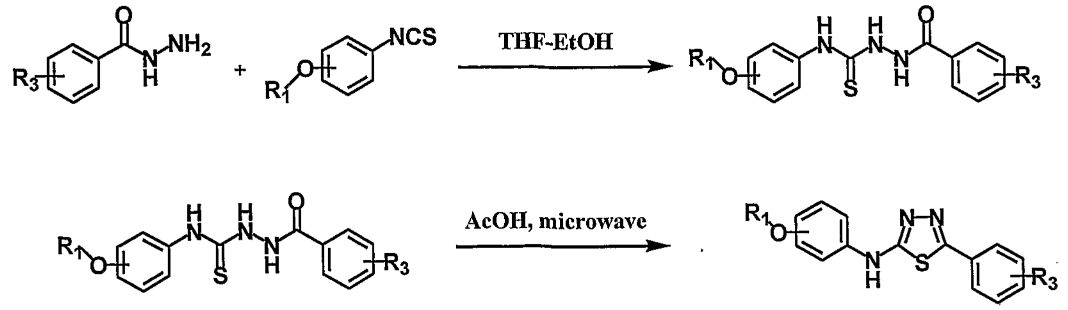
[0097] Appropriately substituted 2-amino-1,3,4-thiadiazoles of type (XI), can be prepared by a method which is outlined in Scheme XV.



Scheme XV

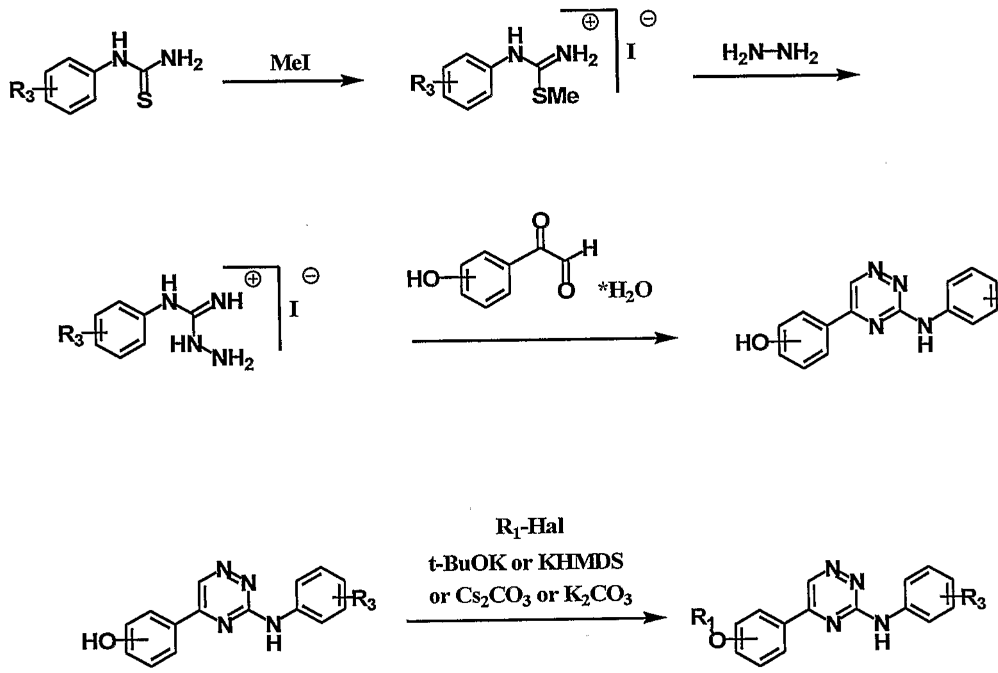
[0098] Appropriately substituted 2-amino-1,3,4-thiadiazoles of type (XII), can be prepared by a method which is outlined in Scheme XVI.



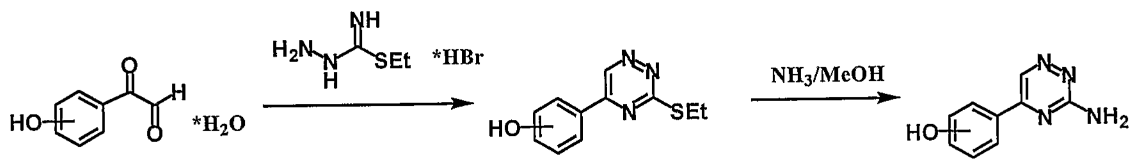


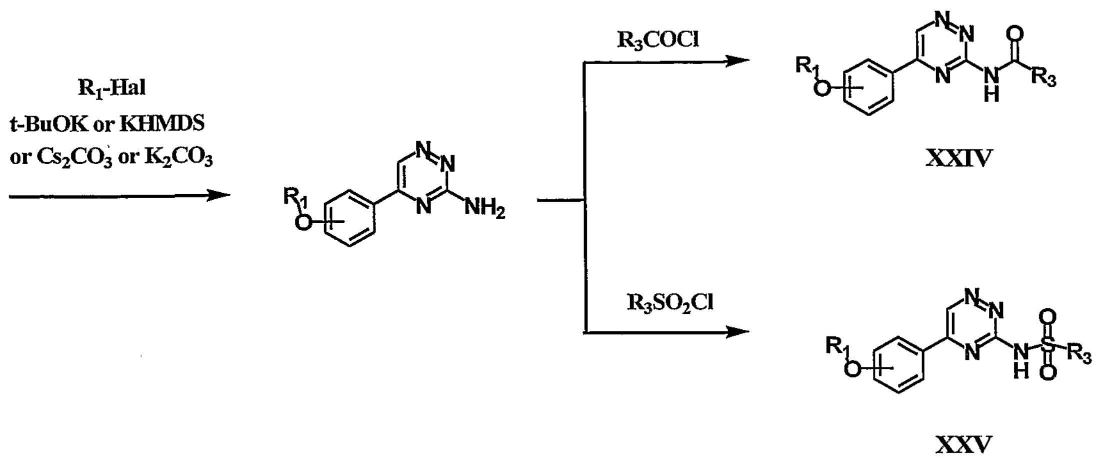
Scheme XVI

[0099] Appropriately substituted 3-amino-1,2,4-triazines of type (XXIII)-(XXV), can be prepared by a method which is outlined in Scheme XVII.



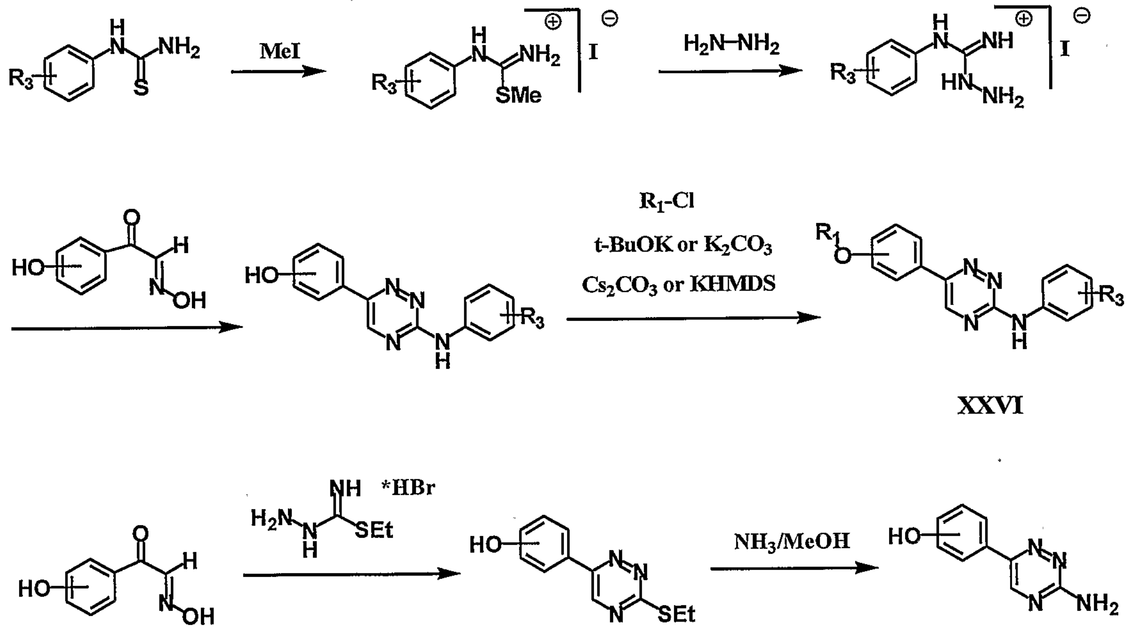
XXIII

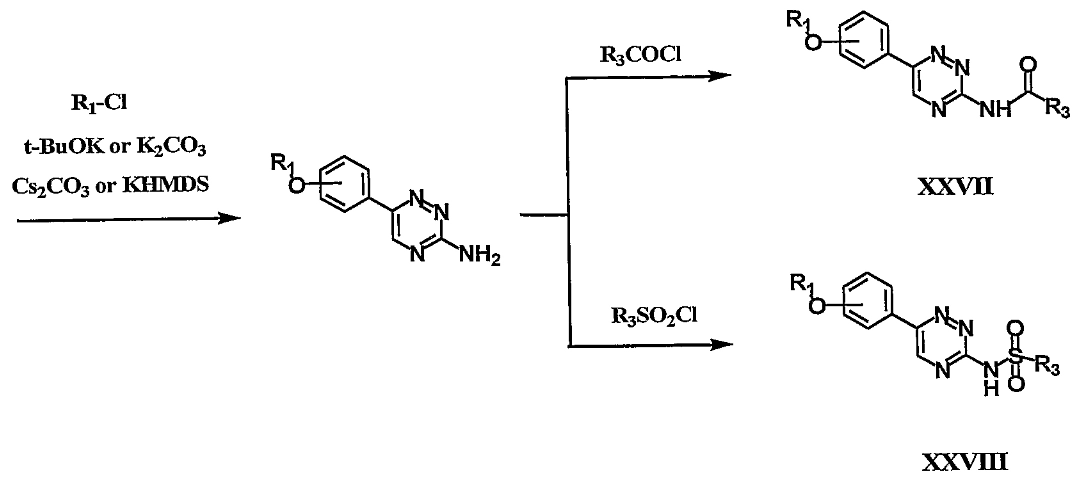




Scheme XVII

Appropriately substituted 3-amino-1,2,4-triazines of type (XXVI)-(XXVIII), can be prepared by a method which is outlined in Scheme XVIII.





Scheme XVIII

[0100] The compounds and methods of the present invention, either when administered alone or in combination with other agents (e.g., chemotherapeutic agents or protein therapeutic agents described below) are useful in treating a variety of disorders, including, but not limited to, for example, cancer, eye disease, inflammation, psoriasis, and a viral infection. The kinds of cancer that can be treated include, but are not limited to, an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

[0101] Embodiments of the present invention also provide articles of manufacture that can include a packaging material and a pharmaceutical composition contained within the packaging material. The packaging material can comprise a label which indicates that the pharmaceutical composition can be used for treatment of one or more disorders identified above.

[0102] The pharmaceutical composition can include a compound according to the present invention. In addition to a compound of the present invention, the pharmaceutical may also contain other therapeutic agents, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques known in the art of pharmaceutical formulation.

[0103] Thus, in one embodiment, the invention provides a pharmaceutical composition including a therapeutic agent and a compound of the invention. The compound is present in a concentration effective to treat cancer.

[0104] The compounds of the invention may be formulated into therapeutic compositions as natural or salt forms. Pharmaceutically acceptable non-toxic salts include the base addition salts (formed with free carboxyl or other anionic groups) which may be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino-ethanol, histidine, procaine, and the like. Such salts may also be formed as acid addition salts with any free cationic groups and will generally be formed with inorganic acids such as, for example, hydrochloric, sulfuric, or phosphoric acids, or organic acids such as acetic, citric, p-toluenesulfonic, methanesulfonic acid, oxalic, tartaric, mandelic, and the like.

[0105] Salts of the invention can include amine salts formed by the protonation of an amino group with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like. Salts of the invention can also include amine salts formed by the protonation of an amino group with suitable organic acids, such as p-toluenesulfonic acid, acetic acid, methanesulfonic acid and the like. Additional excipients which are contemplated for use in the practice of the present invention are those available to those of ordinary skill in the art, for example, those found in the United States Pharmacopeia Vol. XXII and National Formulary Vol. XVII, U.S. Pharmacopeia Convention, Inc., Rockville, MD (1989), the relevant contents of which is incorporated herein by reference. In addition, polymorphs of the invention compounds are included in the present invention.

[0106] Pharmaceutical compositions of the invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, intrathecal, or intracisternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally.

[0107] In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

[0108] The pharmaceutical compositions for the administration of the compounds of this embodiment, either alone or in combination with other therapeutic agents, may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

[0109] Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for control release.

[0110] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0111] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. Also useful as a solubilizer is polyethylene glycol, for example. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0112] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0113] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0114] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0115] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a parenterally-acceptable diluent or solvent or cosolvent or complexing agent or dispersing agent or excipient or combination thereof, for example 1,3-butanediol, polyethylene glycols, polypropylene glycols, ethanol or other alcohols, povidones, various brands of TWEEN surfactant, sodium dodecyl sulfate, sodium deoxycholate, dimethylacetamide, polysorbates, poloxamers, cyclodextrins, lipids, and excipients such as inorganic salts (e.g., sodium chloride), buffering agents (e.g., sodium citrate, sodium phosphate), and sugars (e.g., saccharose and dextrose). Among the acceptable vehicles and solvents that may be employed are water, dextrose solutions, Ringer's solutions and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0116] Depending on the condition being treated, these pharmaceutical compositions may be formulated and administered systemically or locally. Techniques for formulation and administration may be found in the latest edition of "Remington's Pharmaceutical Sciences" (Mack Publishing Co, Easton Pa.). Suitable routes may, for example, include oral or transmucosal administration; as well as parenteral delivery, including intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal administration. For injection, the pharmaceutical compositions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. For tissue or cellular administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0117] The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0118] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles).

[0119] In one embodiment, the invention compounds are administered in combination with an anti-inflammatory agent, antihistamines, chemotherapeutic agent, immunomodulator, therapeutic antibody or a protein kinase inhibitor, e.g., a tyrosine kinase inhibitor, to a subject in need of such treatment. While not wanting to be limiting, chemotherapeutic agents include antimetabolites, such as methotrexate, DNA cross-linking agents, such as cisplatin/carboplatin; alkylating agents, such as canbusil; topoisomerase I inhibitors such as dactinomicin; microtubule inhibitors such as taxol (paclitaxol), and the like. Other chemotherapeutic agents include, for example, a vinca alkaloid, mitomycin-type antibiotic, bleomycin-type antibiotic, antifolate, colchicine, demecoline, etoposide, taxane, anthracycline antibiotic, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-dimethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate, adriamycin-14-naphthaleneacetate, amsacrine, carmustine, cyclophosphamide, cytarabine, etoposide, lovastatin, melphalan, topetecan, oxalaplatin, chlorambucil, methtrexate, lomustine, thioguanine, asparaginase, vinblastine, vindesine, tamoxifen, or mechlorethamine. While not wanting to be limiting, therapeutic antibodies include antibodies directed against the HER2 protein, such as trastuzumab; antibodies directed against growth factors or growth factor receptors, such as bevacizumab, which targets vascular endothelial growth factor, and OSI-774, which targets epidermal growth factor; antibodies targeting integrin receptors, such as Vitaxin (also known as MEDI-522), and the like. Classes of anticancer agents suitable for use in compositions and methods of the present invention include, but are not limited to: 1) alkaloids, including, microtubule inhibitors (e.g., Vincristine, Vinblastine, and Vindesine, etc.), microtubule stabilizers (e.g., Paclitaxel [Taxol], and Docetaxel, Taxotere, etc.), and chromatin function inhibitors, including, topoisomerase inhibitors, such as, epipodophyllotoxins (e.g., Etoposide [VP-16], and Teniposide [VM-26], etc.), and agents that target topoisomerase I (e.g., Camptothecin and Isirinotecan [CPT-11], etc.); 2) covalent DNA-binding agents [alkylating agents], including, nitrogen mustards (e.g., Mechlorethamine, Chlorambucil, Cyclophosphamide, Ifosphamide, and Busulfan [Myleran], etc.), nitrosoureas (e.g., Carmustine, Lomustine, and Semustine, etc.), and other alkylating agents (e.g., Dacarbazine, Hydroxymethylmelamine, Thiotepa, and Mitocycin, etc.); 3) noncovalent DNA-binding agents [antitumor antibiotics], including, nucleic acid inhibitors (e.g., Dactinomycin [Actinomycin D], etc.), anthracyclines (e.g., Daunorubicin [Daunomycin, and Cerubidine], Doxorubicin [Adriamycin], and Idarubicin [Idamycin], etc.), anthracenediones (e.g., anthracycline analogues, such as, [Mitoxantrone], etc.), bleomycins (Blenoxane), etc., and plicamycin (Mithramycin), etc.; 4) antimetabolites, including, antifolates (e.g., Methotrexate, Folex, and Mexate, etc.), purine antimetabolites (e.g., 6-Mercaptopurine [6-MP, Purinethol], 6-Thioguanine [6-TG], Azathioprine, Acyclovir, Ganciclovir, Chlorodeoxyadenosine, 2-Chlorodeoxyadenosine [CdA], and 2'-Deoxycoformycin [Pentostatin], etc.), pyrimidine antagonists (e.g., fluoropyrimidines [e.g., 5-fluorouracil (Adrucil), 5-fluorodeoxyuridine (FdUrd) (Floxuridine)] etc.), and cytosine arabinosides (e.g., Cytosar [ara-C] and Fludarabine, etc.); 5) enzymes, including, L-asparaginase; 6) hormones, including, glucocorticoids, such as, antiestrogens (e.g., Tamoxifen, etc.), nonsteroidal antiandrogens (e.g., Flutamide, etc.), and aromatase inhibitors (e.g., anastrozole [Arimidex], etc.); 7) platinum compounds (e.g., Cisplatin and Carboplatin, etc.); 8) monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides, etc.; 9) biological response modifiers (e.g., interferons [e.g., IFN-.alpha., etc.] and interleukins [e.g., IL-2, etc.], etc.); 10) adoptive immunotherapy; 11) hematopoietic growth factors; 12) agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid, etc.); 13) gene therapy techniques; 14) antisense therapy techniques; 15) tumor vaccines; 16) therapies directed against tumor metastases (e.g., Batimistat, etc.); and 17) inhibitors of angiogenesis.

[0120] The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions. Examples of other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG CoA reductase inhibitors (lovastatin and simvastatin), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and cyclooxygenase inhibitors such as rofecoxib, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF-a inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

[0121] Other agents that may be administered in combination with invention compounds include protein therapeutic agents such as cytokines, immunomodulatory agents and antibodies. As used herein the term “cytokine” encompasses chemokines, interleukins, lymphokines, monokines, colony stimulating factors, and receptor associated proteins, and functional fragments thereof. As used herein, the term "functional fragment" refers to a polypeptide or peptide which possesses biological function or activity that is identified through a defined functional assay.

[0122] The cytokines include endothelial monocyte activating polypeptide II (EMAP-II), granulocyte-macrophage-CSF (GM-CSF), granulocyte-CSF (G-CSF), macrophage-CSF (M-CSF), IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-12, and IL-13, interferons, and the like and which is associated with a particular biologic, morphologic, or phenotypic alteration in a cell or cell mechanism.

[0123] When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one having ordinary skill in the art.

[0124] In the treatment or prevention of conditions which involve cellular proliferation, an appropriate dosage level can generally be between about 0.01 and about 1000 mg per 1 kg of patient body weight per day which can be administered in single or multiple doses. For example, the dosage level can be between about 0.01 and about 250 mg/kg per day; more narrowly, between about 0.5 and about 100 mg/kg per day. A suitable dosage level can be between about 0.01 and about 250 mg/kg per day, between about 0.05 and about 100 mg/kg per day, or between about 0.1 and about 50 mg/kg per day, or about 1.0 mg/kg per day. For example, within this range the dosage can be between about 0.05 and about 0.5 mg/kg per day, or between about 0.5 and about 5 mg/kg per day, or between about 5 and about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing between about 1.0 and about 1,000 mg of the active ingredient, for example, about 1.0, about 5.0, about 10.0, about 15.0, about 20.0, about 25.0, about 50.0, about 75.0, about 100.0, about 150.0, about 200.0, about 250.0, about 300.0, about 400.0, about 500.0, about 600.0, about 750.0, about 800.0, about 900.0, and about 1,000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, such as once or twice per day. There may be a period of no administration followed by another regimen of administration.

[0125] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0126] Compounds of the present invention can be used, alone or in combination with an effective amount of a therapeutic antibody or chemically attached to a tumor tissue targeting antibody (or therapeutic fragment thereof), a chemotherapeutic or an immunotoxic agent, for treatment of tumors. Illustrative examples of chemotherapeutic agents that can be used for this purpose include doxorubicin, docetaxel, or taxol. It should be further understood that the invention includes combination therapy including a compound of the invention, including but not limited to vasculostatic agents, such as tyrosine, serine or threonine kinase inhibitors, for example, Src-family inhibitors, and any chemotherapeutic agent or therapeutic antibody.

[0127] The present invention also provides screening assays using appropriate cells which express any kinases within the MAPK pathway. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. For example, cells which express the Raf polypeptide or any kinase downstream of Raf such as MEK or ERK1/2 or respond to Raf polypeptide or MAPK pathway polypeptides are contacted with a test compound to observe binding, or stimulation or inhibition of a functional response. The cells which are contacted with the candidate compound are compared with the same cells which are not contacted for Raf polypeptide or MAPK pathway polypeptide activity

[0128] This invention contemplates the treatment and/or amelioration of such diseases by administering a MAPK pathway polypeptides inhibiting amount of a compound. Without wishing to be bound by any particular theory of the functioning of the MAPK pathway polypeptides, it is believed that among the useful inhibitors of MAPK pathway polypeptides function are those compounds which inhibit the kinase activity of the MAPK pathway polypeptides. Other sites of inhibition are, of course, possible owing to its position in a signal transduction cascade. Inhibitors of protein-protein interactions between, for example Raf polypeptide or MAPK pathway polypeptides and other factors could lead to the development of pharmaceutical agents for the modulation of Raf polypeptide or MAPK pathway polypeptides activity.

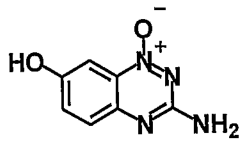
[0129] Targeting an allosteric site of the protein is a very promising approach for pharmaceutical intervention. Further, the traditional approach of inhibiting various protein kinases includes targeting the ATP binding site. The invention is not meant to be limited by any particular mechanism of inhibition. The assays of the invention may test binding of a candidate compound wherein adherence to the cells bearing the Raf polypeptide or MAPK pathway polypeptides is detected by means of a label directly or indirectly associated with the candidate compound or in an assay involving competition with a labeled competitor. Further, these assays may test whether the candidate compound results in a signal generated by activation of MAPK pathway polypeptides, using detection systems appropriate to the cells bearing the Raf polypeptide or MAPK pathway polypeptides. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Standard methods for conducting such screening assays are well understood in the art and are also illustrated in the examples below (e.g., direct and raf1-MEK1 assays or MAPK pathway cellular assays).

[0130] The following examples are provided to further illustrate the advantages and features of the present invention, but are not intended to limit the scope of the invention.

Example 1 --General Methods

[0131] Example 1 describes general synthetic procedures that were used to make the compounds described in the subsequent examples. All solvents were used without further purification. Reactions can be usually conducted without an inert gas atmosphere unless specified otherwise. The reported yields are based on unoptimized conditions and single test runs. The yields can be optimized by changing the reaction conditions, such as solvent, use of base or acid, temperature, use of catalyst and the time of the reaction. Microwave reactions were run in Emrys™ Process vials (2-5 mL) using Initiator module (Biotage/Personal chemistry). All ^{1}H NMR were run on a 500 MHz Bruker NMR or Bruker Avance 400 MHz NMR. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane. Coupling constants are reported in hertz (Hz). A Waters LC/MS system is used in identity and purity analysis. This system includes a 2795 separation module, a 996 photodiode array detector and a ZQ2000 mass spectrometer. A Zorbax SB column (150 x 4.6 mm 3.5μ, Agilent Technologies) was used for the LC. Column temperature was 40°C. Compounds were separated using gradient elution with mobile phases of water (0.05% TFA (A)) and acetonitrile (0.05% TFA (B)). Flow rate was 1mL/min. The gradient program used in separation was 0-15 min: 5-60 % B; 15-15.5 min: 60-100 % B; 15.5-17 min: 100 % B.

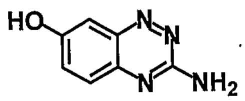
Example 2. Synthesis of 3-amino-benzo[1,2,4]triazine-7-ol-1-oxide



[0132] 7.7 g (0.05 mol) of 4-amino-3-nitrophenol was dissolved in 20 mL of glacial acetic acid and the resulting bright-red solution was heated to approximately 100°C in 500 mL round-bottom flask equipped with a long condenser. To this solution was added a solution of 16.81 g (8.0 equivalent, 0.4 mol) of cyanamide in 20 mL of concentrated hydrochloric acid. In approximately 5-10 min the reaction mixture started to boil vigorously, so the heating was removed and it was stirred without heating until boiling subsided. Then the heating was reapplied and the reaction mixture was refluxed for 48 hrs. Then 150 mL of 30 % NaOH was added and the resulting dark-reddish solution was refluxed for additional 3 hrs. Then it was cooled down to room temperature and dark-red slurry was formed. The red precipitate was filtered, re-dissolved in 200 mL of water and 1N HCl was added in portions with stirring until pH reached 5-4. The solution changed color from dark-red into light-yellow and a light-yellow fine precipitate was formed. The precipitate was filtered, washed twice with 50 mL of water, twice with 50 mL of acetonitrile and finally twice with 50 mL of diethyl ether and dried in vacuum to give 4.6 g of a bright-yellow solid. Yield: 51.7 %.

[0133] ^{1}H NMR (DMSO-d_6): δ 6.96 (s, 2H), 7.35-7.38 (m, 2H), 7.45-7.47 (m, 1H), 10.36 (s, 1H).

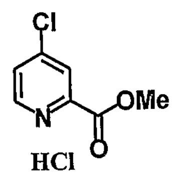
Example 3. Synthesis of 3-amino-benzo[1,2,4]triazine-7-ol



[0134] 4.6 g (25.82 mmol) of 3-amino-benzo[1,2,4]triazine-7-ol-1-oxide was dissolved in 200 mL of 1:1 mixture of dimethylformamide and methanol. 0.5 g of 10% Pd/C was added to this solution and H_2 gas was bubbled through the solution for 3 hours. The progress of the reaction was monitored by TLC, using a 9:1 mixture of dichloromethane/methanol as an eluent and a UV lamp. The starting material is highly fluorescent under UV, while the product is not. When the reaction was complete, the resulting dark solution was filtered through a short pad of silica gel and solvent was removed in vacuum to produce a dirty-brown solid. 40 mL of ethyl acetate and 40 mL of methanol were added to the solid and the resulting suspension was heated to reflux for about 10 min. Then the suspension was allowed to cool down to ambient temperature. The solid was collected by filtration, washed with 40 mL of ethyl acetate, 40 mL of diethyl ether and dried in vacuum to yield 3.2 g of the product in a form of a greenish solid. Yield: 76%.

[0135] ^{1}H NMR (DMSO-d_6): δ 7.18 (s, 1 H), 7.36 (d, J = 2.6 Hz, 1 H), 7.40-7.42 (dd, J_1 = 9.1 Hz, J_2 = 2.6 Hz, 1 H), 7.45-7.46 (d, J = 9.1 Hz, 1H).

Example 4. Synthesis of 4-chloro-pyridine-2-carboxylic acid methyl ester hydrochloride salt

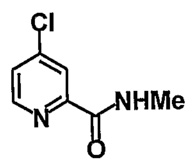


[0136] 2.4 mL (0.031 mol, 0.16 equivalent) of anhydrous N,N-dimethylformamide was added dropwise to 72 mL (1.23 mol, 5.0 equivalent) of thionyl chloride in a temperature range of 40-50°C under argon blanket. The solution was stirred at this temperature for 10 min, then 24.0 g (0.195 mol, 1.0 equivalent) of picolinic acid was added slowly in portions. The reaction mixture was heated at 70-75°C with a reflux condenser under argon for 30 hours. Evolution of SO_2 gas was observed. The reaction mixture changed colors from green to orange, then to purple over 2 hours, then resulted in an orange solution with a yellow precipitate. It was cooled down to ambient temperature and 150 mL of anhydrous toluene was added. The suspension was concentrated to about 50 mL total on rotovap. This process was repeated three times.

[0137] The resulting orange suspension was cooled down to – 20°C and 200 mL of methanol was added. The reaction mixture was left to stir at ambient temperature for 18 hours. Then the clear-yellow solution was transferred into a round-bottom flask and solvent was removed in vacuum. The resulting yellow solid was dissolved with heating to 50°C in 50 mL of methanol, upon cooling 300 mL of diethyl ether were added. The solution was left to stand at 0°C for 18 hours. The white precipitate that formed was collected by filtration, washed extensively with diethyl ether and dried in vacuum to yield 29.05 g of the product as a white fluffy solid. Yield: 71.5 %.

[0138] ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H), 7.81-7.83 (dd, J_1 = 1.9 Hz, J_2 = 5.4 Hz, 1H), 8.06-8.07 (d, J = 1.9 Hz, 1H), 8.68-8.69 (d, J = 5.4 Hz, 1H).

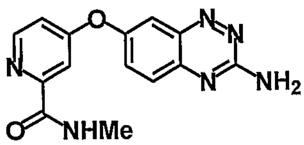
Example 5. Synthesis of 4-chloro-pyridine-2-carboxylic acid methyl amide



[0139] A suspension of 17.8 g (0.103 mol, 1 eq) of 4-chloro-pyridine-2-carboxylic acid methyl ester hydrochloride in 15 mL of methanol was cooled to 0°C and slowly treated with a 2.0 M solution of methylamine in tetrahydrofuran at a rate that kept internal temperature below 5°C. The reaction mixture was stirred at 0°C for 2 hours, then slowly allowed to warm up to ambient temperature and stirred for 18 hours. Solvent was removed in vacuum, approx. 200 mL of ethyl acetate was added and the resulting suspension was filtered. The precipitate was washed with 100 mL of ethyl acetate. The combined ethyl acetate solutions were washed three times with 100 mL of brine and dried over sodium sulfate. Solvent was removed in vacuum to yield 14.16 g of the product as orange oil. Yield: 80.5 %.

[0140] ^{1}H NMR (DMSO-d_6): δ 2.81-2.82 (d, J = 4.8 Hz, 3H), 7.73-7.75 (dd, J_1 = 2.1 Hz, J_2 = 5.4 Hz, 1H), 8.00-8.01 (d, J = 2.1 Hz, 1H), 8.60-8.61 (d, J = 5.4 Hz, 1H), 8.84 (q, J = 4.8 Hz, 1H).

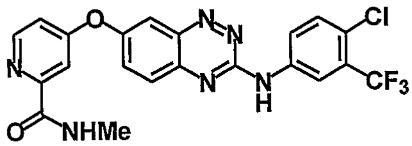
Example 6. Synthesis of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-2-carboxylic acid methylamide



[0141] 3.2 g (19.73 mmol) of 3-amino-benzo[1,2,4]triazine-7-ol was dissolved in 80 mL of anhydrous dimethylformamide under argon atmosphere. 2.44 g (21.71 mmol, 1.1 equivalent) of solid potassium *tert*-butoxide was added to the solution. The resulting dark-red mixture was heated to about 100°C and stirred at that temperature for 15 min. A solution of 3.7 g (21.71 mmol, 1.1 equivalent) of 4-chloro-pyridine-2-carboxylic acid methylamide in 10 mL of anhydrous dimethylformamide was added, followed by 3.28 g (23.68 mmol, 1.2 equivalent) of anhydrous K_2CO_3. The reaction mixture was heated at 140°C for 30 hrs. The progress of the reaction was monitored by LC/MS. Then it was allowed to cool down to ambient temperature. The resulting dark-brown slurry was poured into 500 mL of water and 100 mL of ethyl acetate. The formed precipitate was collected by filtration, washed with 50 mL of water, 50 mL of methanol, 50 mL of diethyl ether and dried in vacuum to produce 3.22 g of the product as a dirty-yellow solid. The filtrate was extracted four times with 100 mL of ethyl acetate. The combined extracts were washed 3 times with 100 mL of water, then with brine and dried over anhydrous sodium sulfate. Solvent was removed in vacuum to yield additional 1.2 g of the product in a form of a yellow solid. Yield: 75% combined.

[0142] ^{1}H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.8 Hz, 3H), 7.25-7.27 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1 H), 7.50-7.51 (d, J = 2.6 Hz, 1H), 7.66-7.68 (d, J = 9.2 Hz, 1H), 7.71-7.73 (dd, J_1 = 2.7 Hz, J_2 = 9.2 Hz, 1 H), 7.71 (s, 2H), 8.03-8.05 (d, J = 2.7 Hz, 1H), 8.54-8.55 (d, J = 5.6 Hz, 1H), 8.78-8.80 (q, J = 4.8 Hz, 1H).

Example 7. Synthesis of 4-[3-(4-chloro-3-trifluoromethyl-phenylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methylamide trifluoroacetate salt

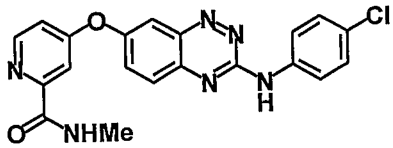


CF_3COOH

[0143] To a vial with 2 mL of anhydrous dimethylformamide under argon atmosphere were added 15.4 mg (0.0168 mmol, 0.05 equivalent) of *tris*(dibenzyllideneatone) dipalladium(0), 21.0 mg (0.033 mmol, 0.1 equivalent) of BINAP, 220.0 mg (0.675 mmol, 2.0 equivalent) of anhydrous cesium carbonate, 175.1 mg (0.675 mmol, 2.0 equivalent) of 5-bromo-2-chlorobenzotrifluoride, and 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide, in that particular order. Argon gas was bubbled through the mixture for 5 min. Then the vial was capped and the reaction mixture was heated to 120°C with stirring under argon atmosphere for 18 hours. At this point LC/MS indicated about 40 % conversion to the product. As pointed out in the previous examples, the longer reaction times result in the formation of the by-product and partial decomposition. So, the reaction mixture was allowed to cool down to ambient temperature, filtered through 0.3 μm syringe filter and purified by reverse-phase prep-HPLC using acetonitrile/water mixture with 0.1 % of TFA.

[0144] ESI-MS: $[M+H]^+$, 475, 477. ^{1}H NMR (DMSO-d_6): δ 2.79-2.90 (d, J = 4.8 Hz, 3H), 7.31-7.33 (dd, J_1 = 2.4 Hz, J_2 = 5.4 Hz, 1H), 7.55-7.55 (d, J = 2.4 Hz, 1H), 7.73-7.75 (d, J = 8.9 Hz, 1H), 7.89-7.91 (dd, J_1 = 2.5 Hz, J_2 = 9.2 Hz, 1H), 7.94-7.95 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 2.5 Hz, 2H), 8.25-8.27 (dd, J_1 = 2.6 Hz, J_2 = 8.9 Hz, 1H), 8.55 (d, J = 2.6 Hz, 1H), 8.60 (d, J = 5.4 Hz, 1H), 8.81-8.82 (q, J = 4.8 Hz, 1H), 11.36 (s, 1H).

Example 8. Synthesis of 4-[3-(4-chloro-phenylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methylamide trifluoroacetate salt

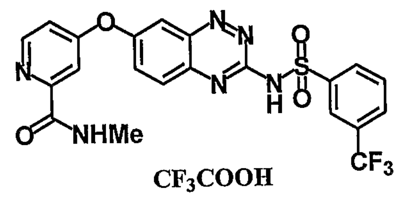


CF_3COOH

[0145] To a vial with 2 mL of anhydrous dimethylformamide under argon atmosphere were added 15.4 mg (0.0168 mmol, 0.05 equivalent) of *tris*(dibenzyllideneatone) dipalladium(0), 21.0 mg (0.033 mmol, 0.1 equivalent) of BINAP, 220.0 mg (0.675 mmol, 2.0 equivalent) of anhydrous cesium carbonate, 161.0 mg (0.675 mmol, 2.0 equivalent) of 1-chloro-4-iodobenzene, and 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide, in that particular order. Argon gas was bubbled through the mixture for 5 min. Then the vial was capped and the reaction mixture was heated to 120°C with stirring under argon atmosphere for 18 hours. At this point LC/MS indicated about 30 % conversion to the product. As it was observed from previous examples, the longer reaction times result in the formation of the by-product and partial decomposition. The reaction mixture was allowed to cool down to ambient temperature, filtered through 0.22 μ syringe filter and purified by reverse-phase preperative HPLC using acetonitrile/water mixture with 0.1 % of TFA.

[0146] ESI-MS: $[M+H]^+$, 407, 409. ^{1}H NMR (DMSO-d_6): δ 2.79-2.80 (d, J = 4.88 Hz, 3H), 7.30-7.32 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.44-7.46 (d, J = 6.8 Hz, 2H), 7.54-7.55 (d, J = 2.6 Hz, 1H), 7.84-7.87 (dd, J_1 = 2.6 Hz, J_2 = 9.05 Hz, 1H), 7.92-7.94 (d, J = 9.05 Hz, 1H), 8.00-8.01 (d, J = 6.8 Hz, 2H), 8.19-8.20 (d, J = 2.6 Hz, 1H), 8.58-8.59 (d, J = 5.6 Hz, 1H), 8.81-8.82 (q, J = 4.88 Hz, 1H), 11.08 (s, 1H).

Example 9. Synthesis of 4-[3-(3-trifluromethyl-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt

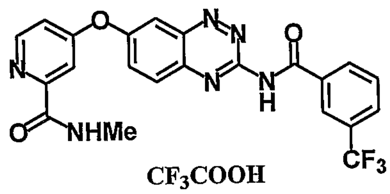


CF_3COOH

[0147] 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide were dissolved in 2 mL of anhydrous dimethylformamide with heating to about 100°C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *tert*-BuOK was added to the solution. The resulting dark-red solution was stirred at 100°C for 30 min, then it was allowed to cool down to ambient temperature. 100 mg (0.405 mmol, 1.2 equivalent) of 3-trifluoromethyl-benzenesulfonyl chloride was added to the mixture via a syringe. It was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through 0.22 μ syringe filter and purified by reverse-phase preperative HPLC using acetonitrile/water mixture with 0.1 % of TFA.

[0148] ESI-MS: $[M+H]^+$, 505, 506, 507. ^{1}H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.8 Hz, 3H), 7.29-7.31 (dd, J_1 = 2.6 Hz, J_2 = 5.7 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.87-7.90 (t, J = 7.8 Hz, 1H), 7.93-7.94 (d, J = 9.2 Hz, 1H), 7.97-7.99 (dd, J_1 = 2.6 Hz, J_2 = 9.2 Hz, 1H), 8.06-8.08 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H), 8.43-8.46 (m, 2H), 8.57-8.58 (d, J = 5.7 Hz, 1H), 8.80-8.81 (q, J = 4.8 Hz, 1H).

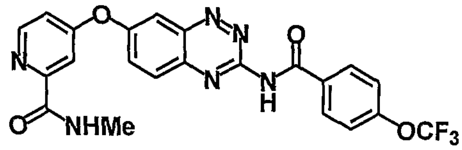
<u>Example 10. Synthesis of 4-[3-(3-trifluromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt</u>



[0149] 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide were dissolved in 2 mL of anhydrous dimethylformamide with heating to about 100°C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *tert*-BuOK was added to the solution. The resulting dark-red solution was stirred at 100°C for 30 min, then it was allowed to cool down to ambient temperature. 84.5 mg (0.405 mmol, 1.2 equivalent) of 3-trifluoromethyl-benzoyl chloride was added to the mixture via a syringe. It was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through 0.22 μ syringe filter and purified by reverse-phase prep-HPLC using acetonitrile/water mixture with 0.1 % of TFA.

[0150] ESI-MS: $[M+H]^+$, 469, 470. ^{1}H NMR (DMSO-d_6): δ 2.80-2.81 (d, J = 4.88 Hz, 3H), 7.37-7.39 (dd, J_1 = 2.6 Hz, J_2 = 5.7 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.81-7.84 (t, J = 7.8 Hz, 1H), 8.03-8.06 (m, 2H), 8.15-8.17 (d, J = 9.2 Hz, 1H), 8.33-8.34 (d, J = 2.6 Hz, 1H), 8.36-8.38 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 8.62-8.63 (d, J = 5.7 Hz, 1H), 8.84-8.85 (q, J = 4.88 Hz, 1H), 12.29 (s, 1H).

Example 11. Synthesis of 4-[4-(triflurometh oxy-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt

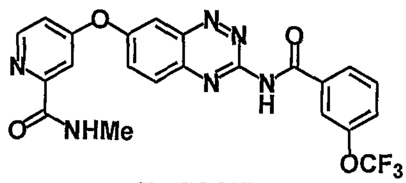


CF_3COOH

[0151] 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide were dissolved in 2 mL of anhydrous DMF with heating to about 100 °C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *t*-BuOK was added to the solution. The resulting dark-red solution was stirred at 100 °C for 30 min, then it was allowed to cool down to ambient temperature. 64 µL (91.0 mg, 0.405 mmol, 1.2 equivalent) of 4-trifluoromethoxy-benzoyl chloride was added to the mixture via a syringe. It was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through 0.22 µ syringe filter and purified by reverse-phase prep-HPLC using acetonitrile/water mixture with 0.1 % of TFA as a solvent system.

[0152] ESI-MS: $[M+H]^+$, 485, 486. ^{1}H NMR (DMSO-d_6): δ 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.37-7.38 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.55-7.57 (d, J = 8.8 Hz, 2H), 7.63-7.64 (d, J = 2.6 Hz, 1H), 8.03-8.05 (dd, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 1H), 8.14-8.15 (d, J = 9.1 Hz, 1H), 8.20-8.22 (d, J = 8.8 Hz, 2H), 8.32-8.33 (d, J =2.7 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.12 (s, 1H).

Example 12. Synthesis of 4-[3-(triflurometh oxy-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



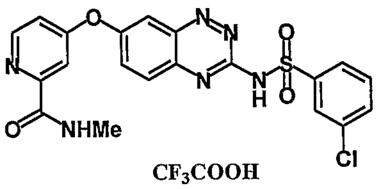
CF_3COOH

[0153] 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide were dissolved in 2 mL of anhydrous DMF with heating to about 100 °C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *t*-BuOK was added to the solution. The resulting dark-red solution was stirred at 100 °C for 30 min, then it was allowed to cool down to ambient temperature. 64 µL (91.0 mg, 0.405 mmol, 1.2 equivalent) of 3-trifluoromethoxy-benzoyl chloride was added to the mixture via a syringe. It was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through

0.22 μ syringe filter and purified by reverse-phase prep-HPLC using acetonitrile/water mixture with 0.1 % of TFA as a solvent system.

[0154] ESI-MS: $[M+H]^+$, 485, 486. ^1H NMR (DMSO-d_6): δ 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.37-7.39 (dd, J_1 = 2.5 Hz, J_2 = 5.6 Hz, 1H), 7.63-7.64 (d, J = 2.6 Hz, 1H), 7.67-7.74 (m, 2H), 8.03-8.05 (dd, J_1 = 2.8 Hz, J_2 = 9.36 Hz, 1H), 8.05 (m, 1H), 8.12-8.14 (m, 1H), 8.14-8.16 (d, J =9.36 Hz, 1H), 8.33 (d, J = 2.8 Hz, 1H), 8.62-8.63 (d, J = 5.7 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.21 (s, 1H).

Example 13. Synthesis of 4-[3-(chloro-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt

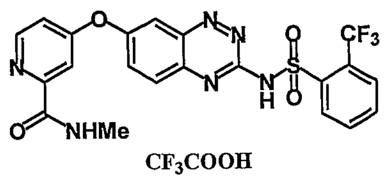


CF_3COOH

[0155] 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide were dissolved in 2 mL of anhydrous DMF with heating to about 100 °C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *t*-BuOK was added to the solution. The resulting dark-red solution was stirred at 100 °C for 30 min, then it was allowed to cool down to ambient temperature. 85.8 mg (0.405 mmol, 1.2 equivalent) of 3-chloro-benzene sulfonyl chloride was added to the mixture via a syringe. It was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through 0.22 μ syringe filter and purified by reverse-phase prep-HPLC using acetonitrile/water mixture with 0.1 % of TFA.

[0156] ESI-MS: $[M+H]^+$, 471, 473, 474. ^1H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.9 Hz, 3H), 7.30-7.32 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.65-7.68 (t, J = 9.0 Hz, 1H), 7.75-7.77 (m, 1H), 7.98-7.99 (m, 2H), 8.10-8.12 (d, J = 7.8 Hz, 1H), 8.15 (t, J = 1.8 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H), 8.57-8.58 (d, J = 5.4 Hz, 1H), 8.80-8.83 (q, J = 4.9 Hz, 1H).

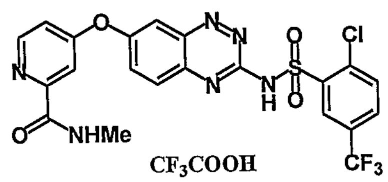
Example 14. Synthesis of 4-[2-(trifluoromethyl-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0157] 100 mg (0.337 mmol, 1.0 equivalent) of 4-(3-amino-benzo[1,2,4]triazin-7-yloxy)-pyridine-carboxylic acid methylamide were dissolved in 2 mL of anhydrous DMF with heating to about 100 °C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *t*-BuOK was added to the solution. The resulting dark-red solution was stirred at 100 °C for 30 min, then it was allowed to cool down to ambient temperature. 100 mg (0.405 mmol, 1.2 equivalent) of 2-trifluoromethyl-benzenesulfonyl chloride was added to the mixture via a syringe. It was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through 0.22 μ syringe filter and purified by reverse-phase prep-HPLC using acetonitrile/water mixture with 0.1 % of TFA.

[0158] ESI-MS: $[M+H]^+$, 505, 506, 507. ^{1}H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.8 Hz, 3H), 7.29-7.31 (dd, J_1 = 2.6 Hz, J_2 = 5.7 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.87-7.99 (m, 5H), 8.21 (d, J = 2.6 Hz, 1H), 8.56-8.58 (d, 1H), 8.59-8.60 (d, J = 8.0 Hz, 1H), 8.80-8.81 (q, J = 4.8 Hz, 1H).

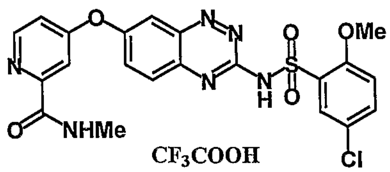
Example 15. Synthesis of 4-[2-chloro-5-(trifluoromethyl-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0159] The experimental procedure that was used was the same as described in Example 9.

[0160] ESI-MS: $[M+H]^+$, 539, 541, 542. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.78-2.79 (d, J = 4.9 Hz, 3H), 7.27-7.29 (dd, J_1 = 2.6 Hz, J_2 = 5.7 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.63-7.65 (d, J = 9.1 Hz, 1H), 7.86-7.88 (d, J = 8.4 Hz, 1H), 7.91-7.94 (dd, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 1H), 8.04-8.06 (dd, , J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 8.17-8.18 (d, J = 2.6 Hz, 1H), 8.56-8.57 (d, J = 5.7 Hz, 1H), 8.60-8.61 (d, J = 2.0 Hz, 1H), 8.80-8.81 (q, J = 4.9 Hz, 1H).

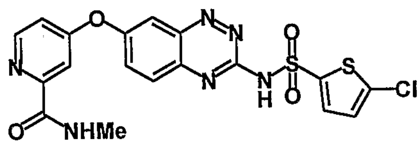
Example 16. Synthesis of 4-[3-chloro-6-methoxy-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxyl]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0161] The experimental procedure that was used was the same as described in Example 9.

[0162] ESI-MS: $[M+H]^+$, 501, 503, 504. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.78-2.79 (d, J = 4.9 Hz, 3H), 3.85 (s, 3H), 7.20-7.22 (d, J = 8.9 Hz, 1H), 7.29-7.31 (dd, J_1 = 2.6 Hz, J_2 = 5.7 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.67-7.70 (dd, J_1 = 2.8 Hz, J_2 = 8.9 Hz, 1H), 7.80-7.81 (d, J = 9.2 Hz, 1H), 7.92-7.95 (dd, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 8.05-8.06 (d, J = 2.8 Hz, 1H), 8.19-8.20 (d, J = 2.6 Hz, 1H), 8.57-8.58 (d, J = 5.6 Hz, 1H), 8.80-8.81 (q, J = 4.9 Hz, 1H), 13.00 (br.s. 1H).

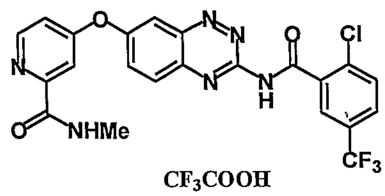
Example 17. Synthesis of 4-[3-(5-chloro-thiophene-2-sulfonylamino)-benzo[1,2,4]triazin-7-yloxyl]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0163] The experimental procedure that was used was the same as described in Example 9.

[0164] ESI-MS: $[M+H]^+$, 477, 479. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.79-2.80 (d, J = 4.8 Hz, 3H), 7.26-7.27 (d, J = 4.1 Hz, 1H), 7.32-7.34 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.59 (d, J = 2.6 Hz, 1H), 7.88-7.89 (d, J = 4.1 Hz, 1H), 7.99-8.02 (dd, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 1H), 8.12-8.14 (d, J = 9.1 Hz, 1H), 8.26 (d, J = 2.7 Hz, 1H), 8.59 (d, J = 5.6 Hz, 1H), 8.82-8.83 (q, J = 4.8 Hz, 1H), 13.00 (br.s. 1H).

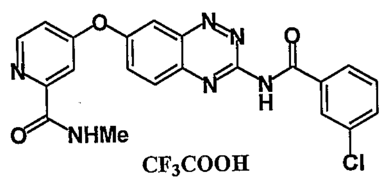
Example 18. Synthesis of 4-[2-chloro-3-trifluromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxyl]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0165] The experimental procedure that was used was the same as described in Example 10.

[0166] ESI-MS: $[M+H]^+$, 503, 505, 506. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.36-7.37 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.61 (d, J = 2.6 Hz, 1H), 7.82-7.83 (d, J = 8.4 Hz, 1H), 7.90-7.92 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 8.00-8.03 (m, 2H), 8.09 (m, 1H), 8.29 (m, 1H), 8.61-8.62 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.41 (s, 1H).

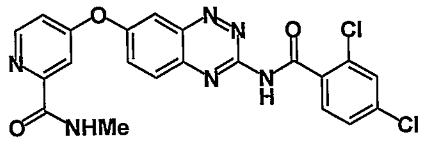
Example 19. Synthesis of 4-[2-chloro-3-trifluromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxyl]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0167] The experimental procedure that was used was the same as described in Example 10.

[0168] ESI-MS: $[M+H]^+$, 435, 437. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.37-7.39 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.59-7.62 (t, J = 7.8 Hz, 1H), 7.63-7.64 (d, J = 2.6 Hz, 1H), 7.72-7.74 (m, 1H), 8.03-8.05 (m, 2H), 8.13 (m, 1H), 8.15 (d, J = 9.1 Hz, 1H), 8.33 (d, J = 2.6 Hz, 1H), 8.62-8.63 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.12 (s, 1H).

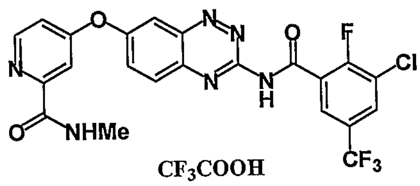
Example 20. Synthesis of 4-[2,4-dichloro-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0169] The experimental procedure that was used was the same as described in Example 10.

[0170] ESI-MS: $[M+H]^+$, 469, 471, 472. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.35-7.37 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.55-7.57 (dd, J_1 = 1.9 Hz, J_2 = 8.3 Hz, 1H), 7.61 (d, J = 2.6 Hz, 1H), 7.68-7.69 (d, J = 8.3 Hz, 1H), 7.76-7.77 (d, J = 1.9 Hz, 1H), 8.01 (m, 2H), 8.28-8.29 (m, 1H), 8.61 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.28 (s, 1H).

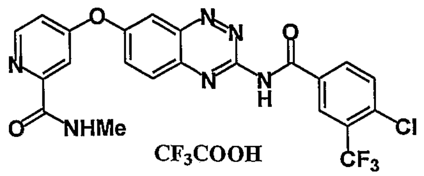
Example 21. Synthesis of 4-[2-fluoro-3-chloro-5-trifluoromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0171] The experimental procedure that was used was the same as described in Example 10.

[0172] ESI-MS: $[M+H]^+$, 521, 523, 524. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.36-7.38 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.62 (d, J = 2.6 Hz, 1H), 8.02-8.05 (dd, J_1 = 2.6 Hz, J_2 = 9.2 Hz, 1H), 8.07-8.09 (d, J = 9.2 Hz, 1H), 8.14-8.15 (dd, 1H), 8.31-8.32 (d, J = 2.6 Hz, 1H), 8.33-8.34 (dd, J_1 = 2.1 Hz, J_2 = 6.4 Hz, 1H), 8.62 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.45 (s, 1H).

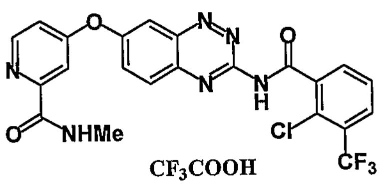
Example 22. Synthesis of 4-[3-(4-chloro-3-trifluoromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0173] The experimental procedure that was used was the same as described in Example 10.

[0174] ESI-MS: $[M+H]^+$, 503, 505, 506. ^1H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.37-7.39 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.63-7.64 (d, J = 2.6 Hz, 1H), 7.95-7.97 (d, J = 8.4 Hz, 1H), 8.04-8.06 (dd, J_1 = 2.7 Hz, J_2 = 9.3 Hz, 1H), 8.15-8.17 (d, J = 9.3 Hz, 1H), 8.33-8.34 (d, J = 2.7 Hz, 1H), 8.34-8.36 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 8.54-8.56 (d, J = 2.1 Hz, 1H), 8.62-8.63 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.35 (s, 1H).

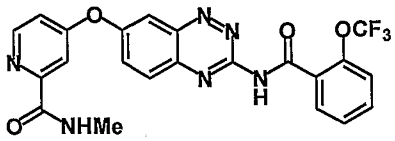
Example 23. Synthesis of 4-[3-(2-chloro-3-trifluoromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



[0175] The experimental procedure that was used was the same as described in Example 10.

[0176] ESI-MS: $[M+H]^+$, 503, 505, 506. ^1H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.35-7.36 (dd, J_1 = 2.6 Hz, J_2 = 5.5 Hz, 1H), 7.60-7.61 (d, J = 2.6 Hz, 1H), 7.66-7.69 (t, J = 7.8 Hz, 1H), 7.92-7.94 (m, 2H), 7.99-8.02 (m, 2H), 8.29 (d, J = 2.8 Hz, 1H), 8.61-8.62 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.43 (s, 1H).

Example 24. Synthesis of 4-[3-(3-trifluoromethoxy-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt

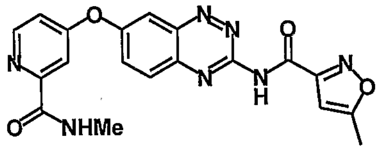


CF_3COOH

[0177] The experimental procedure that was used was the same as described in Example 10.

[0178] ESI-MS: $[M+H]^+$, 485, 486, 487. ^1H NMR (DMSO-d_6): δ (ppm) 2.80-2.81 (d, J = 4.8 Hz, 3H), 7.35-7.37 (dd, J_1 = 2.6 Hz, J_2 = 5.6 Hz, 1H), 7.48-7.50 (d, J = 8.3 Hz, 1H), 7.53-7.56 (dt, J_1= 0.9 Hz, J_2 = 7.6 Hz, 1H), 7.62 (d, J = 2.6 Hz, 1H), 7.66-7.68 (dt, J_1= 1.7 Hz, J_2 = 8.0 Hz, 1H), 7.78-7.79 (dt, J_1 = 1.7 Hz, J_2 = 7.6 Hz, 1H), 7.99-8.02 (m, 2H), 8.29 (d, J = 2.6 Hz, 1H), 8.61 (d, J = 5.6 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.22 (s, 1H).

Example 25. Synthesis of 4-{3-[(5-Methyl-isoxazole-3-carbonyl)-amino]-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide trifluoroacetate salt



CF_3COOH

[0179] The experimental procedure that was used was the same as described in Example 10. ^1H NMR (DMSO-d_6): δ (ppm) 2.53 (s, 3H), 2.80-2.81 (d, J = 4.8 Hz, 3H), 6.79 (s, 1H), 7.37-7.38 (dd, J_1 = 2.5 Hz, J_2 = 5.5 Hz, 1H), 7.63-7.64 (d, J = 2.4 Hz, 1H), 8.04-8.06 (dd, J_1= 2.5 Hz, J_2 = 9.2 Hz, 1H), 8.15-8.17 (d, J = 9.2 Hz, 1H), 8.32-8.33 (d, J = 2.5 Hz, 1H), 8.61-8.62 (d, J = 5.5 Hz, 1H), 8.83-8.84 (q, J = 4.8 Hz, 1H), 12.04 (s, 1H).

Example 26 Testing of Inhibition of Raf Kinase *In Vitro*

[0180] The ability of compounds of general structure (A) of the present invention to inhibit the kinase activity of Raf1 was evaluated using two methods: a direct and a Raf1-MEK1 assay. In the direct assay, kinase reactions were conducted in 96-well plates by combining recombinant human raf1 (29.4 U/well, Upstate, Lake Placid, NY), ATP (3 μM), myelin basic protein substrate (MBP, 1mg/ml, Upstate, Lake Placid, NY), and test agents (at concentrations ranging from about 1 nM/l to about 10 μM), in the presence of kinase reaction buffer. The Raf1-MEK1 assay utilized 2.9U/well raf1 and 0.25 ug/well inactive MEK1 (MEK1 inactive, Upstate, Lake Placid, NY) and 3uM ATP. After reacting for 60 minutes at 30 °C, residual ATP was measured using a luciferase-based assay (KinaseGlo, Promega Corp.) as a measure of kinase activity. Data from four wells were then averaged and used to determine IC_{50} values for the test compounds (Prism software package, GraphPad Software, San Diego CA).

[0181] The test results were as follows: a known Raf inhibitor, compound A, displayed an IC_{50} of 16 nM; a known Raf inhibitor, compound B, displayed an IC_{50} of 43 nM; and an invention compound C, showed an IC_{50} of 76 nM. Other invention compounds exemplified in Figure 1, displayed an IC_{50} below 100 μM.

<u>Example 27. Testing of Inhibition of MAPK Pathway in Cellular Assay</u>

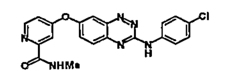
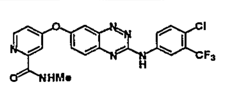
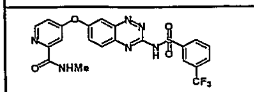
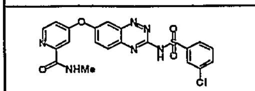
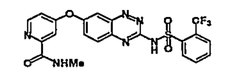
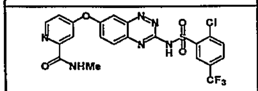
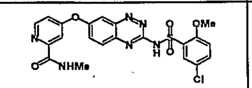
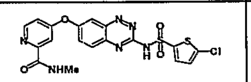
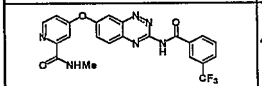
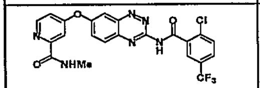
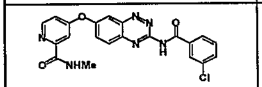
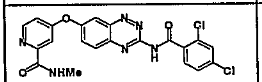
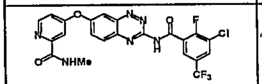
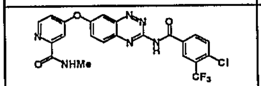
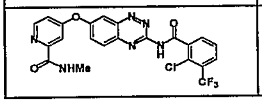
[0182] Western Blot: Early passage primary human umbilical vein endothelial cells (HUVECs) were maintained in EGM-2 containing SingleQuots (Cambrex, East Rutherford, NJ), 10% FBS, 10mM HEPES, and 50 μg/ml gentamicin. Prior to treatment of the cells with inhibitor, the HUVECs were starved for 18h by replacing serum-containing complete media with serum-free and SingleQuot-free media. The starved cells were pre-treated with inhibitors for 60 min at various concentrations (0-20 μM). Next the HUVECs were treated with 50 ng/ml VEGF or FGF (Peprotech, Rocky Hill, NJ) for 6 min and the cells were immediately washed with ice-cold PBS. Cells were lysed with ice-cold RIPA buffer containing 100mM Tris pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% deoxycholate, 1% Triton X-100, 0.1% SDS, 2 mM PMSF, one Complete-Mini protease inhibitor tablet (Roche, Indianapolis, IN; 1 tablet/ 7 ml of lysis buffer) and the phophatase inhibitors NaF (500 mM) and orthovanadate (1 mM). The cells were scraped and lysates transferred and centrifuged at 15,000 g for 10 min. Supernatants were transferred to new tubes and protein concentration was quantitated using the BCA protein reagent (Pierce, Rockford, IL). Cell lysates containing 20 μg of total protein were separated by 10% SDS-PAGE, transferred to nitrocellulose, and blocked in 5% milk in TBST. Anti phospho-ERK Thr 202/Tyr 204 (Cell Signaling, Beverly, MA), anti-phospho-MEK Ser217/221 (Cell Signaling), and c-Raf (BD Biosciences Pharmingen, San Diego, CA) used as primary antibodies were detected with horseradish peroxidase-conjugated goat anti-mouse or rabbit secondary antibodies and bands were visualized using the SuperSignal West Pico chemiluminescence reagent system (Pierce) and Kodak X-ray film (Rochester, NY).

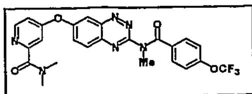
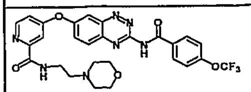
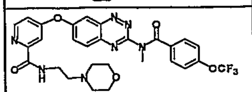
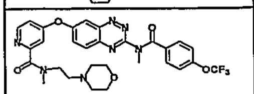
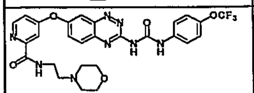
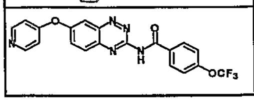
[0183] Bay 43-9006 (Raf/FGF inhibitor) showed reduction of expression of p-MEK and p-ERK with IC50 between 200 and 300 nM when tested in this assay. U0126 (MEK inhibitor) showed reduction in p-Erk levels with IC_{50} between 200 and 300 nM, while p-MEK levels were unaffected. The results are shown in Table 1. As can be seen, compounds of the invention showed reduction in p-MEK and p-ERK levels with IC_{50} between 400 nM and 20 μM.

Example 28. Cell Viability Assay

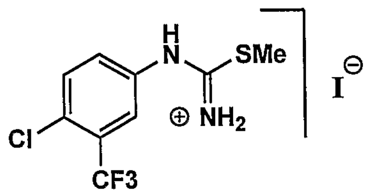
[0184] XTT assay: HUVECs were seeded at 10,000 cells/well of a tissue culture treated 96-well plate treated with collagen type I and grown overnight in the complete EGM-2 media as described above. The following morning, the inhibitors were serial diluted with DMSO and added to the cells with a final DMSO concentration of 1%. After 24-48 hours cell viability was measured with an XTT assay (Sigma, St. Louis, MO). The cells were also photographed to compare morphological differences to the XTT trends observed. Determination of the IC_{50} values was performed with quantitative software (Prism software package, GraphPad Software, San Diego CA). Several inhibitors blocked cell proliferation and induced apoptosis at concentrations below 1 μM and experiments were repeated three times to confirm the observations. The compounds of the invention displayed IC_{50} between 100 nM and 40 uM in this assay (Table 1).

Table 1. Test Results for Examples 26, 27 and 28.

Structure	Examples	RAF-MEK assay (biochemical assay)	Western Blot	Inhibition of HUVEC cell prolifiration (IC50)
	4-[3-(4-Chloro-phenylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	10-50 uM in Raf-Mek; 77 nM in direct assay; 100 % window	not active at 5 uM	
	4-[3-(4-Chloro-3-trifluoromethyl-phenylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	11.6 nM; ~20 % window	not active at 5 uM	
	4-[3-(3-Trifluromethyl-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy] pyridine-2-carboxylic acid methyl amide	flat	not active at 5 uM	
	4-[3-(3-Chloro-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy] pyridine-2-carboxylic acid methyl amide	flat	not active at 5 uM	
	4-[3-(2-trifluoromethyl-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy] pyridine-2-carboxylic acid methyl amide	flat	not active at 5 uM	
	4-[3-(2-chloro-5-trifluoromethyl-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy] pyridine-2-carboxylic acid methyl amide	50 uM	not active at 5 uM	
	4-[3-(5-chloro-2-methoxy-benzenesulfonylamino)-benzo[1,2,4]triazin-7-yloxy] pyridine-2-carboxylic acid methyl amide	> 50 uM	not active at 5 uM	
	4-[3-(5-chloro-thiophene-2-sulfonylamino)-benzo[1,2,4]triazin-7-yloxy] pyridine-2-carboxylic acid methyl amide	> 50 uM	not active at 5 uM	
	4-[3-(3-Trifluromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	655 nM; ~70% window	not active at 5 uM	
	4-[3-(2-Chloro-5-trifluromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide		not active at 5 uM	
	4-[3-(3-Chloro-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	flat	not active at 5 uM	
	4-[3-(2,4-Dichloro-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	flat	not active at 5 uM	
	4-[3-(3-Chloro-2-fluoro-5-trifluoromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	723 nM; ~30% window	not active at 5 uM	
	4-[3-(4-Chloro-5-trifluoromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	10-50 uM	not active at 5 uM	
	4-[3-(2-Chloro-3-trifluoromethyl-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid methyl amide	flat	not active at 5 uM	

	4-{3-[Methyl-(4-trifluoromethoxy-benzoyl)-amino]-benzo[1,2,4]triazin-7-yloxy}-pyridine-2-carboxylic acid dimethyl amide		partially active at 5 uM	
	4-[3-(4-Trifluoromethoxy-benzoylamino)-benzo[1,2,4]triazin-7-yloxy]-pyridine-2-carboxylic acid (2 morpholin-4-yl-ethyl)-amide		active at 5 uM	1.48 uM
	4-{3-[Methyl-(4-trifluoromethoxy-benzoyl)-amino]-benzo[1,2,4]triazin-7-yloxy}-pyridine-2-carboxylic acid (2 morpholin-4-yl-ethyl)-amide		partially active at 5 uM	1.084 uM
	4-{3-[Methyl-(4-trifluoromethoxy-benzoyl)-amino]-benzo[1,2,4]triazin-7-yloxy}-pyridine-2-carboxylic acid (2 morpholin-4-yl-ethyl)-amide		partially active at 5 uM	
	4-{3-[3-(4-Trifluoromethoxy-phenyl)-ureido]-benzo[1,2,4]triazin-7-yloxy}-pyridine-2-carboxylic acid (2 morpholin-4-yl-ethyl)-amide		not active at 5 uM	
	N-[7-(Pyridin-4-yloxy)-benzo[1,2,4]triazin-3-yl]-4-trifluoromethoxy-benzamide		not active at 5 uM	7.38 uM

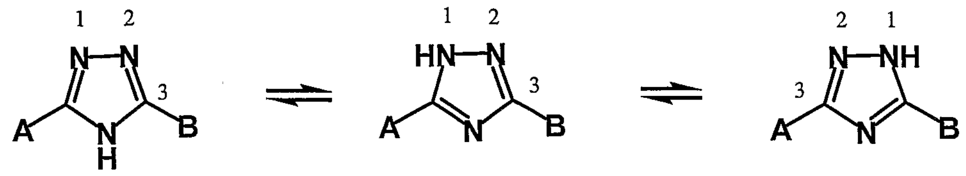
Example 29. Synthesis of S-methyl N-[4-chloro-3 (trifluoromethyl)phenyl]isothiourea hydroiodide



[0185] 4-Chloro-3-trifluoromethyl-phenylthiourea (5.0 g, 19.63 mmol) was dissolved in ca. 80 mL of anhydrous MeOH and methyl iodide (2.93 g, 20.61 mmol) was added via a syringe. The reaction mixture was refluxed for 12 hours. Then it was cooled down to ambient temperature and solvent was removed *in vacuo* to give colorless oil (7.85 g), which was taken to the next step without further purifications.

[0186] S-methyl N-[4-trifluoromethoxyphenyl]isothiourea hydroiodide, S-methyl N-[4-hydroxy-phenyl]isothiourea hydroiodide, S-methyl N-[3-hydroxy-phenyl]isothiourea hydroiodide and S-methyl N-[3-(trifluoromethyl)phenyl]isothiourea hydroiodide were prepared according to the method of this example.

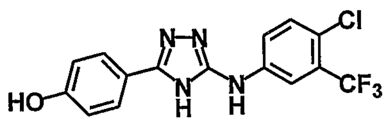
[0187] In the case of 1,2,4-triazoles three tautomeric structures can be present, as shown below:



4*H*-1,2,4-triazole **1*H*-1,2,4-triazole** **1*H*-1,2,4-triazole**

[0188] Even though all three tautomeric structures can exist, all the generic structures and all the examples having 1,2,4-triazole moiety are shown only in one tautomeric form, such as 4*H*-1,2,4-triazole for simplicity and for the comparison with its direct analogues, such as examples containing 1,3,4-oxadiazole moiety. The prevailing tautomeric structure depends on the substituents on the triazole moiety and on the reaction conditions. As has been shown in the literature, 1*H*-1,2,4-triazole is usually the most common tautomeric form, especially if an amino substituent is attached to the ring. Using only 4*H*-tautomeric form to draw the structures for the sake of simplicity, does not imply that the compounds of the examples that follow necessarily exist in that particular tautomeric form. Using this approach, the IUPAC names for the examples below are provided for 4*H*-tautomeric form only, however it is understood, that upon the elucidation of the exact tautomeric structure the numbering of the substituents may differ from the one that is provided.

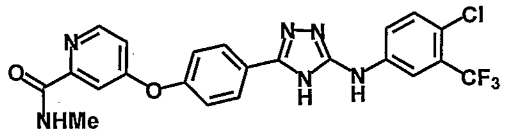
Example 30. Synthesis of 4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol



[0189] 4-hydroxybenzoic acid hydrazide (3.0 g, 19.66 mmol) and S-methyl N-[4-chloro-3-(trifluoromethyl)phenyl]isothiourea hydroiodide (7.8 g, 19.66 mmol) were suspended in 100 mL of anhydrous pyridine. The reaction mixture was refluxed for 18 hours under Ar atmosphere. Then it was cooled down to ambient temperature and pyridine was removed *in vacuo*. The resulting yellow oil was re-dissolved in a small amount of ethyl acetate, loaded on a short pad of silica gel and eluted with 5:1 hexane/ethyl acetate, then with 100 % ethyl acetate to collect the product. The product was re-purified by a second silica gel column chromatography, using ISCO system (80 g pre-packed column, 25 min run, 20% to 50 % EtOAc gradient in hexane). Solvent was removed *in vacuo* to give the title product as a white solid (2.83 g). Yield 40.4 %.

[0190] ESI-MS: $[M+H]^+$ 355.1, 356.8,. ^{1}H NMR (DMSO-d_6): δ 6.89-6.91 (d, J = 8.7 Hz, 2H), 7.53-7.55 (d, J = 8.8 Hz, 1H), 7.70-7.72 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 7.77-7.79 (d, J = 8.7 Hz, 2H), 8.24-8.25 (d, J = 2.6 Hz, 1H), 9.81 (s, 1H), 9.98 (s, 1H), 13.62 (s, 1H).

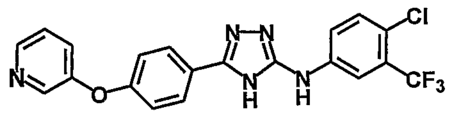
Example 31. Synthesis of 4-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H-[1,2,4]triazol-3-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide trifluoroacetic acid salt



CF_3COOH

[0191] ESI-MS: $[M+H]^+$,490, 491. ^{1}H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.8 Hz, 3H), 7.24-7.25 (m, 1H), 7.40-7.42 (d, J = 8.7 Hz, 2H), 7.48 (s, 1H), 7.56-7.58 (d, J = 8.8 Hz, 1H), 7.79-7.82 (dd, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 1H), 8.07-8.09 (d, J = 8.7 Hz, 2H), 8.24-8.25 (d , J = 2.6 Hz, 1H), 8.55-8.56 (m, 1H), 8.80-8.81 (m, 1H), 9.95 (s, 1H).

Example 32. Synthesis of (4-chloro-3-trifluoromethyl-phenyl)-{5-[4-(pyridin-3-yloxy)-phenyl]-4H-[1,2,4]triazol-3-yl}-amine trifluoroacetic acid salt



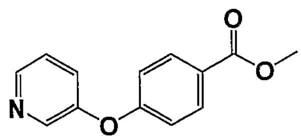
CF_3COOH

[0192] 4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (127.8 mg, 0.36 mmol) was dissolved in 3 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (144.0 mg, 0.72 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 3-bromopyridine (68.3 mg, 0.432 mmol) was added, followed by anhydrous K_2CO_3 (50.0 mg, 0.36 mmol). Then the vial was capped and microwaved at 250 °C for 30 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (15.1 mg).

[0193] ESI-MS: $[M+H]^+$, 432, 433. ^{1}H NMR (DMSO-d_6): δ 7.19-7.21 (d, J = 8.8 Hz, 2H), 7.49-7.51 (dd, J_1 = 4.5 Hz, J_2 = 8.6 Hz, 1H), 7.53-7.55 (d, J = 8.8 Hz, 1H), 7.58-7.60

(m, 1H), 7.74-7.76 (m, 1H), 7.95-7.98 (d , J = 8.8 Hz, 2H), 8.21-8.21 (d , J = 2.6 Hz, 1H), 8.44 (m, 1H), 8.48 (m, 1H), 9.88 (s, 1H).

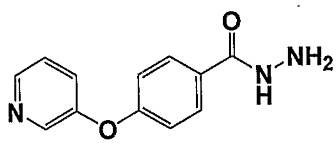
Example 33. Synthesis of methyl 4-(pyridine-3-yloxy)benzoate



[0194] 3-hydroxypyridine (6.17 g, 64.87 mmol) was dissolved in 100 mL of anhydrous DMF under argon atmosphere. Solid K_2CO_3 (8.96 g, 64.87 mmol) was added, followed by neat methyl 4-fluorobenzoate (10.0 g, 64.87 mmol). The reaction mixture was heated at 135 °C for 10 hrs. The absence of the starting material was confirmed by LC/MS. The reaction mixture was cooled down to ambient temperature and poured into ca. 500 mL of H_2O. The resulting solution was extracted 3 times with ca. 150 mL of EtOAc (during the extraction small volumes of MeOH, Et_2O and brine were added to facilitate the separation). Combined EtOAc layers were washed twice with sat. $NaHCO_3$, twice with brine and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo* to give dark-red oil, which was purified by silica gel chromatography using 1:1 mixture of EtOAc/Hexane as eluent to give the title product (4.8 g, 32.3 % yield) as yellow solid.

[0195] ESI-MS: $[M+H]^+$, 230, 231. ^1H NMR (DMSO-d_6): δ 3.83 (s, 3H), 7.09-7.12 (d, J = 8.8 Hz, 2H), 7.48-7.51 (dd, J_1 = 8.4 Hz, J_2 = 4.9 Hz, 1H), 7.58-7.61 (dq, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H), 7.96-7.99 (d, J = 8.8 Hz, 2H), 8.46-8.47 (m, 2H).

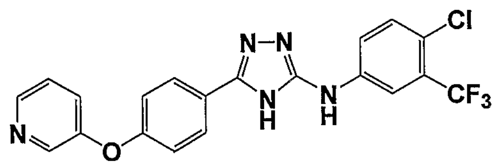
Example 34. Synthesis of 4-(pyridine-3-yloxy)benzohydrazide



[0196] Methyl 4-(pyridine-3-yloxy)benzoate (4.8 g, 20.94 mmol) was dissolved in ca. 150 mL of EtOH and anhydrous hydrazine (4.08 g , 4.0 mL) was added via a syringe. The resulting yellow solution was refluxed for 24 hrs. Then solvent was removed *in vacuo* to give the title product (4.8 g, 100 % yield) as yellow viscous oil, which upon standing slowly solidified.

[0197] ESI-MS: $[M+H]^+$, 230, 231. ^1H NMR (DMSO-d_6): δ 4.13 (br s., 2H), 7.06-7.09 (d, J = 8.7 Hz, 2H), 7.45-7.47 (dd, J_1 = 8.4 Hz, J_2 = 4.9 Hz, 1H), 7.51-7.54 (dq, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H), 7.85-7.88 (d, J = 8.8 Hz, 2H), 8.42-8.43 (m, 2H), 9.74 (s, 1H).

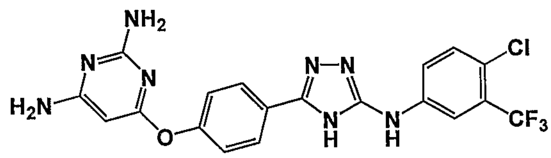
Example 35. Synthesis of (4-chloro-3-trifluoromethyl-phenyl)-{5-[4-(pyridin-3-yloxy)-phenyl]-4H-[1,2,4]triazol-3-yl}-amine



[0198] 4-(pyridine-3-yloxy)benzohydrazide (2.33 g, 10.2 mmol) was dissolved in ca. 70 mL of anhydrous pyridine and S-methyl N-[4-chloro-3-(trifluoromethyl)phenyl] isothiourea hydroiodide (4.04 g, 10.2 mmol) was added. The reaction mixture was refluxed for 18 hrs under Ar. The pyridine was removed *in vacuo* and the resulting residue was purified by silica gel chromatography using EtOAc as eluent to give the title product (0.56 g) as a white solid.

[0199] ESI-MS: $[M+H]^+$, 432, 433. ^1H NMR (DMSO-d_6): δ 7.20-7.23 (d, J = 8.8 Hz, 2H), 7.46-7.49 (dd, J_1 = 8.4 Hz, J_2 = 4.5 Hz, 1H), 7.54-7.57 (m, 2H), 7.75-7.77 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 7.97-7.99 (d , J = 8.8 Hz, 2H), 8.23-8.24 (d , J = 2.6 Hz, 1H), 8.43 (m, 1H), 8.46 (d, J = 2.6 Hz, 1H), 9.88 (s, 1H), 13.91 (s, 1H).

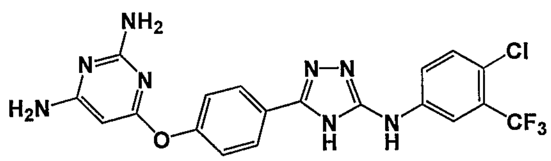
Example 36. Synthesis of 6-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine



[0200] 4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (1.3 g, 3.66 mmol) was dissolved in 18 mL of anhydrous dioxane in a 10-20 mL microwave vial (Personal Chemistry). Solid Cs_2CO_3 (1.19 g, 3.66 mmol, 1.0 eq) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 4-chloro-2,4-diaminopyrimidine (0.530 g, 3.66 mmol) was added. The vial was capped and microwaved at 200 °C for 25 min. Then the reaction mixture was diluted with ca. 10 mL of MeOH, transferred into a round-bottom flask and concentrated *in vacuo* to ca. 20 mL. The resulting reddish solution was loaded on a short pad of silica gel and eluted first with 100 % ethyl acetate to remove the unreacted starting material and then with 20 % MeOH in EtOAc to elute the product. The product was further purified by ISCO system (80 g pre-packed column, 40 min method, 0% to 10 % MeOH gradient in ethyl acetate). Solvent was removed *in vacuo* to give the title product as an off-white solid (0.785 g). Yield 46.3 %.

[0201] ESI-MS: $[M+H]^+$, 463, 464, 465. ^1H NMR (DMSO-d_6): δ 5.15 (s, 1H), 6.03 (s, 2H), 6.31 (s, 2H), 7.25-7.27 (d, *J* = 8.6 Hz, 2H), 7.55-7.57 (d, *J* = 8.8 Hz, 1H), 7.77-7.78 (m, 1H), 7.96-7.97 (d , *J* = 8.8 Hz, 2H), 8.25-8.26 (d , *J* = 2.6 Hz, 1H), 9.91 (s, 1H), 13.91 (s, 1H). Anal. Calcd for ($C_{19}H_{14}ClF_3N_8O$ x 0.4 EtOAc): C, 49.68; H, 3.48; N, 22.50, Found: C, 49.61; H, 3.55; N, 22.90.

Example 37. Synthesis of 6-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine methanesulfonic acid salt

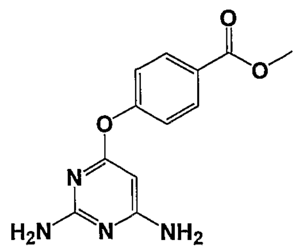


$MeSO_3H$

[0202] 6-{4-[5-(4-Chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine x 0.4 EtOAc complex (470.0 mg, 0.943 mmol) was dissolved in ca. 50 mL of anhydrous methanol and methasulfonic acid (0.0612 mL, 0.943 mmol, 1.0 eq.) was added. The resulting solution was stirred for 30 min. Solvent was removed *in vacuo* and the resulting light-yellow foam was dried at 70 °C in high vacuum for 3 hrs to give the title compound as an off-white solid (527.3 mg). Yield 100%.

[0203] ESI-MS: $[M+H]^+$, 463, 464. ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H), 5.40 (s, 1H), 7.39-7.40 (d, *J* = 8.6 Hz, 2H), 7.57-7.58 (d, *J* = 8.8 Hz, 1H), 7.78 (m, 1H), 7.80 (br.s., 4H), 8.02-8.03 (d , *J* = 8.8 Hz, 2H), 8.25-8.26 (d , *J* = 2.6 Hz, 1H), 9.94 (s, 1H), 13.98 (br..s. 1H). Anal. Calcd for ($C_{19}H_{14}ClF_3N_8O$ x 1 CH_3SO_3H): C, 42.98; H, 3.25; N, 20.05, Fqund: C, 42.93; H, 3.62; N, 20.12.

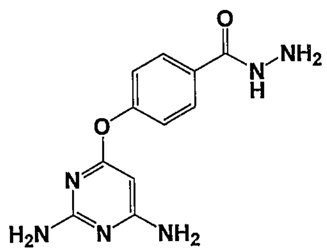
Example 38. Synthesis of methyl 4-[(2,6-diaminopyrimidin-4-yl)oxy]benzoate



[0204] Methyl 4-hydroxybenzoate (1.52 g, 10.0 mmol) was dissolved in 18 mL of anhydrous dioxane in 10-20 mL microwave vial (Personal Chemistry) and solid Cs_2CO_3 was added to this solution. The suspension was stirred at ambient temperature for 10 min, then 4-chloro-2,6-diaminopyrimidine (1.45 g, 10.0 mmol) was added. The vial was capped and microwaved at 200 °C for 40 min. Then MeOH was added to dissolve the formed suspension to produce a clear amber solution. The solution was transferred into a round-bottom flask and concentrated down to ca. 20 mL. This solution was purified by silica gel chromatography using 100 % ethyl acetate as eluent. The product was additionally re-crystallized from ca. 50 mL of 4:1 mixture of EtOAc/MeOH. The product was filtered, washed with 40 mL of EtOAc, 40 mL of anhydrous Et_2O and dried *in vacuo* to give the title product as a white solid (0.812 g). Yield 31.2%.

[0205] ESI-MS: $[M+H]^+$, 261.01. ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H), 5.19 (s, 1H), 6.06 (br. s, 2H), 6.37 (br.s, 2H), 7.19-7.21 (d, J = 8.7 Hz, 2H), 7.95-7.97 (d, J = 8.7 Hz, 2H). ^{13}C NMR (DMSO-d6) 52.1, 78.3, 121.0, 125.3, 130.9, 157.8, 163.2, 165.7, 166.6, 169.2.

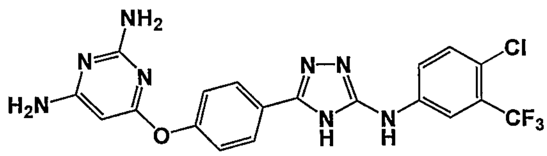
Example 39. Synthesis of 4-[(2,6-diaminopyrimidin-4-yl)oxy]benzohydrazide



[0206] Methyl 4-[(2,6-diaminopyrimidin-4-yl)oxy]benzoate (2.74 g, 10.52 mmol) was suspended in ca. 180 mL of anhydrous methanol and anhydrous hydrazine (1.021 g, 1.0 mL, 31.85 mmol, 3.03 eq) was added to this suspension. The reaction mixture was refluxed for 3 hours, then MeOH was very slowly distilled off till the total volume reached ca. 30 mL. This solution was allowed to stand at ambient temperature for 48 hrs. A white precipitate slowly crystallized out. It was collected, washed with 40 mL of EtOAc, 40 mL of anhydrous Et_2O and dried *in vacuo* to give the title product as a fine white powder (2.02 g). Yield 73.7 %.

[0207] ESI-MS: $[M+H]^+$, 261.12. ^{1}H NMR (DMSO-d_6): δ 4.54 (br.s., 2H), 5.13 (s, 1H), 6.01 (br. s, 2H), 6.30 (br.s, 2H), 7.13-7.14 (d, J = 8.7 Hz, 2H), 7.83-7.84 (d, J = 8.7 Hz, 2H), 9.75 (s, 1H). ^{13}C NMR (DMSO-d6) 77.9, 120.9, 128.5, 129.3, 155.8, 163.3, 165.4, 166.6, 169.7.

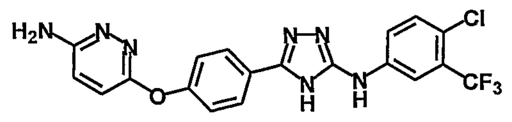
<u>Example 40. Synthesis of 6-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine</u>



[0208] 4-[(2,6-diaminopyrimidin-4-yl)oxy]benzohydrazide (1.48 g, 5.68 mmol) and S-methyl N-[4-chloro-3-(trifluoromethyl)phenyl]isothiourea hydroiodide (2.33 g, 5.89 mmol) were suspended in 30 mL of anhydrous pyridine. The reaction mixture was refluxed for 18 hours under Ar atmosphere. The formed yellow solution was cooled down to ambient temperature and pyridine was removed *in vacuo*. The resulting yellow foamy solid was re-dissolved in 50 mL of 5:1 EtOAc/MeOH; ca. 15 g of silica gel was added and solvent was removed *in vacuo*. The impregnated silica gel was packed into ISCO column and the product was purified using ISCO system (80 g pre-packed column, 50 min run, 0% to 10 % gradient of solvent B in solvent A [Solvent A – 4 mL of MeOH, 4mL of Et_3N in 4 L of CH_2Cl_2; Solvent B – 4 mL of Et_3N in 4 L of MeOH]). Solvent was removed *in vacuo* to give the title product as a white solid (1.33 g). Yield 50.5 %.

[0209] ESI-MS: $[M+H]^+$, 463, 464. ^{1}H NMR (DMSO-d_6): δ 5.15 (s, 1H), 6.03 (s, 2H), 6.31 (s, 2H), 7.25-7.27 (d, J = 8.6 Hz, 2H), 7.55-7.57 (d, J = 8.8 Hz, 1H), 7.77-7.78 (m, 1H), 7.96-7.97 (d , J = 8.8 Hz, 2H), 8.25-8.26 (d , J = 2.6 Hz, 1H), 9.91 (s, 1H), 13.91 (s, 1H). Anal. Calcd for ($C_{19}H_{14}ClF_3N_8O$ x 0.4 EtOAc): C, 49.68; H, 3.48; N, 22.50, Found: C, 49.61; H, 3.55; N, 22.90.

Example 41. Synthesis of 6-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyridazin-3-ylamine trifluoroacetic acid salt

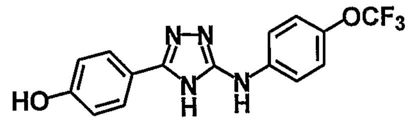


CF_3COOH

[0210] 4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (120.0 mg, 0.338 mmol) was dissolved in 3 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (81.0 mg, 0.406 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 3-amino-6-chloro-pyridazine (48.2 mg, 0.372 mmol) was added, followed by anhydrous K_2CO_3 (46.7 mg, 0.338 mmol). Then the vial was capped and microwaved at 200 °C for 30 min. After reaction was complete, the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (18.2 mg).

[0211] ESI-MS: $[M+H]^+$, 448, 449. ^1H NMR (DMSO-d_6): δ 7.42-7.43 (d, J = 8.7 Hz, 2H), 7.54-7.56 (d, J = 9.7 Hz, 1H), 7.56-7.58 (d, J = 8.8 Hz, 1H), 7.76-7.79 (m, 1H), 7.78-7.80 (d, J = 9.7 Hz, 1H), 8.01-8.04 (d , J = 8.8 Hz, 2H), 8.25-8.26 (d , J = 2.6 Hz, 1H), 8.49 (br.s., 2H), 9.94 (s, 1H).

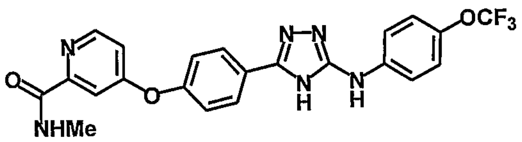
Example 42. Synthesis of 4-[5-(4-trifluoromethoxy-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol



[0212] 4-hydroxybenzoic acid hydrazide (0.643 g, 4.23 mmol) and S-methyl N-[4-(trifluoromethoxy)phenyl]*isothiourea* hydroiodide (1.6 g, 4.23 mmol) were suspended in 10 mL of anhydrous pyridine. The reaction mixture was refluxed for 24 hours, during which time it changed color from yellow into orange-red. Then it was cooled down to ambient temperature and poured with stirring into 150 mL of ice-water. The formed white solid was collected, washed thoroughly with water and dried in air. The resulting residue was purified by silica gel chromatography using Isco column with 10% to 100 % gradient of ethyl acetate in hexane. Solvent was removed *in vacuo* to give the title product as a pinkish solid (575.2 mg). Yield 40.4 %.

[0213] ESI-MS: $[M+H]^+$ 337, 338. ^{1}H NMR (DMSO-d_6): δ 6.85-6.87 (d, J = 8.0 Hz, 2H), 7.19-7.20 (d, J = 8.0 Hz, 2H), 7.61-7.63 (d, J = 8.7 Hz, 2H), 7.75-7.77 (d , J = 8.7 Hz, 2H), 9.39 (s, 1H), 9.92 (s, 1H), 13.42 (s, 1H).

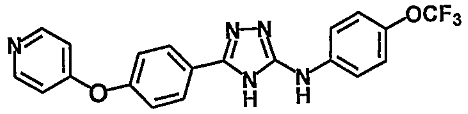
Example 43. Synthesis of 4-{4-[5-(4-trifluoromethoxy-phenylamino)-4H-[1,2,4]triazol-3-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide trifluoroacetic acid salt



[0214] 4-[5-(4-trifluoromethoxy-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (66.4 mg, 0.197 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (39.4 mg, 0.197 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloro-2-pyridinecarboxamide (33.7 mg, 0.197 mmol) was added, followed by anhydrous K_2CO_3 (27.3 mg, 0.197 mmol). Then the vial was capped and microwaved at 200 °C for 15 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (46.6 mg).

[0215] ESI-MS: $[M+H]^+$ 471, 472. ^{1}H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.8 Hz, 3H), 7.23-7.25 (dd, J_1 = 5.6 Hz, J_2 = 2.6 Hz, 1H), 7.25-7.27 (d, J = 8.6 Hz, 2H), 7.38-7.40 (d, J = 8.6 Hz, 2H), 7.47-7.47 (d, J = 2.6 Hz, 1H), 7.66-7.70 (d, J = 8.7 Hz, 2H), 8.08-8.11 (d, J = 8.7 Hz, 2H), 8.55-8.56 (d, J = 5.6 Hz, 1H), 8.79-8.82 (t, J = 4.8 Hz, 1H), 9.58 (s, 1H).

Example 44. Synthesis of {5-[4-(pyridin-4-yloxy)-phenyl]-4*H*-[1,2,4]triazol-3-yl]-(4-trifluoromethoxy-phenyl)-amine trifluoroacetic acid salt

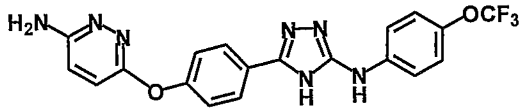


CF_3COOH

[0216] 4-[5-(4-trifluoromethoxy-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (106.0 mg, 0.315 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (157.2 mg, 0.788 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloropyridine hydrochloride (56.7 mg, 0.378 mmol) was added, followed by anhydrous K_2CO_3 (44.0 mg, 0.315 mmol). Then the vial was capped and microwaved at 250 °C for 20 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (66.5 mg of off-white solid).

[0217] ESI-MS: $[M+H]^+$, 415, 416. ^1H NMR (DMSO-d_6): δ 7.26-7.27 (d, J = 8.7 Hz, 2H), 7.46-7.48 (m, 2H), 7.46-7.48 (d, J = 7.1 Hz, 2H), 7.67-7.70 (d, J = 8.7 Hz, 2H), 8.13-8.16 (d, J = 8.7 Hz, 2H), 8.77-8.78 (d, J = 7.1 Hz, 2H), 9.64 (s, 1H).

Example 45. Synthesis of 6-{4-[5-(4-trifluoromethoxy-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyridazin-3-ylamine trifluoroacetic acid salt

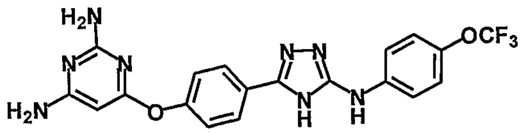


CF_3COOH

[0218] 4-[5-(4-trifluoromethoxy-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (112.0 mg, 0.33 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (132.8 mg, 0.66 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 3-amino-6-chloropyridazine (47.4 mg, 0.366 mmol) was added, followed by anhydrous K_2CO_3 (46.0 mg, 0.33 mmol). Then the vial was capped and microwaved at 250 °C for 15 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (52.1 mg of brown crystalline solid).

[0219] ESI-MS: $[M+H]^+$, 431. ^1H NMR (DMSO-d_6): δ 7.25-7.26 (d, J = 8.7 Hz, 2H), 7.39-7.41 (d, J = 8.7 Hz, 2H), 7.52-7.54 (d, J = 9.7 Hz, 1H), 7.67-7.68 (d, J = 8.7 Hz, 2H), 7.76-7.78 (d, J = 9.7 Hz, 1H), 8.03-8.06 (d, J = 8.7 Hz, 2H), 9.58 (s, 1H).

Example 46. Synthesis of 6-{4-[5-(4-trifluoromethoxy-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine trifluoroacetic acid salt

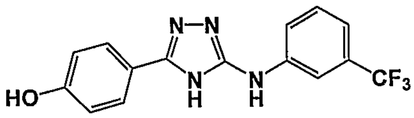


CF_3COOH

[0220] 4-[5-(4-tTrifluoromethoxy-phenylamino)-4H[1,2,4]triazol-3-yl]-phenol (112.0 mg, 0.33 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (132.8 mg, 0.66 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloro-2,6-diamino-pyrimidine (53.0 mg, 0.366 mmol) was added, followed by anhydrous K_2CO_3 (46.0 mg, 0.33 mmol). Then the vial was capped and microwaved at 250 °C for 15 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (51.1 mg of beige solid).

[0221] ESI-MS: $[M+H]^+$, 445, 446. ^1H NMR (DMSO-d_6): δ 5.36 (s, 1H), 7.25-7.27 (br. d, J = 8.0 Hz, 2H), 7.35-7.36 (br. d, J = 8.0 Hz, 2H), 7.67-7.68 (d, J = 8.7 Hz, 2H), 7.67 (br.s., 4H), 8.02-8.04 (d, J = 8.7 Hz, 2H), 9.57 (br. s, 1H).

Example 47. Synthesis of 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)-phenol

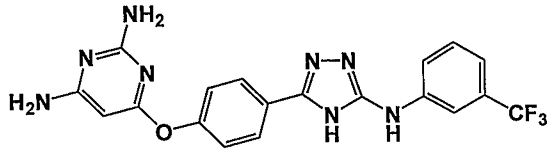


[0222] S-methyl N-[3-(trifluoromethyl)phenyl]isothiourea hydroiodide (9.09 g, 25.11 mmol) and 4-hydroxybenzoic acid hydrazide (3.82 g, 25.11 mmol) were suspended in ca. 50 mL of anhydrous pyridine under Ar. The mixture was brought to reflux and refluxed under Ar for 12 hrs. Then the dark-yellow solution was cooled down to ambient temperature and pyridine was removed *in vacuo*. The resulting reddish-yellow solid was re-dissolved in ca. 50 mL of 4:1 mixture of EtOAc/MeOH, ca. 20 g of silica gel was added and solvent was removed *in vacuo*. The impregnated silica gel was loaded into 25 g ISCO sample cartridge and the product was purified using ISCO system (solid method, 80 g column, 45 min, 0% to

50% EtOAc gradient in hexane). Solvent was removed *in vacuo* to give the title product as a white solid (3.83 g). Yield 47.6%.

[0223] ESI-MS: $[M+H]^+$, 321.09. ^{1}H NMR (DMSO-d_6): δ 6.89-6.90 (d, *J* = 8.6 Hz, 2H), 7.09-7.11 (d, *J* = 7.3 Hz, 1H), 7.42-7.46 (t, *J* = 7.9 Hz, 1H), 7.73-7.74 (d, *J* = 7.0 Hz, 1H), 7.77-7.79 (d, *J* = 8.6 Hz, 2H), 8.09 (s, 1H), 9.65 (s, 1H), 9.97 (br. s., 1H).

<u>Example 48. Synthesis of 6-[4-(5-{[3-(trifluoromethyl)phenyl]amino}-4H-[1,2,4]triazol-3-yl)-phenoxy]-pyrimidine-2,4-diamine</u>

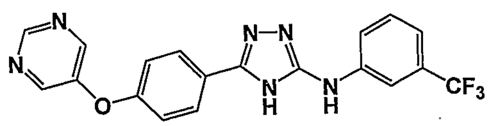


[0224] 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)phenol (160 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous dioxane in 2-5 mL microwave vial (Personal Chemistry). Solid Cs_2CO_3 (163.0 mg, 0.5 mmol) was added, followed by 4-chloro-2,6,-diaminopyrimidine (79.5 mg, 0.55 mmol). The vial was capped and microwaved at 200 °C for 20 min. Then ca. 3 mL of MeOH was added to dissolve the formed suspension, the solution was transferred into a round-bottom flask and solvent was removed *in vacuo*. The residue was re-dissolved in 3 mL of DMF, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetontrile/water system with 0.01% of TFA.

[0225] The fractions containing the product were collected and partitioned between EtOAc and saturated aqueous $NaHCO_3$. Ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title compound as an off-white solid (92.2 mg).

[0226] ESI-MS: $[M+H]^+$, 429.08. ^{1}H NMR (DMSO-d_6): δ 5.15 (s, 1H), 6.02 (s, 2H), 6.30 (s, 2H), 7.12 (m, 1H), 7.25-7.27 (d, *J* = 7.4 Hz, 2H), 7.45-7.47 (m, 1H), 7.75-7.76 (m, 1H), 7.95-7.97 (d, *J* = 8.6 Hz, 2H), 8.10 (s, 1H), 9.73 (s, 1H), 13.84 (s, 1H).

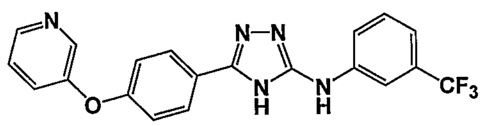
<u>Example 49. Synthesis of 5-[4-(pyrimidin-5-yloxy)phenyl]-N-[3-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-amine</u>



[0227] 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)phenol (100 mg, 0.31 mmol) was dissolved in 3 mL of anhydrous dioxane in 2-5 mL microwave vial (Personal Chemistry). Solid Cs_2CO_3 (203.4 mg, 0.62 mmol) was added, followed by 5-bromo-pyrimidine (100 mg, 0.62 mmol). Then 1 mL of anhydrous DMF was added, the vial was capped and microwaved at 250 °C for 30 min. Then ca. 3 mL of MeOH was added to dissolve the formed suspension, the solution was transferred into a round-bottom flask and solvent was removed *in vacuo*. The residue was re-dissolved in 3 mL of DMF, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetontrile/water system with 0.01% of TFA. The fractions containing the product were collected and partitioned between EtOAc and saturated aqueous $NaHCO_3$. Ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title compound as a light-brown foamy solid (34.7 mg).

[0228] ESI-MS: $[M+H]^+$, 399.06. ^{1}H NMR (DMSO-d_6): δ 7.12 (m, 1H), 7.30-7.32 (d, *J* = 7.4 Hz, 2H), 7.46 (m, 1H), 7.76 (m, 1H), 8.00-8.02 (d, *J* = 8.6 Hz, 2H), 8.09 (s, 1H), 8.73 (s, 2H), 9.06 (s, 1H), 9.73 (s, 1H), 13.95 (s, 1H).

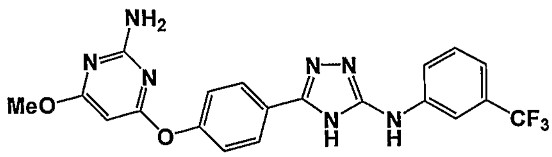
Example 50. Synthesis of 5-[4-(pyridin-3-yloxy)phenyl]-N-[3-(trifluoromethyl)phenyl]-4H-[1,2,4]triazol-3-amine



[0229] 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)phenol (100 mg, 0.31 mmol) was dissolved in 2 mL of anhydrous DMF in 2-5 mL microwave vial (Personal Chemistry). Solid Cs_2CO_3 (203.4 mg, 0.62 mmol) was added, followed by 3-bromopyridine (74.0 mg, 0.468 mmol). The vial was capped and microwaved at 250 °C for 30 min. Then ca. 1 mL of MeOH was added to dissolve the formed suspension. The resulting reddish-brown solution was filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetontrile/water system with 0.01% of TFA. The fractions, containing the product, were collected and partitioned between EtOAc and saturated aqueous $NaHCO_3$. Ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title compound as a yellow solid (22.4 mg).

[0230] ESI-MS: $[M+H]^+$, 398.11. ^{1}H NMR (DMSO-d_6): δ 7.09 (d, *J* = 7.6 Hz, 1H), 7.20-7.22 (d, *J* = 8.6 Hz, 2H), 7.46-7.48 (m, 2H), 7.52-7.54 (m, 1H), 7.75-7.76 (d, *J* = 8.2 Hz, 1H), 7.99-8.02 (d, J = 8.6 Hz, 2H), 8.09 (s, 1H), 8.42-8.43 (d, J = 4.5 Hz, 1H), 8.45-8.46 (d, J = 2.6 Hz, 1H), 9.73 (s, 1H), 13.85 (s, 1H).

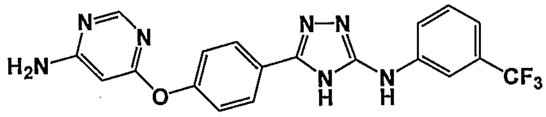
Example 51. Synthesis of 4-Methoxy-6-[4-(5-{[3-(trifluoromethyl)phenyl]amino}-4H-1,2,4-triazol-3-yl)phenoxy]pyrimidin-2-amine



[0231] 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)phenol (100 mg, 0.31 mmol) was dissolved in 3 mL of anhydrous dioxane in 2-5 mL microwave vial (Personal Chemistry). Solid Cs_2CO_3 (101.7 mg, 0.31 mmol) was added, followed by 2-amino-4-chloro-6-methoxypyrimidine (55.0 mg, 0.34 mmol). The vial was capped and microwaved at 200 °C for 15 min. Then ca. 3 mL of MeOH was added to dissolve the formed suspension. The resulting reddish-brown solution was transferred into a round-bottom flask and solvent was removed *in vacuo*. The residue was re-dissolved in 3 mL of DMF, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetontrile/water system with 0.01% of TFA. The fractions, containing the product, were collected and partitioned between EtOAc and saturated aqueous $NaHCO_3$. Ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title compound as an off-white solid (55.6 mg).

[0232] ESI-MS: $[M+H]^+$, 443.87. ^1H NMR (DMSO-d_6): δ 3.80 (s, 3H), 5.53 (s, 1H), 6.70 (s, 2H), 7.11-7.12 (d, J = 7.4 Hz, 1H), 7.30-7.32 (d, J = 8.4 Hz, 2H), 7.44-7.47 (t, J = 7.6 Hz, 1H), 7.74-7.76 (d, J = 8.4 Hz, 1H), 7.97-7.98 (d, J = 8.4 Hz, 2H), 8.10 (s, 1H), 9.73 (s, 1H), 13.88 (s, 1H).

Example 52. Synthesis of 6-[4-(5-{[3-(trifluoromethyl)phenyl]amino}-4H-[1,2,4]triazol-3-yl)-phenoxy]-pyrimidin-4-amine

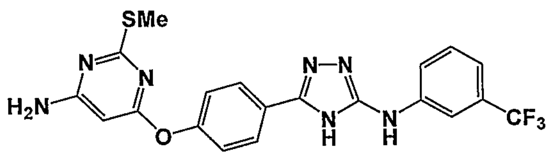


[0233] 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)phenol (100 mg, 0.31 mmol) was dissolved in 3 mL of anhydrous dioxane in 2-5 mL microwave vial (Personal

Chemistry). Solid Cs_2CO_3 (101.7 mg, 0.31 mmol) was added, followed by 4-amino-6-chloro-pyrimidine (48.5 mg, 0.37 mmol). The vial was capped and microwaved at 200 °C for 5 min. Then ca. 3 mL of MeOH was added to dissolve the formed suspension. The resulting reddish-brown solution was transferred into a round-bottom flask and solvent was removed *in vacuo*. The residue was re-dissolved in 3 mL of DMF, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetontrile/water system with 0.01% of TFA. The fractions, containing the product, were collected and partitioned between EtOAc and saturated aqueous $NaHCO_3$. Ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title compound as a white solid (76.6 mg).

[0234] ESI-MS: $[M+H]^+$, 461.0. ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H), 5.49 (s, 1H), 6.93 (s, 2H), 7.14 (m, 1H), 7.33-7.35 (d, J = 7.5 Hz, 2H), 7.45-7.48 (t, J = 7.6 Hz, 1H), 7.75 (m, 1H), 8.00-8.02 (d, J = 8.6 Hz, 2H), 8.10 (s, 1H), 9.75 (s, 1H), 13.88 (s, 1H).

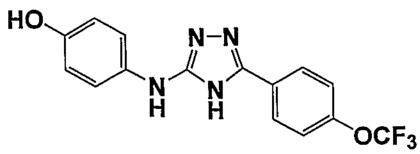
Example 53. Synthesis of 2-(Methylthio)-6-[4-(5-{[3-(trifluoromethyl)phenyl]amino}-4H-1,2,4-triazol-3-yl)-phenoxy]-pyrimidin-4-amine



[0235] 4-(5-{[3-(trifluromethyl)phenyl]amino}-4*H*-1,2,4-triazol-3-yl)phenol (100 mg, 0.31 mmol) was dissolved in 3 mL of anhydrous dioxane in 2-5 mL microwave vial (Personal Chemistry). Solid Cs_2CO_3 (101.7 mg, 0.31 mmol) was added, followed by 4-amino-6-chloro-2-(methylthio)-pyrimidine (60.3 mg, 0.34 mmol). The vial was capped and microwaved at 200 °C for 10 min. Then ca. 3 mL of MeOH was added to dissolve the formed suspension. The resulting reddish-brown solution was transferred into a round-bottom flask and solvent was removed *in vacuo*. The residue was re-dissolved in 3 mL of DMF, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetontrile/water system with 0.01% of TFA. The fractions, containing the product, were collected and partitioned between EtOAc and saturated aqueous $NaHCO_3$. Ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title compound as a white solid (39.5 mg).

[0236] ESI-MS: $[M+H]^+$, 461.0. ^1H NMR (DMSO-d_6): δ 3.80 (s, 3H), 5.53 (s, 1H), 6.70 (s, 2H), 6.30 (s, 2H), (d, J = 8.6 Hz, 2H),

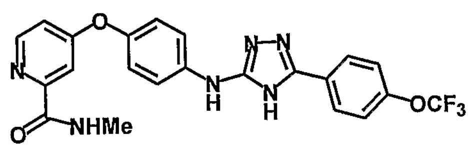
Example 54. Synthesis of 4-[5-(4-trifluoromethoxy-phenyl)-4*H*-[1,2,4]triazol-3-ylamino]-phenol



[0237] 4-trifluoromethoxybenzoic acid hydrazide (1.1 g, 5.0 mmol) and S-methyl N-[4-hydroxy-phenyl]isothiourea hydroiodide (1.55 g, 5.0 mmol) were suspended in 10 mL of anhydrous pyridine. The reaction mixture was refluxed for 24 hours, during which time it changed color from yellow into orange-red. Then it was cooled down to ambient temperature and poured with stirring into 150 mL of ice-water. The aqueous layer was decanted and the resulting residue was purified by silica gel chromatography using 1:1 mixture of ethyl acetate/hexane. Solvent was removed *in vacuo* to give the title product as a pinkish-grey solid (684.0 mg). 40.6 % yield.

[0238] ESI-MS: $[M+H]^+$, 337, 338. ^1H NMR (DMSO-d_6): δ 7.68-6.71 (d, J = 8.8 Hz, 2H), 7.32-7.35 (d, J = 8.8 Hz, 2H), 7.47-7.49 (d, J = 8.8 Hz, 2H), 8.04-8.07 (d, J = 8.8 Hz, 2H), 9.05 (br. s, 1H).

Example 55. Synthesis of 4-{4-[5-(4-trifluoromethoxy-phenyl)-4*H*-[1,2,4]triazol-3-ylamino]-phenoxy}-pyridine-2-carboxylic acid methylamide trifluoroacetic acid salt

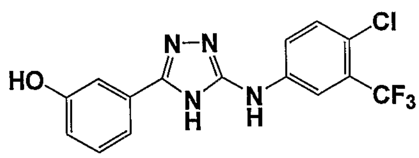


CF_3COOH

[0239] 4-[5-(4-trifluoromethoxy-phenyl)-4H[1,2,4]triazol-3-ylamino]-phenol (134.5 mg, 0.4 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (120.0 mg, 0.6 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloro-2-pyridine-carboxamide (68.2 mg, 0.4 mmol) was added, followed by anhydrous K_2CO_3 (62.0 mg, 0.44 mmol). Then the vial was capped and microwaved at 150 °C for 30 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (31.7 mg of white solid).

[0240] ESI-MS: $[M+H]^+$ 471, 472. ^{1}H NMR (DMSO-d_6): δ 2.77-2.78 (d, J = 4.8 Hz, 3H), 7.13-7.15 (d, J = 8.3 Hz, 2H), 7.13 (m, 1H), 7.40 (br. s, 1H), 7.51-7.53 (d, J = 8.3 Hz, 2H), 7.70-7.73 (d, J = 8.8 Hz, 2H), 8.09-8.11 (d, J = 8.8 Hz, 2H), 8.48-8.49 (d, J = 5.3 Hz, 1H), 8.77-8.78 (q, J = 4.8 Hz, 1H), 9.56 (s, 1H).

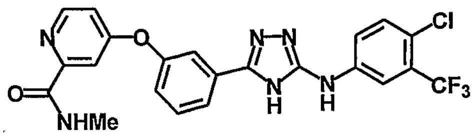
Example 56. Synthesis of 3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol



[0241] 3-hydroxybenzoic acid hydrazide (2.98 g, 19.58 mmol) and S-methyl N-[4-chloro-3-(trifluoromethyl)phenyl]isothiourea hydroiodide (7.78 g, 19.63mmol) were suspended in 40 mL of anhydrous pyridine. The reaction mixture was refluxed for 18 hours, during which time it changed color from yellow into dark-red. Then it was cooled down to ambient temperature and poured with stirring into 250 mL of ice-water. The aqueous solution was decanted and the oily residue was purified by silica gel chromatography on Isco column using 0 => 50 % gradient of ethyl acetate in hexane. Solvent was removed *in vacuo* to give the title product as a white solid (2.176 g). 31.3 % yield.

[0242] ESI-MS: $[M+H]^+$ 355.1, 356.8,. ^{1}H NMR (DMSO-d_6): δ 6.88-6.90 (dq, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 7.31-7.34 (t, J = 7.9 Hz, 1H), 7.35-7.39 (m, 2H), 7.54-7.56 (d, J = 8.8 Hz, 1H), 7.74-7.76 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 8.23-8.24 (d, J = 2.7 Hz, 1H), 9.79 (s, 1H), 9.87 (s, 1H), 13.86 (s, 1H).

Example 57. Synthesis of 4-{3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H-[1,2,4]triazol-3-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide trifluoroacetic acid salt

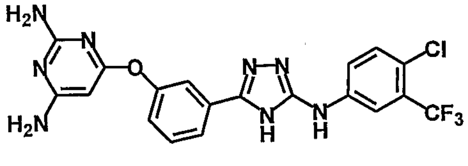


CF_3COOH

[0243] 3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloro-2-pyridine-carboxamide (52.9 mg, 0.31 mmol) was added, followed by anhydrous K_2CO_3 (19.5 mg, 0.141 mmol). Then the vial was capped and microwaved at 250 °C for 20 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (25.0 mg of white solid).

[0244] ESI-MS: $[M+H]^+$ 489, 490, 491. ^1H NMR (DMSO-d_6): δ 2.78-2.79 (d, J = 4.8 Hz, 3H), 7.25-7.26 (dd, J_1 = 2.5 Hz, J_2= 5.5 Hz, 1H), 7.38 (m, 1H), 7.48-7.49 (d, J = 2.5 Hz, 1H), 7.55-7.57 (d, J = 8.8 Hz, 1H), 7.67-7.70 (t, J = 7.8 Hz, 1H), 7.73 (br. s., 1H), 7.78 (br. s., 1H), 7.91-7.93 (d, J = 7.8 Hz, 1H), 8.20-8.21 (d, J = 2.6 Hz, 1H), 8.56-8.57 (d, J = 5.5 Hz, 1H), 8.80-8.81 (q, J = 4.8 Hz, 1H), 9.93 (s, 1H).

Example 58. Synthesis of 6-{3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine trifluoroacetic acid salt

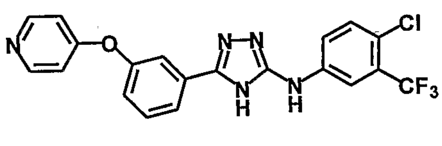


CF_3COOH

[0245] 3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was *added* and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloro-2,6-diamino-pyrimidine (44.8 mg, 0.31 mmol) was added, followed by anhydrous K_2CO_3 (19.5 mg, 0.141 mmol). Then the vial was capped and microwaved at 250 °C for 20 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (37.8 mg of beige solid).

[0246] ESI-MS: $[M+H]^+$ 464, 465. ^{1}H NMR (DMSO-d_6): δ 5.40 (s, 1H), 7.33-7.35 (d, *J*= 7.6 Hz, 1H), 7.57-7.59 (d, *J* = 8.8 Hz, 1H), 7.62-7.65 (t, *J* = 7.8 Hz, 1H), 7.73 (br. s., 1H), 7.80 (br. m., 1H), 7.88-7.89 (d, *J* = 7.8 Hz, 1H), 8.21-8.22 (d, *J* = 2.6 Hz, 1H), 9.96 (s, 1H).

Example 59. Synthesis of (4-chloro-3-trifluoromethyl-phenyl)-{5-[3-(pyridin-4-yloxy)-phenyl]-4H-[1,2,4]triazol-3-yl}-amine trifluoroacetic acid salt

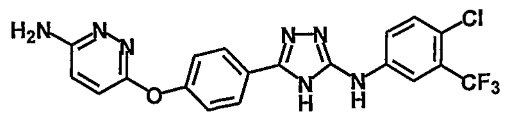


CF_3COOH

[0247] 3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 4-chloro-pyridine hydrochloride (46.5 mg, 0.31 mmol) was added, followed by anhydrous K_2CO_3 (19.5 mg, 0.141 mmol). Then the vial was capped and microwaved at 250 °C for 20 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (34.6 mg of beige solid).

[0248] ESI-MS: $[M+H]^+$ 432, 433. ^{1}H NMR (DMSO-d_6): δ 7.43-7.45 (br. s. 1H), 7.46-7.47 (d, *J*= 7.0 Hz, 2H), 7.56-7.58 (d, *J* = 8.8 Hz, 1H), 7.72-7.75 (t, *J* = 7.8 Hz, 1H), 7.80 (br. s., 1H), 7.81 (br. s, 1H), 7.98-8.00 (d, *J* = 7.8 Hz, 1H), 8.21-8.22 (d, *J* = 2.6 Hz, 1H8.76-8.78 (d, *J* = 7.0 Hz, 1H), 9.98 (s, 1H).

Example 60. Synthesis of 6-{3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyridazin-3-ylamine trifluoroacetic acid salt

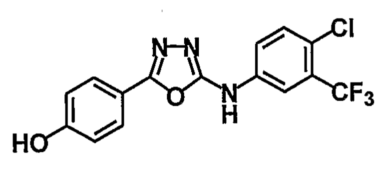


CF_3COOH

[0249] 3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*[1,2,4]triazol-3-yl]-phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF in a 5 mL microwave vial. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 3-amino-6-chloro-pyridazine (40.2 mg, 0.31 mmol) was added, followed by anhydrous K_2CO_3 (19.5 mg, 0.141 mmol). Then the vial was capped and microwaved at 250 °C for 20 min. Then the reaction mixture was diluted with ca. 1mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (35.5 mg of light-brown solid).

[0250] ESI-MS: $[M+H]^+$ 448, 449. ^{1}H NMR (DMSO-d_6): δ 7.38-7.39 (br. s. 1H), 7.55-7.57 (d, *J*= 9.6 Hz, 1H), 7.57-7.58 (d, *J* = 8.6 Hz, 1H), 7.62-7.65 (t, *J* = 7.8 Hz, 1H), 7.78 (br. s., 1H), 7.80 (br. s, 1H), 7.82-7.84 (d, *J* = 9.6 Hz, 1H), 7.86-7.88 (d, *J* = 7.8 Hz, 1H), 8.22-8.23 (d, *J* = 2.6 Hz, 1H), 8.52 (br.s., 2H), 9.94 (s, 1H).

Example 61. Synthesis of 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol

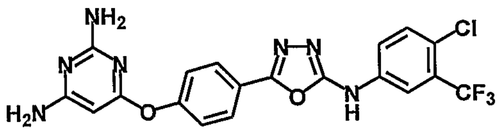


[0251] Mercury (II) oxide (yellow) (4.55 g, 21.0 mmol) was suspended in 60 mL of anhydrous MeOH under Ar. A bright-orange suspension was formed. To this suspension was added 4-hydroxybenzoic acid hydrazide (3.20 g, 21.0 mmol) and 4-chloro-3-trifluoromethyl-phenylisothiocyanate (5.0 g, 21.0 mmol). The reaction mixture was refluxed for 2 hours. The solvent was removed *in vacuo*. The black residue was redissolved in 100 mL of EtOAc and the resulting black suspension was filtered through a short pad of silica gel.

The filtrate was mixed with 10 g of dry silica gel and solvent was removed *in vacuo*. The impregnated silica gel was loaded on silica gel column and the product was separated using a gradient of hexane:ethyl acetate mixture starting from 50:50 ratio and finishing at 0:100. All fractions containing the product were combined; solvent was removed *in vacuo* to give a grey solid. The solid was heated in 50 mL of 4:1 mixture of EtOAc/MeOH. The formed suspension was cooled down to ambient temperature and filtered to give the title product as a white crystalline solid (4.54 g, 60.7 % yield).

[0252] ESI-MS: $[M+H]^+$ 356.0. ^{1}H NMR (DMSO-d_6): δ 6.92-6.95 (d, J= 8.8 Hz, 2H), 7.69-7.70 (d, J = 8.8 Hz, 1H), 7.71-7.73 (d, J= 8.8 Hz, 2H), 7.82-7.84 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 8.16-8.17 (d, J = 2.6 Hz, 1H), 10.21 (br s., 1H), 11.11 (br s., 1H).

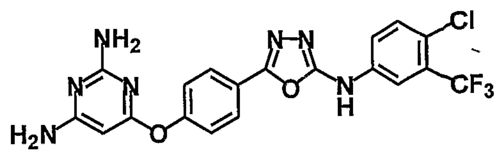
<u>Example 62. Synthesis of 6-[4-(5-{[4-Chloro-3-trifluoromethyl-phenyl]amino}-1,3,4-oxadiazol-2-yl)-phenoxy]-pyrimidine-2,4-diamine</u>



[0253] 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (1.067 g, 3.0 mmol) was dissolved in ca. 70 mL of anhydrous DMF under argon. Solid potassium bis(trimethylsilyl)amide (0.718 g, 3.6 mmol) was added and the resulting yellow solution was heated at 70 °C for 1.5 hours. Then solid K_2CO_3 (0.414 g, 3.0 mmol) was added, followed by 2,6-diamino-4-chloropyrimidine (0.520 g, 3.6 mmol). The reaction mixture was left to reflux under argon for 30 hours. Then it was allowed to cool down to ambient temperature and poured into ca. 500 mL of water. The aqueous mixture was extracted 5 times with 100 mL of EtOAc. Combined EtOAc extracts were washed three times with 100 mL of brine, and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo* to a give a reddish-yellow residue, which was purified by silica gel chromatography using EtOAc as an eluent. Fractions, containing the product, were collected; solvent was removed in vacuo to give the product as a reddish-yellow solid. The solid was re-crystallized from 10 mL of EtOAc, collected, washed thoroughly with diethyl ether and dried *in vacuo* to give the title compound (0.527 g, 38 % yield) as beige solid.

[0254] ESI-MS: $[M+H]^+$ 464, 465. ^{1}H NMR (DMSO-d_6): δ 5.20 (s, 1H), 6.05 (br s., 2H), 6.34 (br.s., 2H), 7.27-7.30 (d, J= 8.7 Hz, 2H), 7.71-7.72 (d, J = 8.8 Hz, 1H), 7.84-7.88 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 7.89-7.91 (d, J= 8.7 Hz, 2H), 8.18-8.19 (d, J = 2.6 Hz, 1H), 11.26 (s, 1H). Anal. Calcd for $C_{19}H_{13}ClF_3N_7O_2$: C, 49.20; H, 2.83; N, 21.14, Found: C, 49.08; H, 3.21; N, 20.95.

Example 63. Synthesis of 6-[4-(5-{[4-chloro-3-trifluoromethyl-phenyl]amino}-1,3,4-oxadiazol-2-yl)-phenoxy]-pyrimidine-2,4-diamine trifluoroacetic acid salt

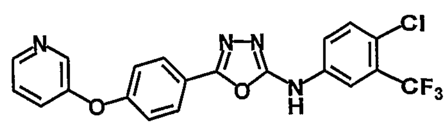


CF_3COOH

[0255] 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (100 mg, 0.281 mmol) was dissolved in 2.5 mL of anhydrous DMF in a 5 mL microwave vial. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.703 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 15 min, then 6-chloro-2,4-diamino-pyrimidine (81.3 mg, 0.562 mmol) was added, followed by anhydrous K_2CO_3 (19.5 mg, 0.141 mmol). Then the vial was capped and microwaved at 200 °C for 15 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. The product was isolated as a TFA salt (75.8 mg of beige solid).

[0256] ESI-MS: $[M+H]^+$ 464, 465. ^1H NMR (DMSO-d_6): δ 5.41 (s, 1H), 7.39-7.42 (d, J= 8.7 Hz, 2H), 7.63 (br s., 4H), 7.72-7.74 (d, J = 8.8 Hz, 1H), 7.85-7.87 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 7.95-7.97 (d, J= 8.7 Hz, 2H), 8.20 (d, J = 2.7 Hz, 1H), 11.29 (s, 1H).

Example 64. Synthesis of N-[4-chloro-3-(trifluoromethyl)phenyl]-5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine trifluoroacetate salt

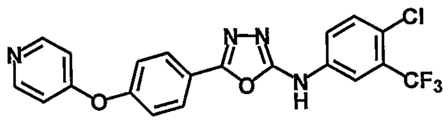


CF_3COOH

[0257] 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (100 mg, 0.281 mmol) was dissolved in ca. 2 mL of anhydrous DMF under argon. Solid potassium bis(trimethylsilyl)amide (140.2 mg, 0.702 mmol) was added and the resulting yellow solution was heated at 80°C for 15 min. Then solid K_2CO_3 (19.4 mg, 0.140 mmol) was added, followed by 3-bromopyridine (89.0 mg, 0.562 mmol). The reaction mixture was microwaved at 250 °C for 10 min. Then it was diluted with 1 mL of MeOH, filtered and purified by preparative reverse-phase chromatography using acetonitrile/water with 0.1 % TFA gradient. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give the title product as a brown oil (20.6 mg).

[0258] ESI-MS: $[M+H]^+$ 433.5, 434.3. ^{1}H NMR (DMSO-d_6): δ 7.24-7.26 (d, J = 8.8 Hz, 2H), 7.57-7.59 (dd, J_1 = 8.4 Hz, J_2 = 4.7 Hz, 1H), 7.68-7.71 (dq, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H), 7.71-7.73 (d, J = 8.8 Hz, ^{1H}), 7.84-7.86 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 7.92-7.94 (d, J = 8.8 Hz, 2H), 8.17-8.18 (d, J = 2.7 Hz, 1H), 8.50 (br d, J = 4.0 Hz, 1H), 8.54 (br s, 1H), 11.24 (s, 1H).

<u>Example 65. Synthesis of N-[4-chloro-3-(trifluoromethyl)phenyl]-5-[4-(pyridin-4-yloxy)phenyl]-1,3,4-oxadiazol-2-amine trifluoroacetate salt</u>

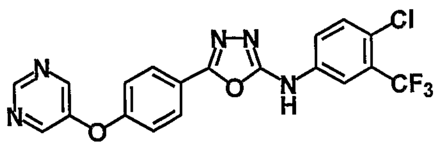


CF_3COOH

[0259] 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (100 mg, 0.281 mmol) was dissolved in ca. 2 mL of anhydrous DMF under argon. Solid potassium bis(trimethylsilyl)amide (225 mg, 1.12 mmol) was added and the resulting yellow solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (38.8 mg, 0.281 mmol) was added, followed by 4-chloropyridine hydrochloride (84.3 mg, 0.562 mmol). The reaction mixture was microwaved at 200 °C for 25 min (Initiator, Biotage). Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give the title product as a white fluffy solid (85.6 mg).

[0260] ESI-MS: $[M+H]^+$ 435.3. ^{1}H NMR (DMSO-d_6): δ 7.37-7.38 (d, J = 4.8 Hz, 2H), 7.48-7.50 (d, J = 8.8 Hz, 2H), 7.72-7.74 (d, J = 8.8 Hz, 1H), 7.85-7.88 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 8.03-8.06 (d, J = 8.8 Hz, 1H), 8.19-8.20 (d, J = 2.7 Hz, 1H), 8.74 (br s., 2H), 11.31 (s, 1H).

Example 66. Synthesis of N-[4-chloro-3-(trifluoromethyl)phenyl]-5-[4-(pyrimidin-5-yloxy)phenyl]-1,3,4-oxadiazol-2-amine trifluoroacetate salt

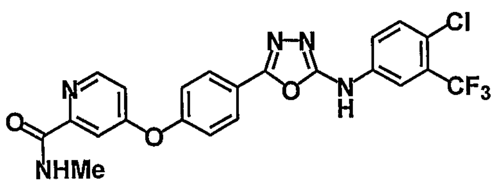


CF_3COOH

[0261] 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (100 mg, 0.281 mmol) was dissolved in ca. 2 mL of anhydrous DMF under argon. Solid potassium bis(trimethylsilyl)amide (140.2 mg, 0.702 mmol) was added and the resulting yellow solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (19.4 mg, 0.140 mmol) was added, followed by 3-bromopyrimidine (89.4 mg, 0.562 mmol). The reaction mixture was microwaved at 200 °C for 15 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give the title product as a white fluffy solid (73.0 mg of white crystalline solid).

[0262] ESI-MS: $[M+H]^+$ 434.3, 435.3. 1H NMR (DMSO-d_6): δ 7.31-7.33 (d, J = 8.8 Hz, 2H), 7.71-7.73 (d, J = 8.8 Hz, 1H), 7.84-7.86 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 7.93-7.95 (d, J = 8.8 Hz, 2H), 8.17-8.18 (d, J = 2.7 Hz, 1H), 8.77 (s, 2H), 9.09 (s, 1H), 11.25 (s, 1H).

Example 67. Synthesis of 4-[4-(5-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenoxy]-N-methylpyridine-2-carboxamide trifluoroacetate salt

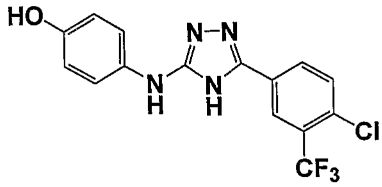


CF_3COOH

[0263] 4-(5-{[4-chloro-3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (100 mg, 0.281 mmol) was dissolved in ca. 2 mL of anhydrous DMF under argon. Solid potassium bis(trimethylsilyl)amide (140.2 mg, 0.702 mmol) was added and the resulting yellow solution was heated at 80°C for 15 min. Then solid K_2CO_3 (19.4 mg, 0.140 mmol) was added, followed by 4-chloro-2-pyridine-carboxamide (52.7 mg, 0.309 mmol). The reaction mixture was microwaved at 200 C for 15 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give the title product as a white solid (67.5 mg).

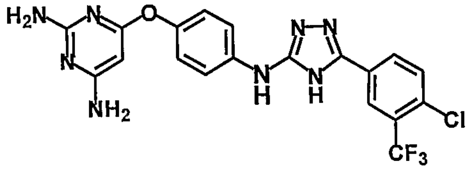
[0264] ESI-MS: $[M+H]^+$ 490.4, 491.3 . ^1H NMR (DMSO-d_6): δ 2.79-2.80 (d, J = 4.9 Hz, 3H), 7.26-7.28 (dd, J_1 = 5.6 Hz, J_2 = 2.6 Hz, 1H), 7.43-7.44 (d, J = 6.8 Hz, 2H), 7.49 (d, J = 2.6 Hz, 1H), 7.72-7.74 (d, J= 8.8 Hz, 1H), 7.85-7.86 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 8.01-8.03 (d, J = 6.8 Hz, 2H), 8.19 (d, J = 2.6 Hz, 1H), 8.57-8.58 (d, J = 5.7 Hz, 1H), 8.79-8.81 (q, J = 4.9 Hz, 1H), 11.28 (s, 1H).

Example 68. Synthesis of 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol



[0265] 4-chloro-3-trifluoromethylbenzoic acid hydrazide (2.89 g, 12.1 mmol) and S-methyl N-(4-hydroxyphenyl)isothiourea hydroiodide (3.75 g, 12.1 mmol) were suspended in 40 mL of anhydrous pyridine. The reaction mixture was refluxed for 18 hours, during which time it changed color from yellow into dark-red. Then it was cooled down to ambient temperature and poured with stirring into 250 mL of ice-water. The aqueous solution was decanted and the oily residue was purified by silica gel chromatography using 1:1 mixture of ethyl acetate/hexane. Solvent was removed *in vacuo* to give the title product as a white solid (1.95 g). Yield 45.5 %.

Example 69. Synthesis of 6-[4-({5-[4-chloro-3-(trifluoromethyl)phenyl-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]pyrimidine-2,4-diamine trifluoroacetate salt

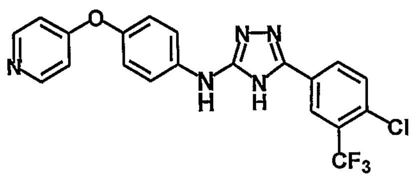


CF_3COOH

[0266] 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was added and the resulting solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (20 mg, 0.141 mmol) was added, followed by 4-chloro-2,6-diamino-pyrimidine (61.1 mg, 0.422 mmol). The reaction mixture was microwaved at 200 °C for 20 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected, solvent was removed *in vacuo* to give trifluoroacetate salt of the product as a white solid (28.6 mg).

[0267] ESI-MS: $[M+H]^+$ 463.4, 464.4 . 1H NMR (DMSO-d_6): δ 5.24 (s, 1H), 7.14-7.16 (d, J = 8.8 Hz, 2H), 7.65-7.66 (d, J = 8.8 Hz, 2H), 7.81 (br s., 4H), 7.88-7.90 (d, J = 8.4 Hz, 1H), 8.23-8.25 (dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H), 8.37 (s, 1H), 9.66 (br s., 1H).

<u>Example 70. Synthesis of 5-[4-chloro-3-(trifluoromethyl)phenyl]-N-[4-(pyridine-4-yloxy)phenyl]-4*H*-1,2,4-triazol-3-amine trifluoroacetate salt</u>



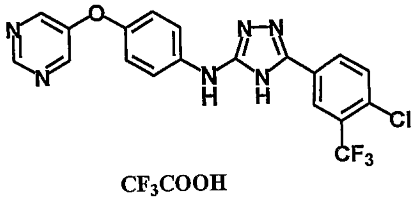
CF_3COOH

[0268] 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF. Solid potassium bis(trimethylsilyl)amide (196.2 mg, 0.983 mmol) was added and the resulting solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (20 mg, 0.141 mmol) was added, followed by 4-chloropyridine hydrochloride (63.2 mg, 0.421 mmol). The reaction mixture was microwaved at 220 °C for 30 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected, solvent was removed *in vacuo* to give trifluoroacetate salt of the product as a light-brown solid (23.5 mg).

[0269] ESI-MS: $[M+H]^+$ 432, 433 . ^{1}H NMR (DMSO-d_6): δ 7.23-7.25 (d, J = 8.8 Hz, 2H), 7.39-7.40 (d, J = 7.2 Hz, 2H), 7.74-7.77 (d, J = 8.8 Hz, 2H), 7.89-7.90 (m, 1H), 8.24-8.26

(dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.38 (s, 1H), 8.73-8.74 (d, J = 7.2 Hz, 2H), 9.75 (br s., 1H).

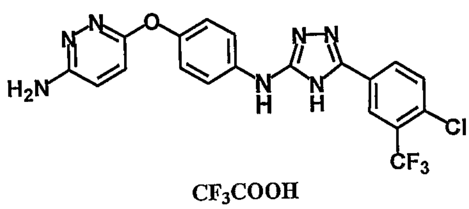
Example 71. Synthesis of 5-[4-chloro-3-(trifluoromethyl)phenyl]-N-[4-(pyrimidin-5-yloxy)phenyl]-4*H*-1,2,4-triazol-3-amine trifluoroacetate salt



[0270] 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF. Solid potassium bis(trimethylsilyl)amide (84.1 mg, 0.421 mmol) was added and the resulting solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (20 mg, 0.141 mmol) was added, followed by 5-bromopyrimidine (67.0 mg, 0.421 mmol). The reaction mixture was microwaved at 220 °C for 20 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give trifluoroacetate salt of the product as a light-brown solid (25.0 mg).

[0271] ESI-MS: $[M+H]^+$ 432.9, 435. ^{1}H NMR (DMSO-d_6): δ 7.14-7.16 (d, J = 8.9 Hz, 2H), 7.63-7.67 (d, J = 8.9 Hz, 2H), 7.87-7.89 (d, J = 8.4 Hz, 1H), 8.22-8.24 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.36 (s, 1H), 8.54 (s, 2H), 8.93 (s, 1H), 9.57 (br s., 1H).

Example 72. Synthesis of 6-[4-({5-[4-chloro-3-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]pyridazin-3-amine trifluoroacetate salt

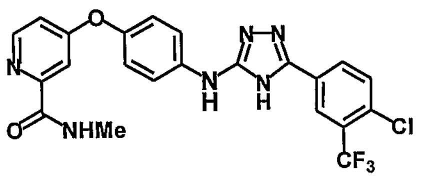


[0272] 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was added and the resulting solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (20 mg, 0.141 mmol) was added, followed by

3-amino-6-chloropyridazine (54.6 mg, 0.421 mmol). The reaction mixture was microwaved at 220 °C for 40 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give trifluoroacetate salt of the product as a light-brown solid (23.1 mg).

[0273] ESI-MS: $[M+H]^+$ 448, 449. ^1H NMR (DMSO-d_6): δ 7.16-7.18 (d, J = 8.9 Hz, 2H), 7.51-7.53 (d, J = 9.7 Hz, 1H), 7.62-7.66 (d, J = 8.9 Hz, 2H), 7.73-7.75 (d, J = 9.7 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.23-8.25 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.36 (s, 1H), 8.48 (br s., 2H), 9.62 (br s., 1H).

Example 73. Synthesis of 4-[4-({5-[4-chloro-3-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]-N-methylpyridine-2-carboxamide trifluoroacetate salt

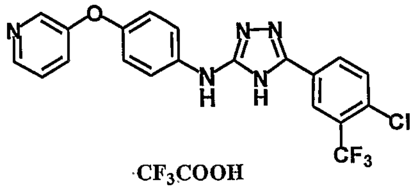


CF_3COOH

[0274] 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol (100 mg, 0.282 mmol) was dissolved in 2 mL of anhydrous DMF. Solid potassium bis(trimethylsilyl)amide (140.6 mg, 0.705 mmol) was added and the resulting solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (20 mg, 0.141 mmol) was added, followed by 4-chloro-2-pyridine-carboxamide (71.9 mg, 0.421 mmol). The reaction mixture was microwaved at 220 °C for 20 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected; solvent was removed *in vacuo* to give trifluoroacetate salt of the product as yellow solid (25.4 mg).

[0275] ESI-MS: $[M+H]^+$ 489, 490. ^1H NMR (DMSO-d_6): δ 2.77-2.78 (d, J = 4.8 Hz, 3H), 7.14-7.15 (dd, J_1 = 5.6 Hz, J_2 = 2.5 Hz, 1H), 7.15-7.17 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 2.5 Hz, 1H), 7.68-7.71 (d, J = 9.0 Hz, 2H), 7.87-7.89 (d, J = 8.4 Hz, 1H), 8.23-8.25 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.37 (s, 1H), 8.49-8.50 (d, J = 5.6 Hz, 1H), 8.75-8.78 (q, J = 4.8 Hz, 1H), 9.65 (br s., 1H).

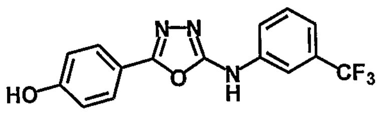
Example 74. Synthesis of 5-[4-chloro-3-(trifluoromethyl)phenyl]-N-[4-(pyridine-3-yloxy)phenyl]-4*H*-1,2,4-triazol-3-amine trifluoroacetate salt



[0276] 4-[5-(4-chloro-3-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-3-ylamino]phenol (200 mg, 0.562 mmol) was dissolved in 2 mL of anhydrous DMF. Solid potassium bis(trimethylsilyl)amide (280.3 mg, 1.405 mmol) was added and the resulting solution was heated at 80 °C for 15 min. Then solid K_2CO_3 (40 mg, 0.282 mmol) was added, followed by 3-bromopyridine (177.6 mg, 1.12 mmol). The reaction mixture was microwaved at 250 °C for 20 min. Then it was diluted with 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by preparative reverse-phase chromatography using acetonitrile/water gradient with 0.1 % TFA. The major peak having the mass of the product was collected, solvent was removed *in vacuo* to give trifluoroacetate salt of the product as a yellow solid (17.0 mg).

[0277] ESI-MS: $[M+H]^+$ 432, 433 . ^{1}H NMR (DMSO-d_6): δ 7.09-7.11 (d, J = 9.0 Hz, 2H), 7.50-7.52 (m, 2H), 7.63-7.66 (d, J = 9.0 Hz, 2H), 7.87-7.89 (d, J = 8.4 Hz, 1H), 8.22-8.25 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.37-8.38 (m, 2H), 8.43 (m, 1H), 9.56 (br s., 1H).

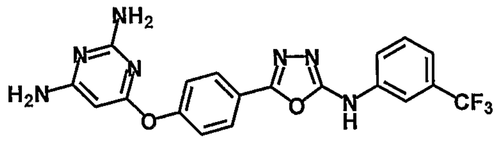
Example 75. Synthesis of 4-(5-{[3-(Trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol



[0278] Mercury (II) oxide yellow (5.33 g, 24.60 mmol) was suspended in ca. 70 mL of anhydrous methanol. 4-Hydroxybenzoic acid hydrazide (3.74 g, 24.60 mmol) was added to this bright-orange suspension, followed by 3-triflurormethylphenylisothiocyanate (5.0 g, 24.60 mmol). The reaction mixture was brought to reflux and refluxed for 2 hours. The reaction mixture turned pitch-black in color and formed black precipitate. Then it was cooled down to ambient temperature and filtered through a short pad of Celite, then through a short pad of silica gel. Then methanol was removed *in vacuo* and the resulting grey precipitate was re-crystallized from ca. 100 mL of EtOAc. The formed white crystalline solid was filtered, washed with a small amount of EtOAc and dried *in vacuo* to give the title product as white crystals (7.182 g). Yield 71.3%.

[0279] ESI-MS: $[M+H]^+$ 322.0 . ^1H NMR (DMSO-d_6): δ 6.92-6.95 (d, J = 8.7 Hz, 2H), 7.33-7.35 (d, J = 8.3 Hz, 1H), 7.57-7.60 (t, J = 8.0 Hz, 1H), 7.72-7.75 (d, J = 8.7 Hz, 2H), 7.80-7.82 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 8.06 (s, 1H), 10.21 (s, 1H), 10.99 (br s., 1H). ^{13}C NMR (DMSO-d6) 112.9, 114.5, 116.1, 117.9, 120.6, 127.6, 129.7, 130.0, 130.3, 139.6, 158.3, 158.9, 160.1.

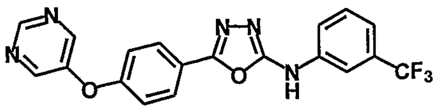
Example 76. Synthesis of 6-[4-(5-{[3-(trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenoxy}pyrimidine-2,4-diamine



[0280] 4-(5-{[3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (160.6 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (119.7 mg, 0.6 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 6-chloro-2,4-diamino-pyrimidine (86.7 mg, 0.6 mmol) was added, followed by anhydrous K_2CO_3 (69.1 mg, 0.5 mmol). Then the vial was capped and microwaved at 200 °C for 20 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a beige solid (81.0 mg). Yield 37.7%.

[0281] ESI-MS: $[M+H]^+$ 430.29. ^1H NMR (DMSO-d_6): δ 5.19 (s, 1H),6.04 (s, 2H), 6.33 (s, 2H), 7.27-7.30 (d, J= 8.7 Hz, 2H), 7.36-7.37 (d, J = 7.9 Hz, 1H), 7.59-7.63 (t, J = 8.0 Hz, 1H), 7.82-7.83 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.89-7.92 (d, J= 8.7 Hz, 2H), 8.08 (s, 1H). 11.11 (s, 1H).

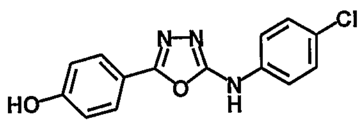
Example 77. Synthesis of 5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[3-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2-amine



[0282] 4-(5-{[3-(trifluoromethyl)-phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (160.6 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (149.6 mg, 0.75 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 5-bromopyrimidine (119.2 mg, 0.75 mmol) was added, followed by anhydrous K_2CO_3 (69.1 mg, 0.5 mmol). Then the vial was capped and microwaved at 200 °C for 20 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a beige solid (87.0 mg). Yield 43.5%.

[0283] ESI-MS: $[M+H]^+$ 400.16. ^{1}H NMR (DMSO-d_6): δ 7.31-7.33 (d, J= 8.7 Hz, 2H), 7.35-7.37 (d, J = 7.9 Hz, 1H), 7.59-7.62 (t, J = 8.0 Hz, 1H), 7.81-7.83 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.93-7.95 (d, J= 8.7 Hz, 2H), 8.07 (s, 1H), 8.76 (s, 2H), 9.08 (s, 1H), 11.11 (s, 1H).

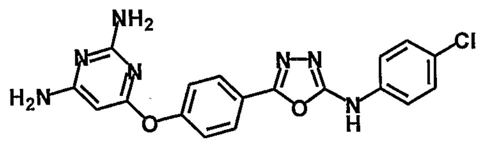
Example 78. Synthesis of 4-{5-[(4-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenol



[0284] Mercury (II) oxide yellow (6.38 g, 29.47 mmol) was suspended in ca. 70 mL of anhydrous methanol. 4-Hydroxybenzoic acid hydrazide (4.48 g, 29.47 mmol) was added to this bright-orange suspension, followed by 4-chlorophenylisothiocyanate (5.0 g, 29.47 mmol). The reaction mixture was brought to reflux and refluxed for 2 hours. The reaction mixture turned pitch-black in color and formed black precipitate. Then it was cooled down to ambient temperature and filtered through a short pad of Celite, then through a short pad of silica gel. Then methanol was removed *in vacuo* and the resulting grey precipitate was re-crystallized from ca. 40 mL of EtOAc. The formed white precipitate was filtered, washed with a small amount of EtOAc and dried *in vacuo* to give the title product as a white powder.

[0285] ESI-MS: $[M+H]^+$ 287.94. ^1H NMR (DMSO-d_6): δ 6.91-6.94 (d, J = 8.7 Hz, 2H), 7.39-7.41 (d, J = 8.9 Hz, 2H), 7.61-7.63 (d, J = 8.9 Hz, 2H), 7.71-7.74 (d, J = 8.7 Hz, 2H), 10.19 (s, 1H), 10.73 (s, 1H). ^{13}C NMR (DMSO-d6) 114.6, 116.1, 118.5, 125.3, 127.5, 128.9, 137.8, 158.1, 159.1, 160.0.

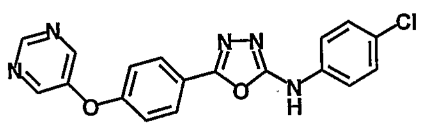
Example 79. Synthesis of 6-(4-{5-[(4-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenoxy) pyrimidine-2,4-diamine



[0286] 4-{5-[(4-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenol (144.0 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (100.0 mg, 0.5 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 6-chloro-2,4-diamino-pyrimidine (72.3 mg, 0.5 mmol) was added, followed by anhydrous K_2CO_3 (34.5 mg, 0.25 mmol). Then the vial was capped and microwaved at 200 °C for 15 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a beige solid (24.5 mg).

[0287] ESI-MS: $[M+H]^+$ 396.25. ^1H NMR (DMSO-d_6): δ 5.19 (s, 1H), 6.04 (s, 2H), 6.33 (s, 2H), 7.26-7.29 (d, J = 8.7 Hz, 2H), 7.41-7.43 (d, J = 8.9 Hz, 2H), 7.63-7.65 (d, J = 8.9 Hz, 2H), 7.88-7.90 (d, J = 8.7 Hz, 2H), 10.85 (s, 1H).

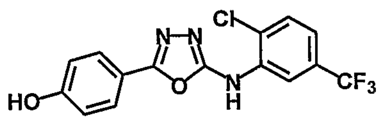
Example 80. Synthesis of 5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[4-chloro-phenyl]-1,3,4-oxadiazol-2-amine



[0288] 4-{5-[(4-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenol (144.0 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (100.0 mg, 0.5 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 5-bromopyrimidine (79.5 mg, 0.5 mmol) was added, followed by anhydrous K_2CO_3 (34.5 mg, 0.25 mmol). Then the vial was capped and microwaved at 200 °C for 15 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a beige solid (61.6 mg).

[0289] ESI-MS: $[M+H]^+$ 366.24. ^{1}H NMR (DMSO-d_6): δ 7.30-7.32 (d, J = 8.7 Hz, 2H), 7.41-7.43 (d, J = 8.9 Hz, 2H), 7.63-7.65 (d, J = 8.9 Hz, 2H), 7.92-7.94 (d, J = 8.7 Hz, 2H), 8.76 (s, 2H), 9.08 (s, 1H), 10.85 (s, 1H).

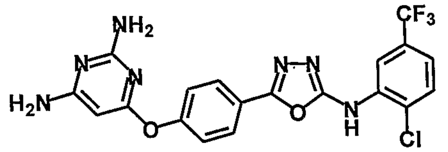
<u>Example 81. Synthesis of 4-(5-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol</u>



[0290] Mercury (II) oxide yellow (1.82 g, 8.41 mmol) was suspended in ca. 50 mL of anhydrous methanol. 4-Hydroxybenzoic acid hydrazide (1.28 g, 8.41 mmol) was added to this bright-orange suspension, followed by 2-chloro-5-trifluoromethyl-phenylisothiocyanate (2.0 g, 8.41 mmol). The reaction mixture was brought to reflux and refluxed for 2 hours. The reaction mixture turned pitch-black in color and formed black precipitate. Then it was cooled down to ambient temperature and filtered through a short pad of Celite, then through a short pad of silica gel. Then methanol was removed *in vacuo* and the resulting grey solid was re-crystallized from ca. 20 mL of EtOAc. The formed white precipitate was filtered, washed with anhydrous Et_2O and dried *in vacuo* to give the title product as a white solid (2.638 g). Yield 88.1%

[0291] ESI-MS: $[M+H]^+$ 356.22. ^{1}H NMR (DMSO-d_6): δ 6.93-6.96 (d, J = 8.7 Hz, 2H), 7.41-7.43 (dd, J_1 = 8.3 Hz, J_2 = 1.7 Hz, 1H), 7.72-7.75 (m, 3H), 8.61 (s, 1H), 10.23 (s, 1H), 10.30 (s, 1H).

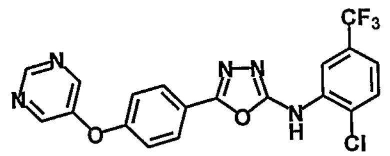
Example 82. Synthesis of 6-(4-{5-[(2-chloro-5-trifluoromethyl-phenyl)amino]-1,3,4-oxadiazol-2-yl}phenoxy) pyrimidine-2,4-diamine



[0292] 4-(5-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (177.85 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (200.0 mg, 1.0 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 6-chloro-2,4-diamino-pyrimidine (86.7 mg, 0.6 mmol) was added, followed by anhydrous K_2CO_3 (69.1 mg, 0.5 mmol). Then the vial was capped and microwaved at 180 °C for 30 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 50 mL of EtOAc and ca. 50 mL of saturated aqueous $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as an off-white solid (131.1 mg). Yield 56.5%.

[0293] ESI-MS: $[M+H]^+$ 464.21. ^{1}H NMR (DMSO-d_6): δ 5.20 (s, 1H), 6.05 (s, 2H), 6.34 (s, 2H), 7.28-7.31 (d, J = 8.7 Hz, 2H), 7.46-7.48 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.76-7.78 (d, J = 8.3 Hz, 1H), 7.90-7.92 (d, J = 8.7 Hz, 2H), 8.62 (s, 1H), 10.47 (s, 1H).

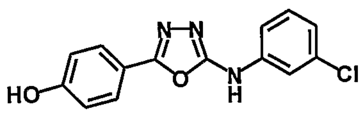
Example 83. Synthesis of 5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[2-chloro-5-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2-amine



[0294] 4-(5-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenol (177.85 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (200.0 mg, 1.0 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 5-bromopyrimidine (95.4 mg, 0.6 mmol) was added, followed by anhydrous K_2CO_3 (69.1 mg, 0.5 mmol). Then the vial was capped and microwaved at 180 °C for 40 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 50 mL of EtOAc and ca. 50 mL of saturated aqueous $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a beige solid (129.1 mg). Yield 59.5%.

[0295] ESI-MS: $[M+H]^+$ 434.20. ^{1}H NMR (DMSO-d_6): δ 7.32-7.35 (d, J = 8.7 Hz, 2H), 7.46-7.48 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.76-7.78 (d, J = 8.3 Hz, 1H), 7.94-7.96 (d, J = 8.7 Hz, 2H), 8.61 (s, 1H), 8.77 (s, 2H), 9.09 (s, 1H), 10.47 (s, 1H).

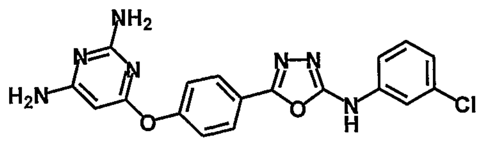
Example 84 . Synthesis of 4-{5-[(3-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenol



[0296] Mercury (II) oxide yellow (6.38 g, 29.47 mmol) was suspended in ca. 100 mL of anhydrous methanol. 4-Hydroxybenzoic acid hydrazide (4.48 g, 29.47 mmol) was added to this bright-orange suspension, followed by 3-chlorophenylisothiocyanate (5.0 g, 29.47 mmol). The reaction mixture was brought to reflux and refluxed for 2 hours. The reaction mixture turned pitch-black in color and formed black precipitate. Then it was cooled down to ambient temperature and filtered through a short pad of Celite. Then it was purified by silica gel chromatography using 0% to 20 % methanol gradient in EtOAc. Solvent was removed *in vacuo* and the resulting grey precipitate was re-crystallized from ca. 50 mL of EtOAc. The formed white crystalline solid was filtered, washed with a small amount of EtOAc, anhydrous Et_2O and dried *in vacuo* to give the title product as a white powder (7.606 g). Yield 89.7%.

[0297] ESI-MS: $[M+H]^+$ 288.26 . ^{1}H NMR (DMSO-d_6): δ 6.92-6.94 (d, J = 8.7 Hz, 2H), 7.00-7.02 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1H), 7.33-7.36 (t, J = 8.1 Hz, 1H), 7.47-7.49 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 7.72-7.74 (d, J = 8.7 Hz, 2H), 7.76-7.78 (t, J = 2.1 Hz, 1H), 10.19 (s, 1H), 10.81 (s, 1H). ^{13}C NMR (DMSO-d6) 114.6, 115.5, 116.1, 116.4, 121.3, 127.6, 130.6, 133.5, 140.3, 158.3, 159.0, 160.1.

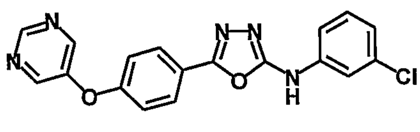
Example 85. Synthesis of 6-(4-{5-[(3-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenoxy) pyrimidine-2,4-diamine



[0298] 4-{5-[(3-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenol (143.8 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (200.0 mg, 1.0 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 6-chloro-2,4-diamino-pyrimidine (86.7 mg, 0.6 mmol) was added, followed by anhydrous K_2CO_3 (69.1 mg, 0.5 mmol). Then the vial was capped and microwaved at 180 °C for 40 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 50 mL of EtOAc and ca. 50 mL of saturated aqueous $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a light-yellow solid (62.0 mg). Yield 31.3%.

[0299] ESI-MS: $[M+H]^+$ 396.22. ^1H NMR (DMSO-d_6): δ 5.19 (s, 1H), 6.04 (s, 2H), 6.33 (s, 2H), 7.06-7.08 (m, 1H), 7.27-7.29 (d, J = 8.7 Hz, 2H), 7.37-7.41 (t, J = 8.1 Hz, 1H), 7.50-7.52 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 7.78-7.79 (t, J = 2.1 Hz, 1H), 7.89-7.90 (d, J = 8.7 Hz, 2H), 10.95 (s, 1H).

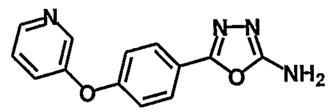
Example 86. Synthesis of 5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[3-chloro-phenyl]-1,3,4-oxadiazol-2-amine



[0300] 4-{5-[(3-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenol (143.8 mg, 0.5 mmol) was dissolved in 3 mL of anhydrous DMF in a 2-5 mL microwave vial (Personal Chemistry). Solid potassium bis(trimethylsilyl)amide (200.0 mg, 1.0 mmol) was added and the reaction mixture was stirred with heating at 80 °C for 10 min, then 5-bromopyrimidine (95.4 mg, 0.6 mmol) was added, followed by anhydrous K_2CO_3 (69.1 mg, 0.5 mmol). Then the vial was capped and microwaved at 180 °C for 30 min. Then the reaction mixture was diluted with ca. 1 mL of MeOH, filtered through 0.22 um syringe filter and purified by reverse-phase preparative HPLC in acetonitrile/water system with 0.01% TFA. Fractions, containing the product, were partitioned between ca. 50 mL of EtOAc and ca. 50 mL of saturated aqueous $NaHCO_3$. EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed *in vacuo* to give the title product as a light-yellow solid (74.7 mg). Yield 40.8%.

[0301] ESI-MS: $[M+H]^+$ 366.23. ^{1}H NMR (DMSO-d_6): δ 7.06-7.08 (m, 1H), 7.31-7.33 (d, J = 8.7 Hz, 2H), 7.37-7.41 (t, J = 8.1 Hz, 1H), 7.50-7.52 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 7.77-7.79 (t, J = 2.0 Hz, 1H), 7.93-7.94 (d, J = 8.7 Hz, 2H), 8.77 (s, 2H), 9.09 (s, 1H), 10.96 (s, 1H).

<u>Example 87. Synthesis of 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt</u>

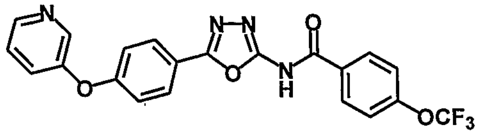


HBr

[0302] 4-(pyridine-3-yloxy)benzohydrazide (3.7 g, 16.14 mmol) was dissolved in 100 mL of anhydrous THF and 3.0 M solution of cyanogen bromide (5.38 mL, 16.14 mmol) was added via syringe. Within 5-10 min of stirring an orange precipitate started to form. The reaction mixture was brought to reflux and refluxed for 1 hr. Then it was cooled down to ambient temperature and filtered. The collected orange precipitate was washed with ca. 100 mL of THF, ca. 100 mL of EtOAc, anhydrous Et2O and dried *in vacuo* to give the title product as an orange solid (4.40 g). Yield 81.4%.

[0303] ESI-MS: $[M+H]^+$ 255.05. ^{1}H NMR (DMSO-d_6): δ 7.27-7.29 (d, J = 8.8 Hz, 2H), 7.75-7.78 (dd, J_1 = 8.5 Hz, J_2 = 5.0 Hz, 1H), 7.85-7.87 (d, J = 8.8 Hz, 2H), 7.92-7.94 (m, 1H), 8.59-8.60 (dd, J_1 = 5.0 Hz, J_2 = 1.0 Hz, 1H), 8.69-8.70 (d, J = 2.7 Hz, 1H).

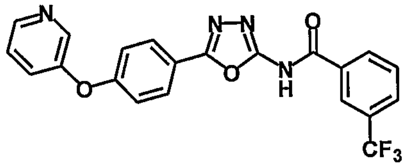
Example 88. Synthesis of N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-4-(trifluoromethoxy)benzamide



[0304] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. 4-Trifluoromethoxybenzoyl chloride (167.2 mg, 117 uL, 0.75 mmol) was added directly into the solution. The reaction mixture formed an orange-red solution with a small amount of precipitate. It was left to stir for 6 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (89.0 mg). Yield 40.2%.

[0305] ESI-MS: $[M+H]^+$ 442.82. ^{1}H NMR (DMSO-d_6): δ 7.20-7.22 (d, J = 8.8 Hz, 2H), 7.44-7.46 (d, J = 8.6 Hz, 2H), 7.48-7.51 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.59-7.62 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.94-7.96 (d, J = 8.8 Hz, 2H), 8.17-8.19 (d, J = 8.6 Hz, 2H), 8.45-8.46 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.48-8.49 (d, J = 2.8 Hz, 1H).

Example 89. Synthesis of N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethyl)benzamide

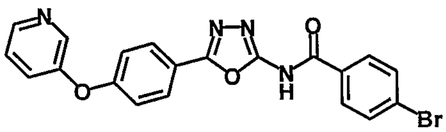


[0306] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. 3-Trifluoromethylbenzoyl chloride (156.4 mg, 0.75 mmol) was added to the solution. The reaction mixture formed an orange-red solution with a small amount of white precipitate. It was left to stir for 3 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of

TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (50.0 mg). Yield 23.4%.

[0307] ESI-MS: $[M+H]^+$ 426.94. ^{1}H NMR (DMSO-d_6): δ 7.21-7.23 (d, J = 8.8 Hz, 2H), 7.49-7.51 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.60-7.62 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.75-7.76 (t, J = 7.7 Hz, 1H), 7.95-7.98 (m, 3H), 8.33-8.34 (d, J = 7.7 Hz, 1H), 8.39 (s, 1H), 8.46-8.47 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.48-8.49 (d, J = 2.8 Hz, 1H).

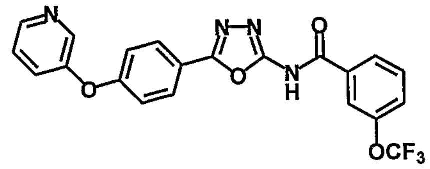
Example 90. Synthesis of 4-Bromo-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-benzamide



[0308] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. 4-Bromobenzoyl chloride (164.6 mg, 0.75 mmol) was added to the solution. The reaction mixture formed an orange-red solution with a small amount of white precipitate. It was left to stir for 3 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (46.5 mg). Yield 21.2%.

[0309] ESI-MS: $[M+H]^+$ 438.84. ^{1}H NMR (DMSO-d_6): δ 7.20-7.22 (d, J = 8.8 Hz, 2H), 7.49-7.51 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.60-7.62 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.68-7.70 (d, J = 8.4 Hz, 2H), 7.95-7.97 (d, J = 8.8 Hz, 2H), 8.00-8.02 (d, J = 8.4 Hz, 2H), 8.45-8.46 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.48-8.49 (d, J = 2.8 Hz, 1H).

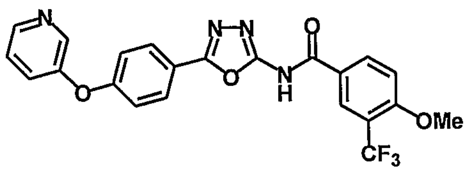
Example 91. Synthesis of N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethoxy)-benzamide



[0310] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. Neat 3-trifluoromethoxybenzoyl chloride (117 uL) was added directly into the solution. The reaction mixture formed an orange-red solution with a small amount of white precipitate. It was left to stir for 3 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (38.8 mg). Yield 17.5%.

[0311] ESI-MS: $[M+H]^+$ 442.85. ^1H NMR (DMSO-d_6): δ 7.22-7.24 (d, J = 8.8 Hz, 2H), 7.49-7.51 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.60-7.62 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.61-7.63 (m, 1H), 7.68.-7.71 (t, J = 7.7 Hz, 1H), 7.97-7.98 (m, 3H), 8.08-8.10 (d, J = 7.7 Hz, 1H), 8.46-8.47 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.48-8.49 (d, J = 2.8 Hz, 1H).

Example 92. Synthesis of 4-methoxy-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethyl)-benzamide

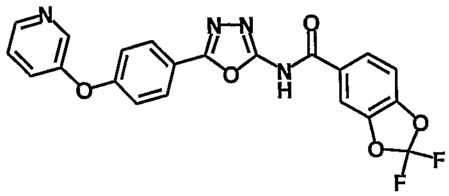


[0312] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. Neat 4-methoxy-3-trifluoromethylbenzoyl chloride (179.0 mg, 0.75 mmol) was added directly into the solution. The reaction mixture formed an orange-red solution with a small amount of white precipitate. It was left to stir for 3 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through

0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (37.0 mg). Yield 16.2%.

[0313] ESI-MS: $[M+H]^+$ 456.85. ^{1}H NMR (DMSO-d_6): δ 3.97 (s, 3H), 7.21-7.23 (d, J = 8.8 Hz, 2H), 7.38-7.40 (d, J = 9.1 Hz, 1H), 7.49-7.51 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.60-7.62 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.95-7.97 (d, J = 8.8 Hz, 2H), 8.34-8.35 (m, 2H), 8.46-8.47 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.48-8.49 (d, J = 2.8 Hz, 1H).

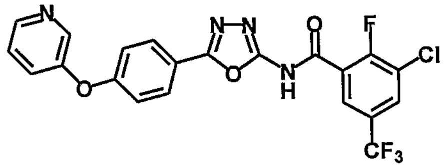
Example 93. Synthesis of 2,2-Difluoro-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-1,3-benzodioxole-5-carboxamide



[0314] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. Neat 2,2-difluoro-1,3-benzodioxole-5-carbonyl chloride (165.4 mg, 0.75 mmol) was added directly into the solution. The reaction mixture formed an orange-red solution with a small amount of white precipitate. It was left to stir for 3 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (27.0 mg). Yield 12.3%.

[0315] ESI-MS: $[M+H]^+$ 456.85. ^{1}H NMR (DMSO-d_6): δ 7.19-7.21 (d, J = 8.8 Hz, 2H), 7.47-7.51 (m, 2H), 7.58-7.60 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.93-7.95 (d, J = 8.8 Hz, 2H), 7.99-8.01 (m, 2H), 8.45-8.46 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.48-8.49 (d, J = 2.8 Hz, 1H).

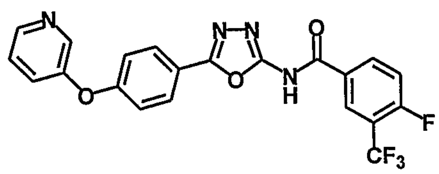
Example 94. Synthesis of 3-Chloro-2-fluoro-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-5-(trifluoromethyl)-benzamide



[0316] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. Neat 3-chloro-2-fluoro-5-trifluoromethylbenzoyl chloride (250 uL) was added directly into the solution. The reaction mixture formed a red solution with a small amount of white precipitate. It was left to stir for 18 hours. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (83.4 mg). Yield 34.8%.

[0317] ESI-MS: $[M+H]^+$ 480.71. ^{1}H NMR (DMSO-d_6): δ 7.18-7.20 (d, J = 8.8 Hz, 2H), 7.47-7.50 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.58-7.60 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.92-7.94 (d, J = 8.8 Hz, 2H), 8.13-8.16 (m, 2H), 8.44-8.45 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.47-8.48 (d, J = 2.8 Hz, 1H).

Example 95. Synthesis of 4-Fluoro-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethyl)-benzamide

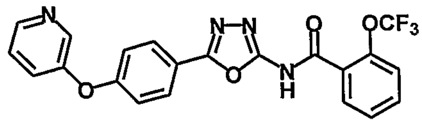


[0318] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. Neat 4-fluoro-3-trifluoromethylbenzoyl chloride (200 uL) was added directly into the solution. It was left to stir for 18 hours. The reaction mixture formed a red solution with a yellow precipitate. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA.

Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a yellow solid (105.1 mg). Yield 47.3%.

[0319] ESI-MS: $[M+H]^+$ 444.79. ^{1}H NMR (DMSO-d_6): δ 7.18-7.20 (d, J = 8.8 Hz, 2H), 7.47-7.50 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 7.53-7.60 (m, 2H), 7.93-7.94 (d, J = 8.8 Hz, 2H), 8.40-8.43 (m, 1H), 8.43-8.45 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 8.47-8.48 (d, J = 2.8 Hz, 1H).

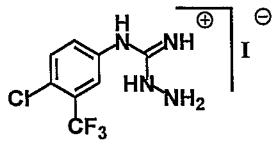
Example 96. Synthesis of N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-2-(trifluoromethoxy)-benzamide



[0320] 5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine hydrobromide salt (167.5 mg, 0.5 mmol) was suspended in 2 mL of anhydrous pyridine. Neat 2-trifluoromethoxybenzoyl chloride (100 uL) was added directly into the solution. It was left to stir for 18 hours. The reaction mixture formed an orange solution with a yellow precipitate. Then it was diluted with ca. 1 mL of MeOH, filtered through 0.22 u syringe filter and purified by reverse phase preparative HPLC using acetonitrile/water mixture containing 0.01% of TFA. Fractions, containing the product, were combined and partitioned between ca. 40 mL of EtOAc and ca. 40 mL of saturated aqueous NaHCO3. The EtOAc layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Solvent was removed *in vacuo* to give the title product as a bright-yellow solid (20.2 mg). Yield 9.1%.

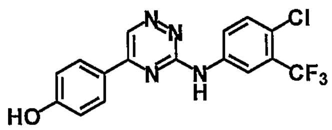
[0321] ESI-MS: $[M+H]^+$ 443.04. ^{1}H NMR (DMSO-d_6): δ 7.22-7.24 (d, J = 8.8 Hz, 2H), 7.48-7.54 (m, 4H), 7.60-7.63 (ddd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, J_3 = 1.2 Hz, 1H), 7.69-7.71 (t, J = 7.8 Hz, 1H), 7.80-7.81 (d, J = 7.5 Hz, 1H), 7.94-7.96 (d, J = 8.8 Hz, 2H), 8.47-8.49 (m, 2H).

Example 97. Synthesis of N-amino-N'-(4-chloro-3-trifluoromethyl-phenyl-guanidine hydroiodide



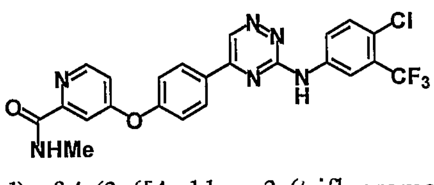
[0322] A mixture of 2.54 g 4-chloro-3-trifluoromethyl-phenylthiourea, 0.62 ml of iodomethane in 50 mL of anhydrous EtOH was refluxed for 1 hr to give 1-[4-chloro-3-(trifluoromethyl)phenyl]-S-methylisothiourea hydroiodide. Then it was cooled down to ambient temperature and treated with 0.35 g of 98 % hydrazine, heated gently with stirring until the initial vigorous evolution of MeSH subsided and then refluxed for additional 1 hour.

Example 98. Synthesis of 4-(3-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1,2,4-triazin-5-yl)phenol



[0323] N-amino-N'-[4-chloro-3-(trifluoromethyl)phenyl]-guanidine hydroiodide can be reacted with about 1.0-1.5 equivalents of 4-hydroxy-phenylglyoxale in 1:1 mixture of methanol/water to yield the title product. The product can be isolated by precipitation or by extraction with a number of solvents, such as ethyl acetate, methylene chloride or diethyl ether or by silica gel column chromatography.

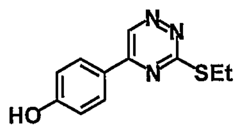
Example 99. Synthesis of 4-[4-(3-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-[1,2,4]triazin-5-yl)-phenoxy]-N-methylpyridine-2-carboxamide



[0324] 7.23 g (19.73 mmol) of 4-(3-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1,2,4-triazin-5-yl)phenol can be dissolved in 80 mL of anhydrous DMF under argon atmosphere. 2.44 g (21.71 mmol, 1.1 equivalent) of solid potassium *tert*-butoxide can be added to the solution. The resulting mixture can be heated to about 100°C and stirred at that temperature for 15 min. Then a solution of 3.7 g (21.71 mmol, 1.1 equivalent) of 4-chloro-pyridine-2-carboxylic acid methylamide in 10 mL of anhydrous DMF can be added, followed by 3.28 g (23.68 mmol, 1.2 equivalent) of anhydrous K_2CO_3. The reaction mixture can be heated at

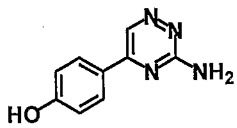
140 °C for 30 hrs. The progress of the reaction can be monitored by LC/MS. Then it can be allowed to cool down to ambient temperature. The resulting mixture can be poured into 500 mL of water and 100 mL of ethyl acetate. The aqueous layer can be extracted with a number of solvents, such as ethyl acetate, methylene chloride or ether. The combined extracts can be washed 3 times with 100 mL of water, then with brine and dried over anhydrous sodium sulfate. Solvent can be removed in vacuum to yield crude 4-[4-(3-phenylamino-[1,2,4]triazin-6-yl)-phenoxy]-pyridine-2-carboxylic acid methylamide. The product can be than purified using silica gel column chromatography. Those having ordinary skill in the art can determine which solvent system can be used as an eluents in the chromatographic purification.

Example 100. Synthesis of 4-(3-ethylsulfanyl-[1,2,4]triazin-5-yl)-phenol



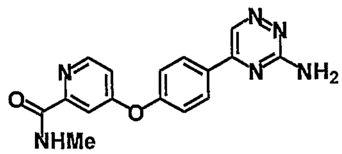
[0325] 1.0-1.5 equivalent of 4-hydroxyphenylglyoxale can be reacted with 1-amino-S-ethylisothiourea hydrobromide in 1:1 mixture of methanol/water with 1.0-2.0 equivalent of K_2CO_3 to yield 4-(3-ethylsulfanyl-[1,2,4]triazin-5-yl)-phenol. The product can be isolated by a number of methods known to one skilled in the art, such as precipitation or by extraction with a number of solvents, such as ethyl acetate, methylene chloride or diethyl ether or by silica gel column chromatography.

Example 101. Synthesis of 4-(3-amino-[1,2,4]triazin-5-yl)-phenol



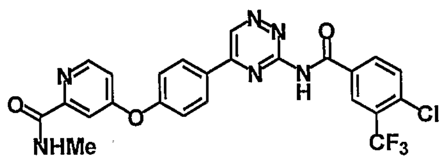
[0326] 1.0 equivalent of 4-(3-ethylsulfanyl-[1,2,4]triazin-6-yl)-phenol can be reacted with 1-5 equivalent of ammonia in dioxane to give 4-(3-amino-[1,2,4]triazin-5-yl)-phenol. The product can be isolated by a number of methods known to one skilled in the art, such as precipitation or by extraction with a number of solvents, such as ethyl acetate, methylene chloride or diethyl ether or by silica gel column chromatography.

Example 102. Synthesis of 4-[4-(3-amino-[1,2,4]triazin-5-yl)-phenoxy]-N-methylpyridine-2-carboxamide



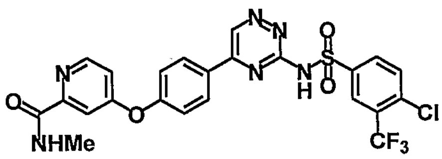
[0327] 3.71 g (19.73 mmol) of 4-(3-amino-[1,2,4]triazin-5-yl)-phenol can be dissolved in 80 mL of anhydrous DMF under argon atmosphere. 2.44 g (21.71 mmol, 1.1 equivalent) of solid potassium *tert*-butoxide can be added to the solution. The resulting mixture can be heated to about 100 °C and stirred at that temperature for 15 min. Then a solution of 3.7 g (21.71 mmol, 1.1 equivalent) of 4-chloro-pyridine-2-carboxylic acid methylamide in 10 mL of anhydrous DMF can be added, followed by 3.28 g (23.68 mmol, 1.2 eq.) of anhydrous K_2CO_3. The reaction mixture can be heated at 140 °C for 30 hrs. The progress of the reaction can be monitored by LC/MS. Then it can be allowed to cool down to ambient temperature. The resulting mixture can be poured into 500 mL of water and 100 mL of ethyl acetate. The aqueous layer can be extracted with a number of solvents, such as ethyl acetate, methylene chloride or ether. The combined extracts can be washed 3 times with 100 mL of water, then with brine and dried over anhydrous sodium sulfate. Solvent can be removed in vacuum to give crude 4-[4-(3-amino-[1,2,4]triazin-5-yl)-phenoxy]-N-methylpyridine-2-carboxamide. The product can be than purified using silica gel column chromatography. Those having ordinary skill in the art can determine which solvent system can be used as an eluents in the chromatographic purification.

Example 103. Synthesis of 4-[4-(3-{[4-chloro-3-(trifluoromethyl)benzoyl]amino}-[1,2,4]triazin-5-yl)-phenoxy]-N-methylpyridine-2-carboxamide



[0328] 108.6 mg (0.337 mmol, 1.0 eq) of 4-[4-(3-amino-[1,2,4]triazin-5-yl)-phenoxy]-N-methylpyridine-2-carboxamide can be dissolved in 2 mL of anhydrous DMF with heating to about 100 °C. 45.4 mg (0.405 mmol, 1.2 equivalent) of solid *t*-BuOK can be added to the solution, followed by 0.405 mmol (1.2 equivalent) of 4-chloro-3-trifluoromethylbenzoyl chloride. It can be allowed to stir at ambient temperature for 1-2 hours. The product can be isolated by a number of methods known to those skilled in the art, such as precipitation or by extraction with a number of solvents, such as ethyl acetate, methylene chloride or diethyl ether or by silica gel column chromatography, or by reverse-phase prep-HPLC chromatography.

Example 104. Synthesis of 4-{4-[3-({[4-chloro-3-(trifluoromethyl)phenyl]sulfonyl}amino)-[1,2,4]triazin-5-yl)-phenoxy}-N-methylpyridine-2-carboxamide



[0329] 108.6 mg (0.337 mmol, 1.0 equivalent) of 4-[4-(3-amino-[1,2,4]triazin-5-yl)-phenoxy]-N-methylpyridine-2-carboxamide can be dissolved in 2 mL of anhydrous pyridine with heating to about 100 °C. 0.405 mmol (1.2 equivalent) of 4-chloro-3-trifluoromethyl-benzenesulfonyl chloride can be added. The reaction mixture can be allowed to stir at ambient temperature for 1-2 hours. The product can be isolated by a number of methods known to one skilled in the art, such as precipitation or by extraction with a number of solvents, such as ethyl acetate, methylene chloride or diethyl ether or by silica gel column chromatography, or by reverse-phase preparative HPLC.

Example 105. Testing of Inhibition of MAPK Pathway in Cellular Assay

[0330] Some compounds described by the general structure (B) were tested for inhibition of MAPK pathway in cellular assay. Western Blot: Early passage primary human umbilical vein endothelial cells (HUVECs) were maintained in EGM-2 containing SingleQuots (Cambrex, East Rutherford, NJ), 10% FBS, 10mM HEPES, and 50 μg/ml gentamicin. Prior to treatment of the cells with inhibitor, the HUVECs were starved for 18h by replacing serum-containing complete media with serum-free and SingleQuot-free media. The starved cells were pre-treated with inhibitors for 60 min at various concentrations (0-20 μM). Next the HUVECs were treated with 50 ng/ml VEGF or FGF (Peprotech, Rocky Hill, NJ) for 6 min and the cells were immediately washed with ice-cold PBS. Cells were lysed with ice-cold RIPA buffer containing 100mM Tris pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% deoxycholate, 1% Triton X-100, 0.1% SDS, 2 mM PMSF, one Complete-Mini protease inhibitor tablet (Roche, Indianapolis, IN; 1 tablet/ 7 ml of lysis buffer) and the phophatase inhibitors NaF (500 mM) and orthovanadate (1 mM). The cells were scraped and lysates transferred and centrifuged at 15,000 g for 10 min. Supernatants were transferred to new tubes and protein concentration was quantitated using the BCA protein reagent (Pierce, Rockford, IL). Cell lysates containing 20 μg of total protein were separated by 10% SDS-PAGE, transferred to nitrocellulose, and blocked in 5% milk in TBST. Anti phospho-ERK Thr 202/Tyr 204 (Cell Signaling, Beverly, MA), anti-phospho-MEK Ser217/221 (Cell Signaling), and c-Raf (BD Biosciences Pharmingen, San Diego, CA) used as primary antibodies were detected with horseradish peroxidase-conjugated goat anti-mouse or rabbit secondary antibodies and bands were visualized using the SuperSignal West Pico chemiluminescence reagent system (Pierce) and Kodak X-ray film (Rochester, NY).

[0331] Bay 43-9006 (Raf/FGF inhibitor) showed reduction of expression of p-MEK and p-ERK with IC50 between 200 and 300 nM when tested in this assay. U0126 (MEK inhibitor) showed reduction in p-Erk levels with IC_{50} between 200 and 300 nM, while p-MEK levels were unaffected. The results are shown in Table 1. As can be seen, compounds of the invention showed reduction in p-MEK and p-ERK levels with IC_{50} between 400 nM and 20 μM.

Example 106. Cell Viability Assay

[0332] Some compounds described by the general structure (B) were tested for cell viability. XTT assay: HUVECs were seeded at 10,000 cells/well of a tissue culture treated 96-well plate treated with collagen type I and grown overnight in the complete EGM-2 media as described above. The following morning, the inhibitors were serial diluted with DMSO and added to the cells with a final DMSO concentration of 1%. After 72 hours cell viability was measured with an XTT assay (Sigma, St. Louis, MO). The cells were also photographed to compare morphological differences to the XTT trends observed. Determination of the IC_{50} values was performed with quantitative software (Prism software package, GraphPad Software, San Diego CA). Several inhibitors blocked cell proliferation and induced apoptosis at concentrations below 1 μM and experiments were repeated three times to confirm the observations. The compounds of the invention displayed IC_{50} between 100 nM and 40 uM in this assay (Table 2).

Table 2. Test Results for Examples 105 and 106

Examples	Western Blot	Inhibition of HUVEC cell prolifiration (IC50)
4-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H-[1,2,4]triazol-3-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide	active at 10 uM	2.85 uM
4-{4-[5-(4-trifluoromethoxy-phenyl)-4*H*-[1,2,4]triazol-3-ylamino]-phenoxy}-pyridine-2-carboxylic acid methylamide	not active	2.2 uM
(4-chloro-3-trifluoromethyl-phenyl)-{5-[4-(pyridin-3-yloxy)-phenyl]-4H-[1,2,4]triazol-3-yl}-amine	active at 5 uM	1.81 uM
4-{4-[5-(4-trifluoromethoxy-phenylamino)-4H-[1,2,4]triazol-3-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide	not active	> 40 uM
{5-[4-(pyridin-4-yloxy)-phenyl]-4*H*-[1,2,4]triazol-3-yl]-(4-trifluoromethoxy-phenyl)-amine	not active	> 40 uM
6-{4-[5-(4-trifluoromethoxy-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyridazin-3-ylamine	not active	> 20 uM
6-{4-[5-(4-trifluoromethoxy-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine	not active	6.0 uM
6-[4-({5-[4-(trifluoromethoxy)-phenyl-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]pyrimidine-2,4-diamine	not active	6.58 uM
6-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine	active at 5 uM	0.089 uM
6-{4-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyridazin-3-ylamine	not active	1.79 uM
4-{3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4H-[1,2,4]triazol-3-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide	not active	> 20 uM
6-{3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyrimidine-2,4-diamine	active at 5 uM	0.404 uM

(4-chloro-3-trifluoromethyl-phenyl)-{5-[3-(pyridin-4-yloxy)-phenyl]-4H-[1,2,4]triazol-3-yl}-amine	active at 5 uM	1.79 uM
6-{3-[5-(4-chloro-3-trifluoromethyl-phenylamino)-4*H*-[1,2,4]triazol-3-yl]-phenoxy}-pyridazin-3-ylamine	not active	> 10 uM
6-[4-(5-{[4-Chloro-3-trifluoromethyl-phenyl]amino}-1,3,4-oxadiazol-2-yl)-phenoxy]-pyrimidine-2,4-diamine	active at 5 uM	1.57 uM
N-[4-chloro-3-(trifluoromethyl)phenyl]-5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine	active at 5 uM	1.72 uM
N-[4-chloro-3-(trifluoromethyl)phenyl]-5-[4-(pyridin-4-yloxy)phenyl]-1,3,4-oxadiazol-2-amine	active at 5 uM	8.6 uM
N-[4-chloro-3-(trifluoromethyl)phenyl]-5-[4-(pyrimidin-5-yloxy)phenyl]-1,3,4-oxadiazol-2-amine	active at 5 uM	9.65 uM
4-[4-(5-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenoxy]-N-methylpyridine-2-carboxamide	active at 5 uM	5.6 uM
6-[4-({5-[4-chloro-3-(trifluoromethyl)phenyl-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]pyrimidine-2,4-diamine	active at 5 uM	9.57 uM
5-[4-chloro-3-(trifluoromethyl)phenyl]-N-[4-(pyridine-4-yloxy)phenyl]-4*H*-1,2,4-triazol-3-amine	not active	> 40 uM
5-[4-chloro-3-(trifluoromethyl)phenyl]-N-[4-(pyrimidin-5-yloxy)phenyl]-4*H*-1,2,4-triazol-3-amine	active at 5 uM	> 10 uM
6-[4-({5-[4-chloro-3-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]pyridazin-3-amine	active at 5 uM	> 40 uM
4-[4-({5-[4-chloro-3-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazol-3-yl}amino)phenoxy]-N-methylpyridine-2-carboxamide	not active	> 40 uM
5-[4-chloro-3-(trifluoromethyl)phenyl]-N-[4-(pyridine-3-yloxy)phenyl]-4*H*-1,2,4-triazol-3-amine	active at 5 uM	> 40 uM

6-[4-(5-{[3-(Trifluoromethyl)phenyl]amino}-1,3,4-oxadiazol-2-yl)phenoxy}pyrimidine-2,4-diamine	active at 5 uM	> 10 uM
5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[3-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2-amine	active at 5 uM	> 10 uM
6-(4-{5-[(4-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenoxy) pyrimidine-2,4-diamine	active at 5 uM	2.6 uM
5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[4-chloro-phenyl]-1,3,4-oxadiazol-2-amine	active at 5 uM	> 20 uM
6-(4-{5-[(2-chloro-5-trifluoromethyl-phenyl)amino]-1,3,4-oxadiazol-2-yl}phenoxy) pyrimidine-2,4-diamine	not active	~ 20 uM
5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[2-chloro-5-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2-amine	not active	~ 20 uM
6-(4-{5-[(3-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}phenoxy) pyrimidine-2,4-diamine	active at 5 uM	~ 20 uM
5-[4-(Pyrimidin-5-yloxy)phenyl]-N-[2-chloro-phenyl]-1,3,4-oxadiazol-2-amine	active at 5 uM	~ 20 uM
5-[4-(Pyridin-3-yloxy)phenyl]-N-[4-chloro-phenyl]-1,3,4-oxadiazol-2-amine	active at 10 uM	9.6 uM
5-[4-(Pyridin-3-yloxy)phenyl]-N-[3-trifluoromethyl-phenyl]-1,3,4-oxadiazol-2-amine	active at 10 uM	> 20 uM
5-[4-(Pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-amine	not active at 10 uM	> 40 uM
N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-4-(trifluoromethoxy)benzamide	not active at 10 uM	> 40 uM
N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethyl)benzamide	active at 10 uM	> 40 uM

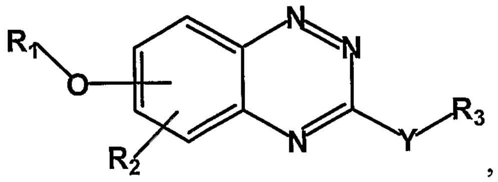
4-Bromo-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-benzamide	not active at 10 uM	> 40 uM
N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethoxy)-benzamide	not active at 10 uM	> 40 uM
4-Methoxy-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethyl)-benzamide	active at 10 uM	> 40 uM
2,2-Difluoro-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-1,3-benzodioxole-5-carboxamide	not active at 10 uM	> 40 uM
3-Chloro-2-fluoro-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-5-(trifluoromethyl)-benzamide	not active at 10 uM	> 40 uM
4-Fluoro-N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-3-(trifluoromethyl)-benzamide	active at 10 uM	~20 uM
N-{5-[4-(pyridin-3-yloxy)phenyl]-1,3,4-oxadiazol-2-yl}-2-(trifluoromethoxy)-benzamide	not active at 10 uM	~20 uM

[0333] Although the invention has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

CLAIMS

WHAT IS CLAIMED IS:

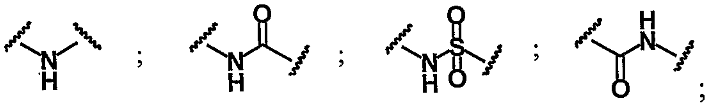
1. A compound having the structure (A) or an N-oxide, N,N'-dioxide, N,N',N''-trioxide, or a pharmaceutically acceptable salt thereof:



(A)

wherein:

Y is absent or is a moiety selected from a group consisting of:



R_1 is a substituent selected from a group consisting of an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl;

R_2 is a substituent selected from a group consisting of hydrogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkylamino, halogen, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, and $-C{\equiv}N$; and

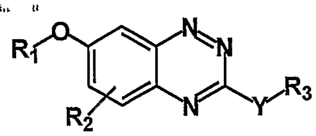
R_3 is a substituent selected from a group consisting of an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl.

2. The compound of claim 1, wherein:

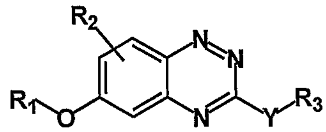
R_1 is selected from a group consisting of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from N, S, and O, substituted C_6-C_{12} aryl, substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl;

R_3 is selected from a group consisting of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from N, S, and O, substituted C_6-C_{12} aryl, substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl.

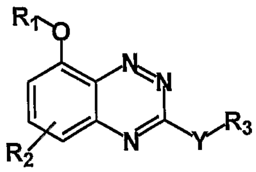
3. The compound of claim 1, wherein the compound having the structure (A) is selected from the group of compounds having the structures (A1), (A2), (A3), and (A4):



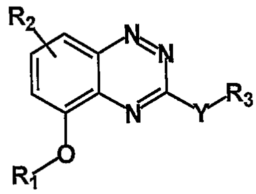
(A1)



(A2)



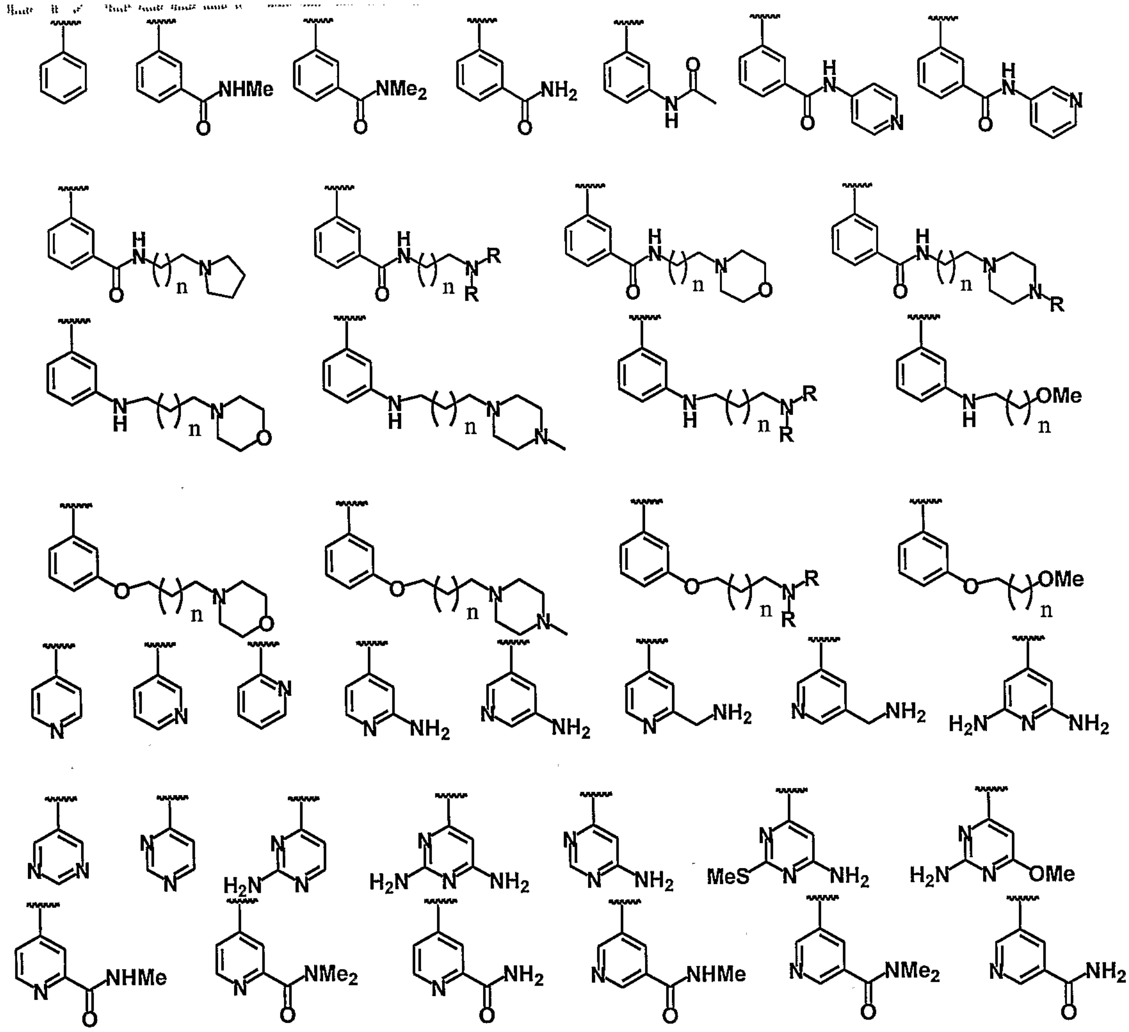
(A3)

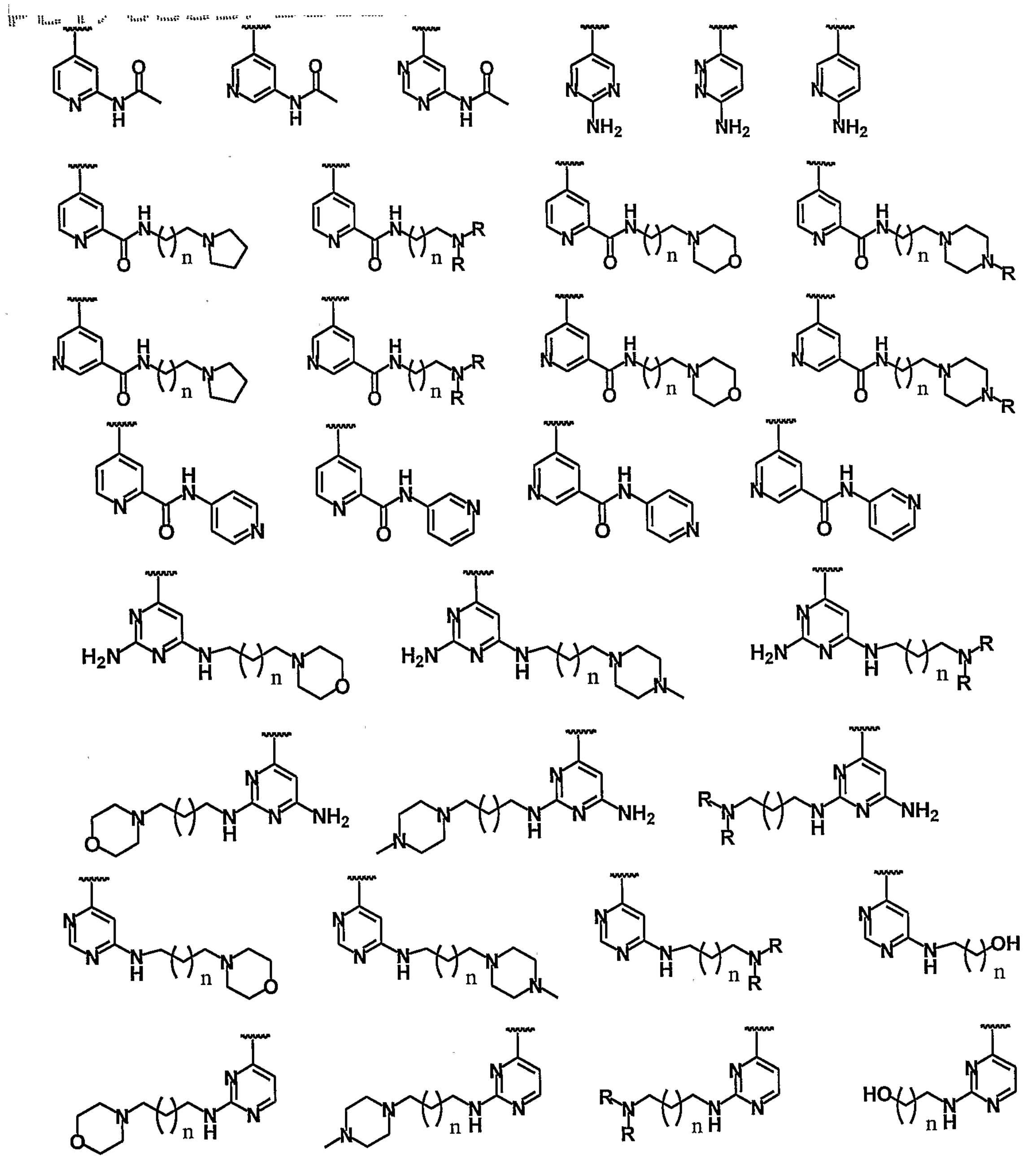


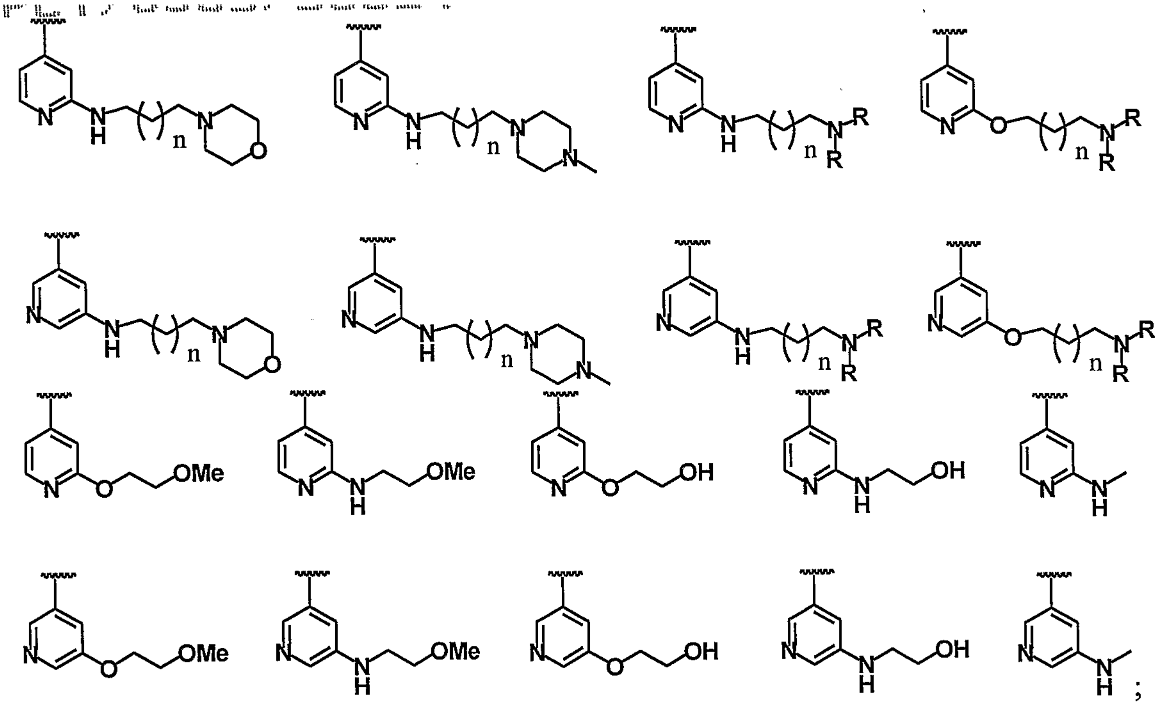
(A4)

4. The compound of claim 3, wherein the compound has the structure (A1) and wherein:

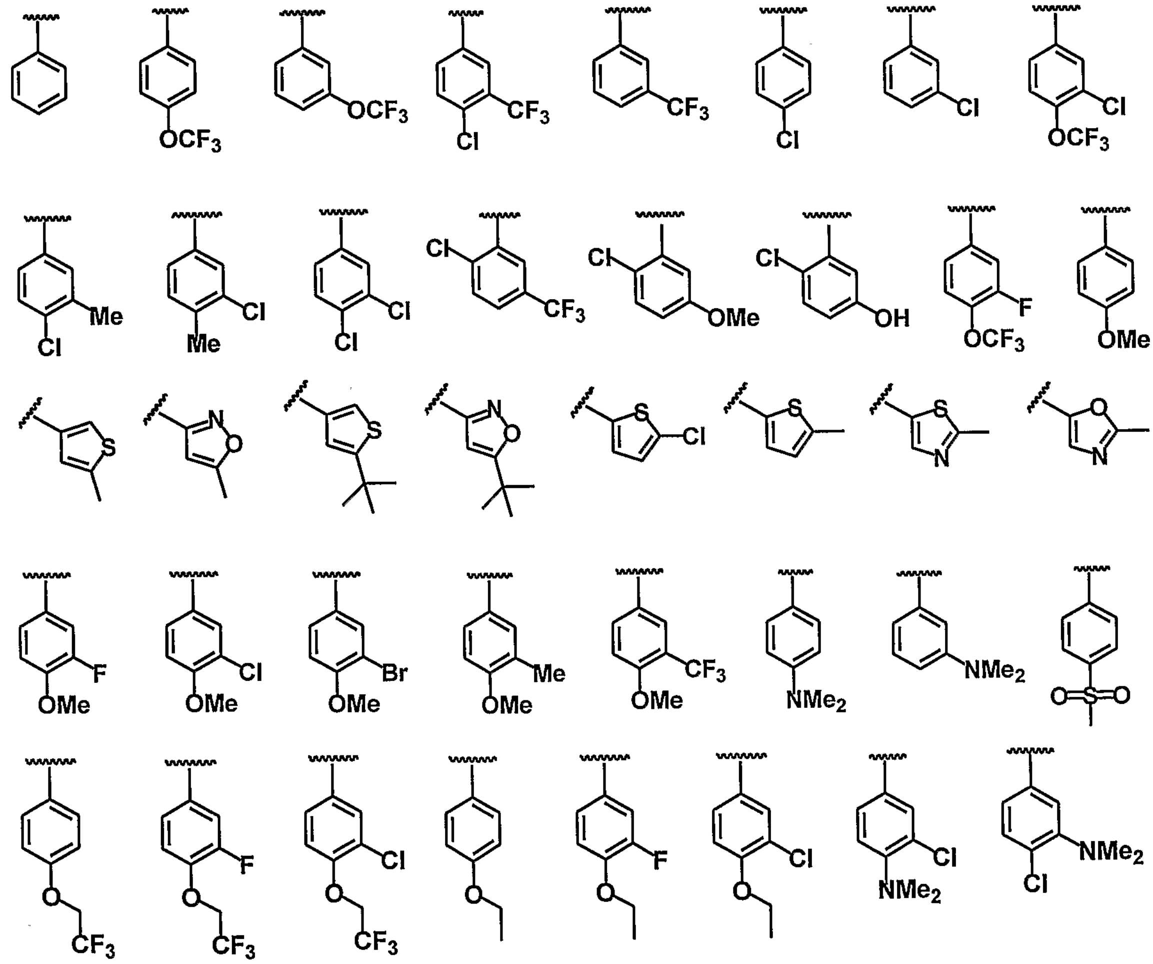
R_1 is selected from a group consisting of

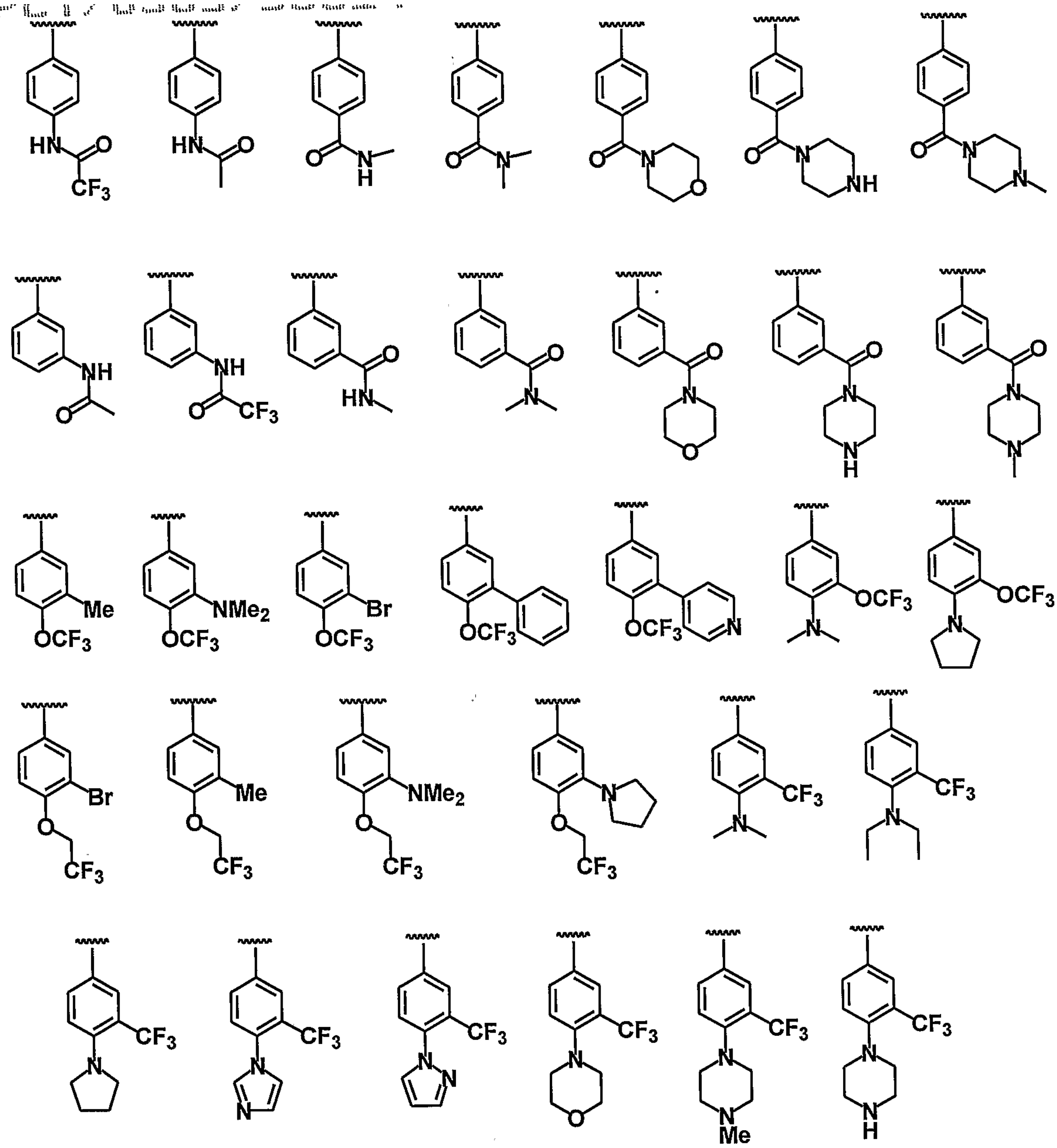


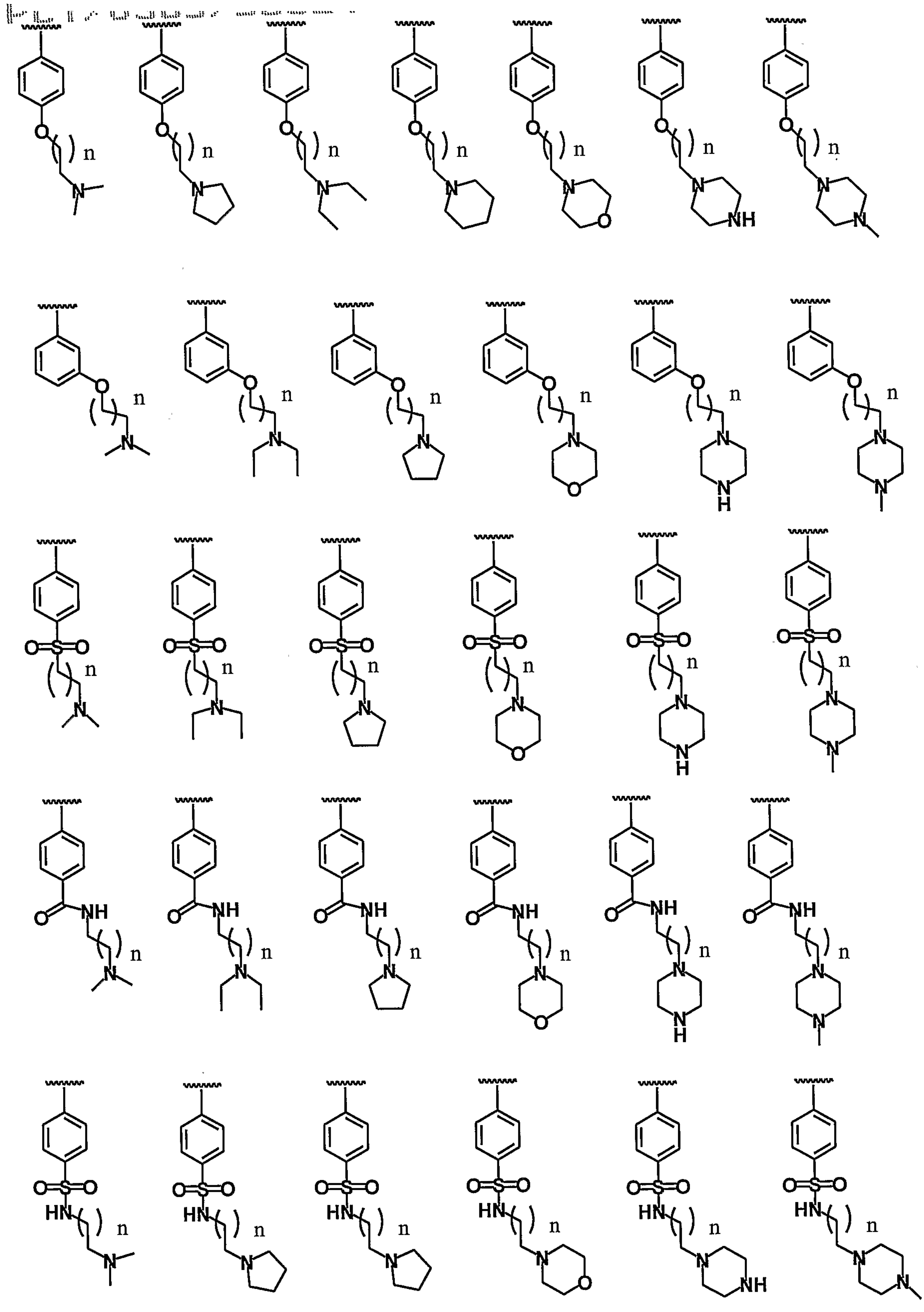


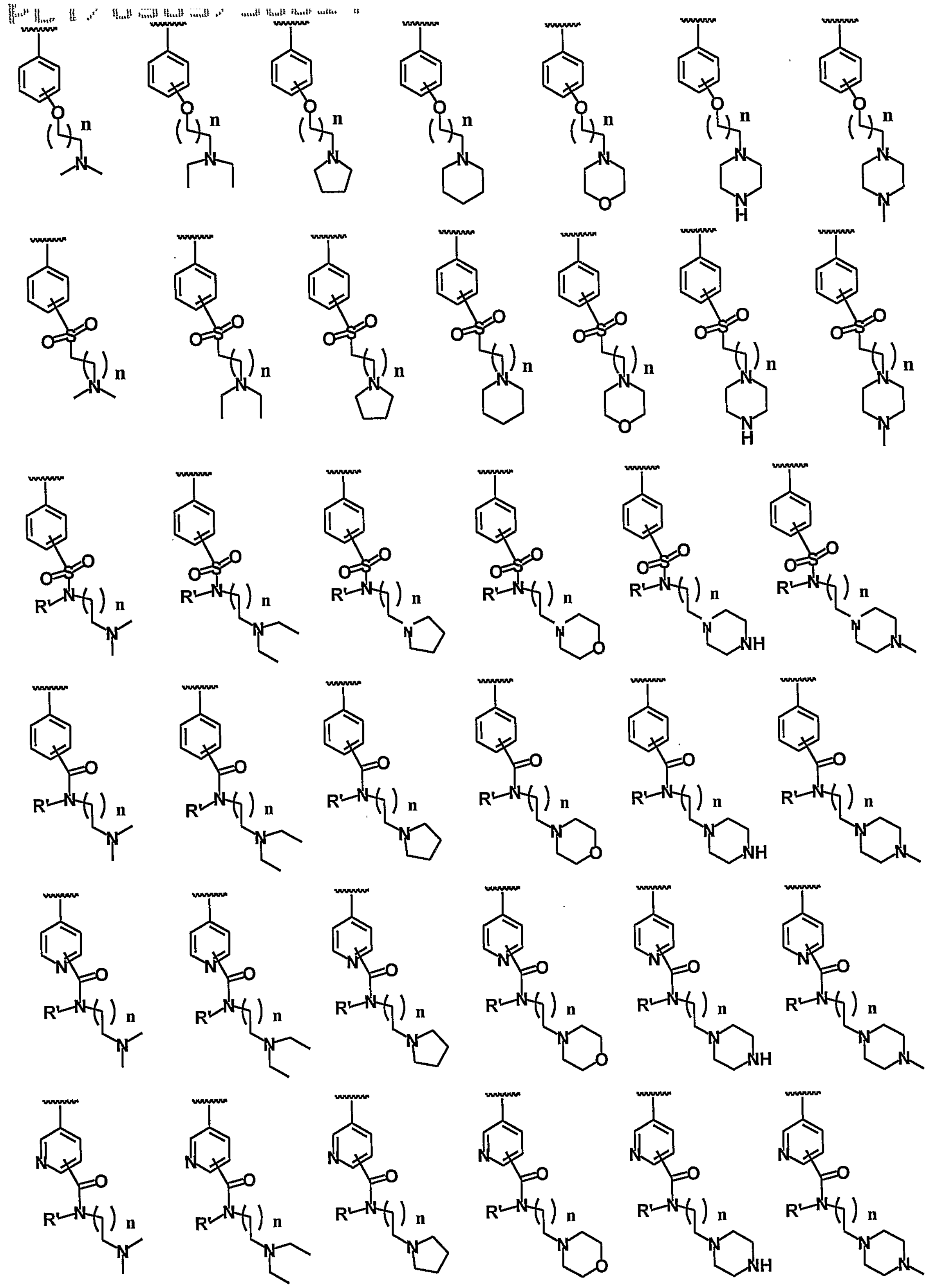


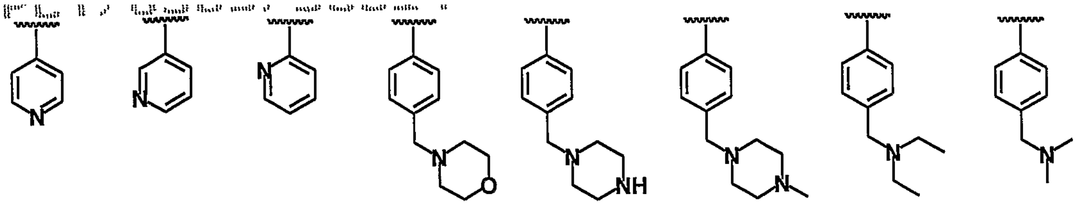
R_3 is selected from a group consisting of:

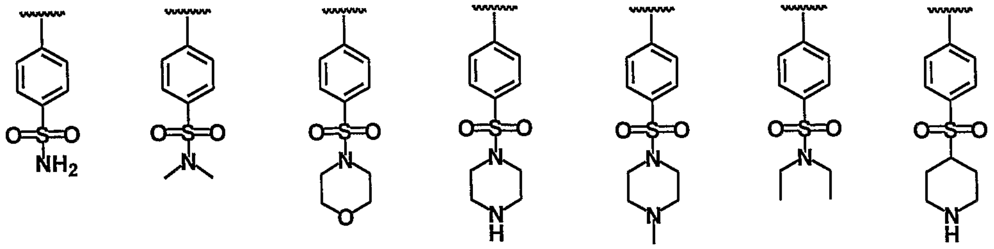






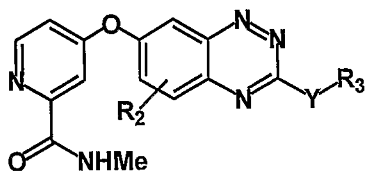




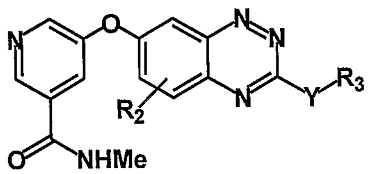

; and

n is an integer selected from a group consisting of 0, 1, 2, and 3.

5. The compound of claim 3, wherein the compound having the structure (A1) is selected from a group consisting of compounds having structures (1) and (2):

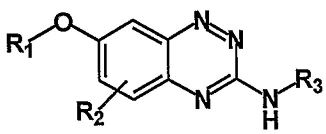


(1)

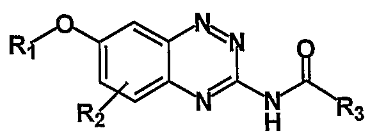


(2)

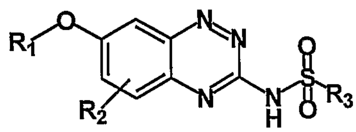
6. The compound of claim 3, wherein the compound having structure (A1) is selected from a group consisting of compounds having the structures (3), (4), (5) and (6):



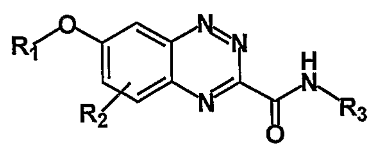
(3)



(4)

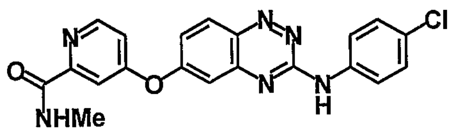


(5)

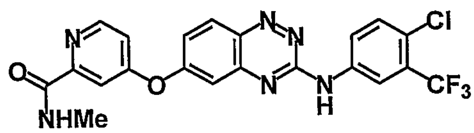


(6)

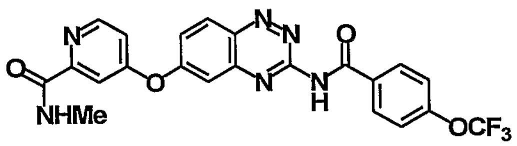
7. The compound of claim 3, wherein the compound having structure (A1) is selected from a group consisting of compounds having the structures (7)-(16):



(7)



(8)



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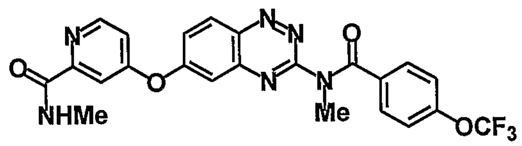
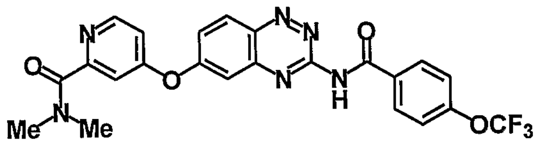


(10)



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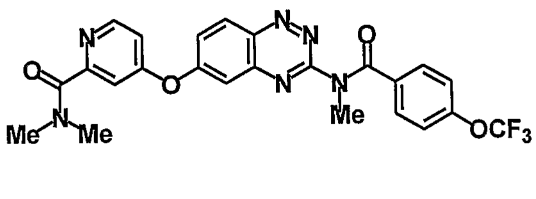
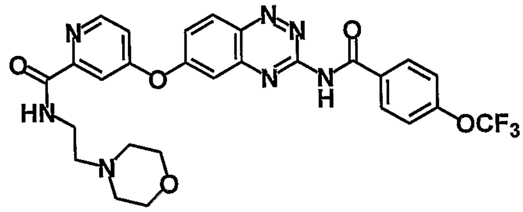


(12)



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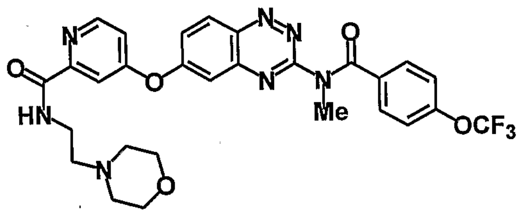
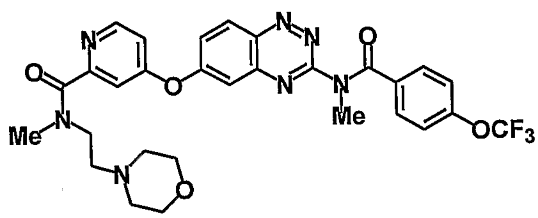
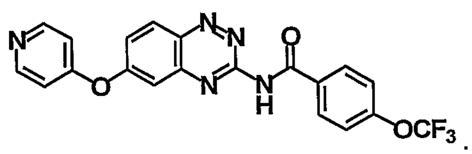


(14)

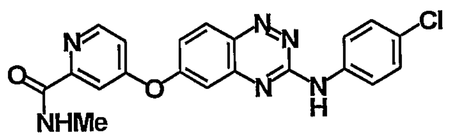


(15)

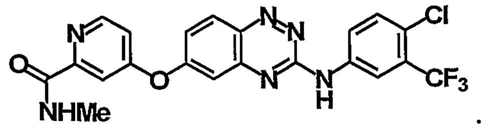


(16)

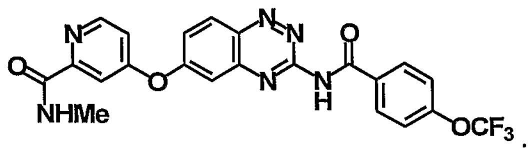
8. The compound of claim 7, wherein the compound has the formula:



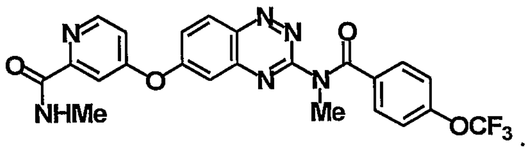
9. The compound of claim 7, wherein the compound has the formula:



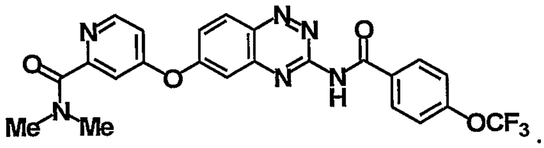
10. The compound of claim 7, wherein the compound has the formula:



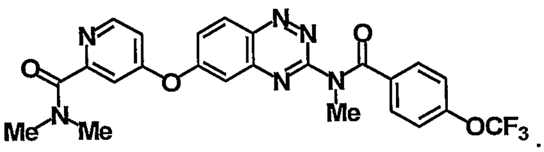
11. The compound of claim 7, wherein the compound has the formula:



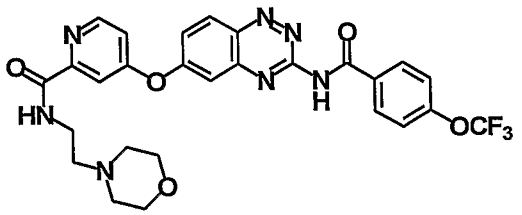
12. The compound of claim 7, wherein the compound has the formula:



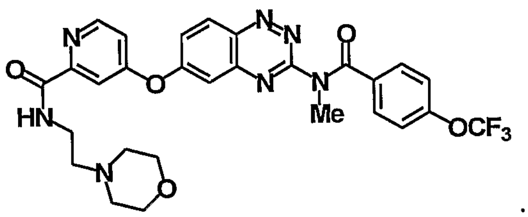
13. The compound of claim 7, wherein the compound has the formula:



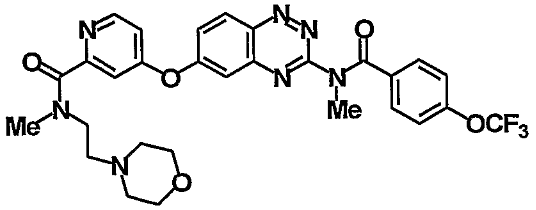
14. The compound of claim 7, wherein the compound has the formula:



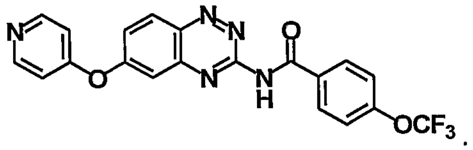
15. The compound of claim 7, wherein the compound has the formula:



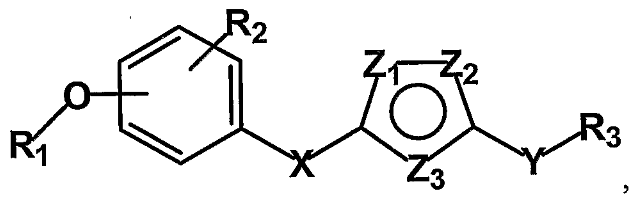
16. The compound of claim 7, wherein the compound has the formula:



17. The compound of claim 7, wherein the compound has the formula:



18. A compound having the structure (B) or an N-oxide, N,N'-dioxide, N,N',N"-trioxide, or a pharmaceutically acceptable salt thereof:



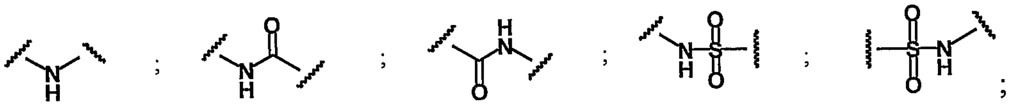
(B)

wherein:

each of Z_1, Z_2 and Z_3 is independently selected from a group consisting of N, CH, N=CH, O, S and N-R^4, wherein R^4 is hydrogen or lower alkyl, with the further proviso that at least one of Z_1, Z_2 and Z_3 is not CH;

X is absent or is NH; and

Y is absent or is selected from a group consisting of the following moieties:

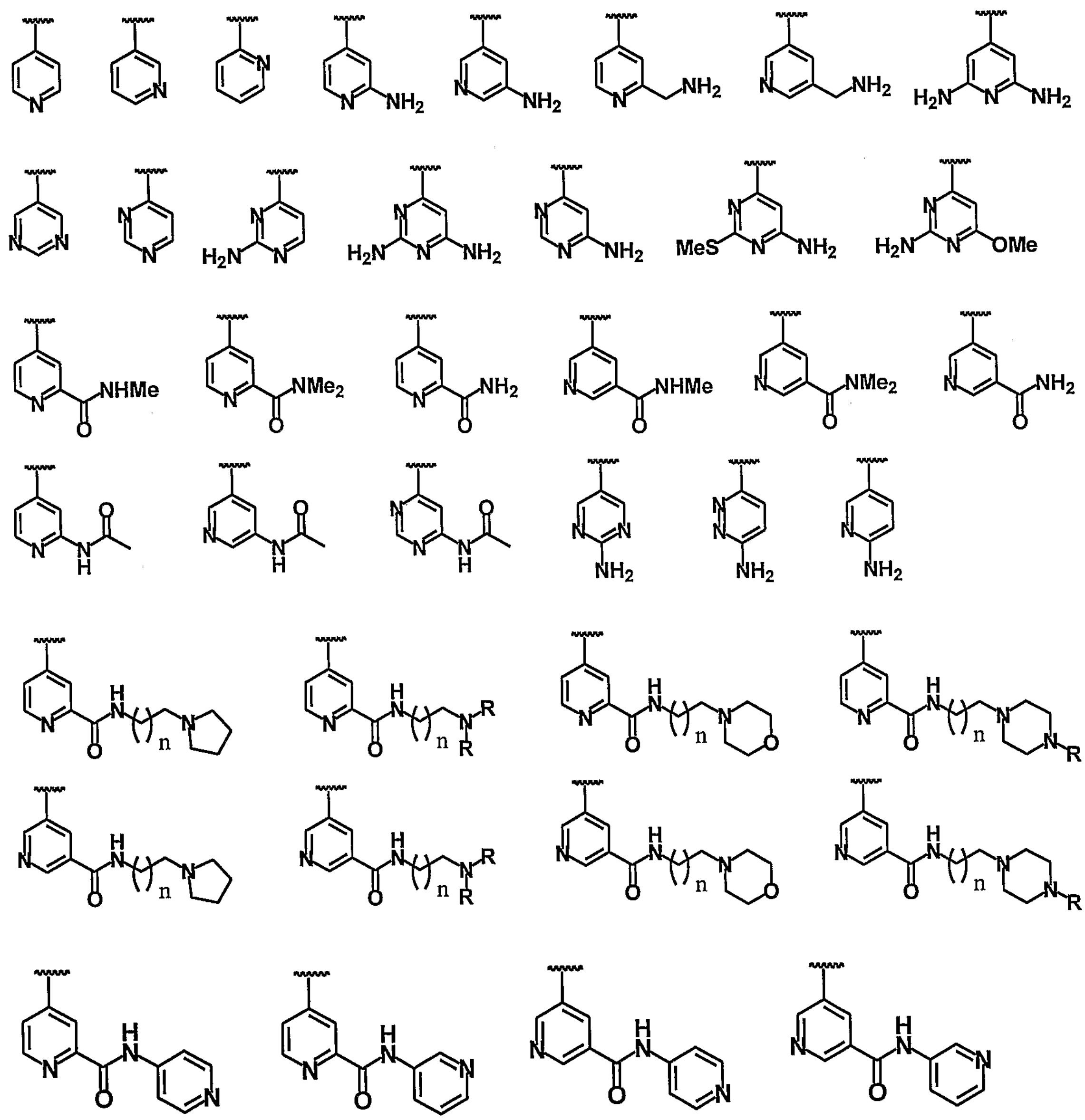


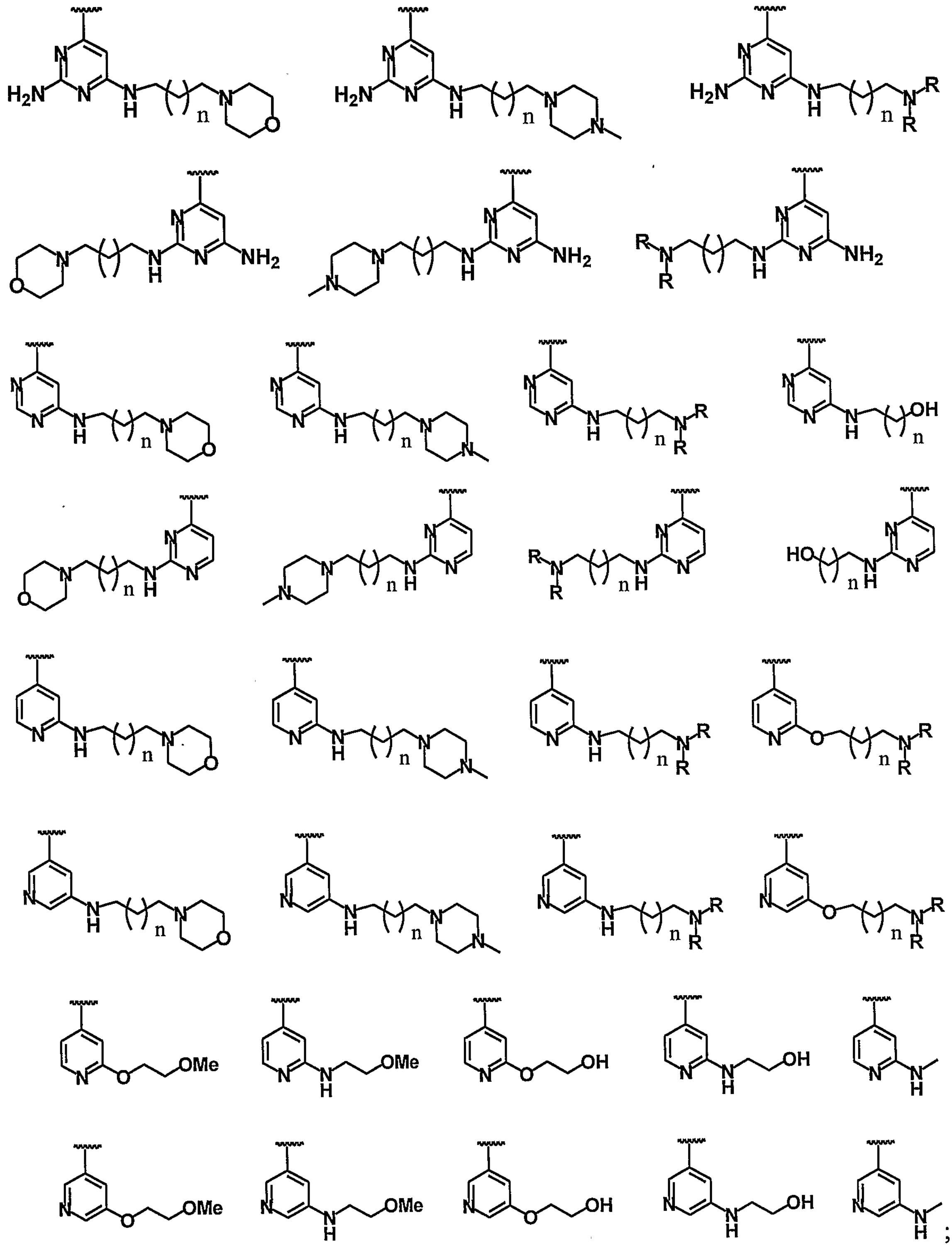
R_1 is an unsubstituted or a substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms;

R_2 is selected from a group consisting of of hydrogen, halogen, C_1-C_{18} alkyl, -OH, -NO_2, -CN, C_1-C_{18} alkoxy, -$NHSO_2R^5$, -SO_2NHR^5, -$NHCOR^5$, -NH_2, -NR^5R^6, -S(O)R^5, -S(O)$_2R^5$, -CO_2R^5, -$CONR^5R^6$, wherein R^5 and R^6 are independently selected from a group consisting of hydrogen, a C_1-C_{18} alkyl, and a substituted C_1-C_{12} alkyl; and

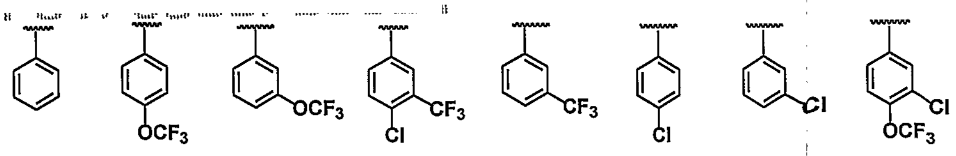
R_3 is selected from a group consisting of hydrogen, a C_1-C_{18} alkyl, a substituted C_1-C_{12} alkyl, a C_1-C_{12} cycloalkyl, a substituted C_1-C_{12} cycloalkyl, a substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms, an C_6-C_{12} aryl, a substituted C_6-C_{12} aryl, a heterocycle, a substituted heterocycle, a C_3-C_{12} heteroaryl having 1-3 heteroatoms, a substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms, a C_7-C_{24} aralkyl, a substituted C_7-C_{24} aralkyl, a C_7-C_{24} alkylaryl, and a substituted C_7-C_{24} alkaryl.

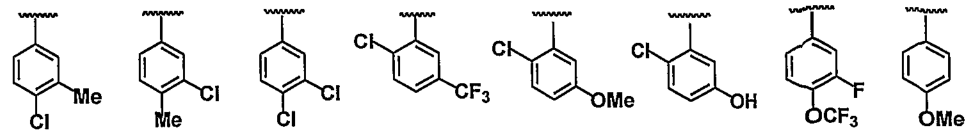
19. The compound of claim 18, wherein R_1 is selected from the group consisting of:

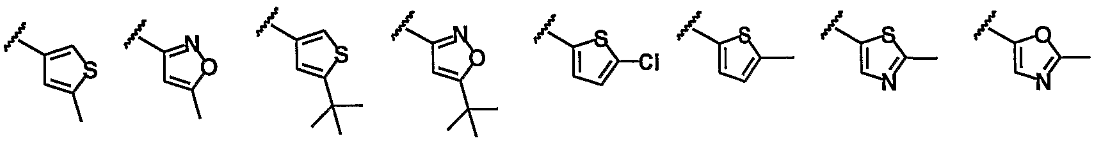


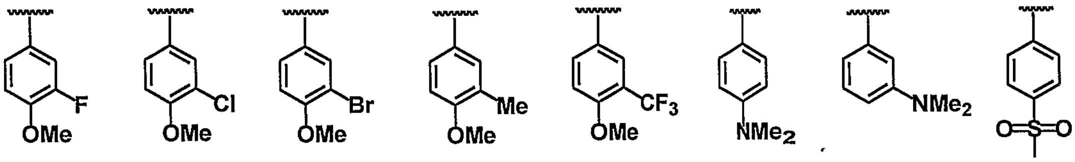


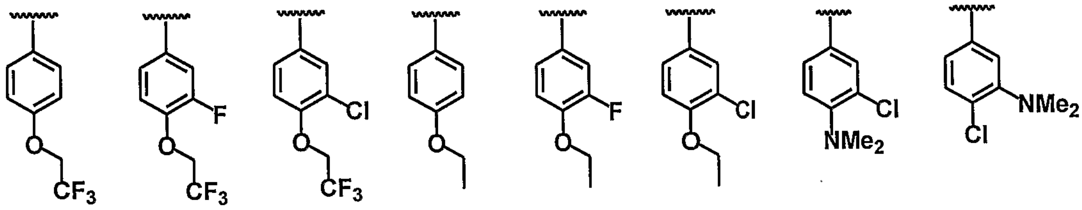
R_3 is selected from the group consisting of:

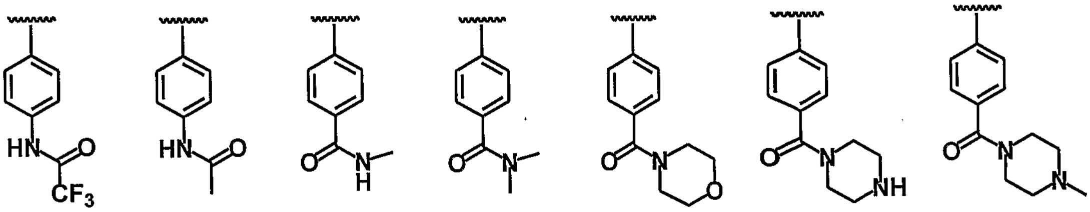


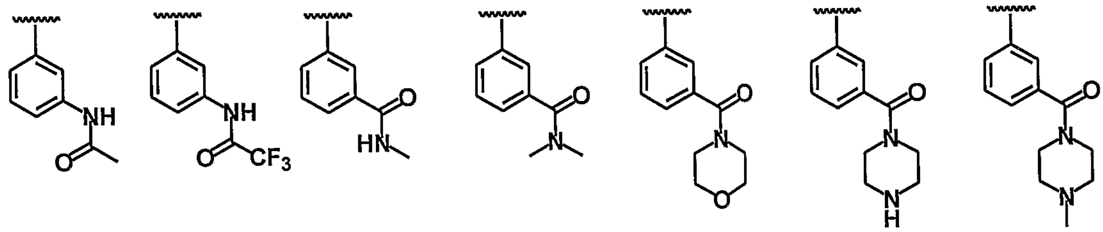


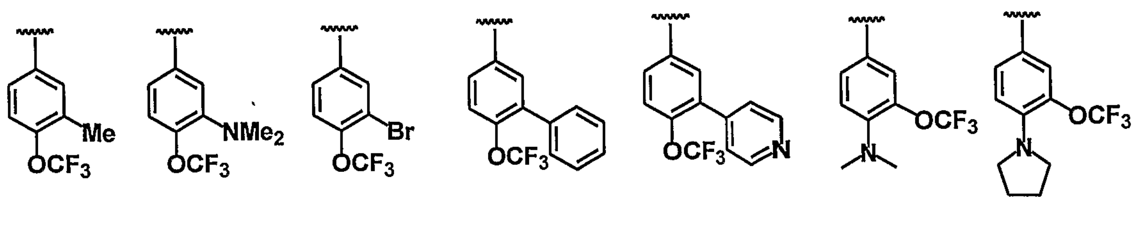


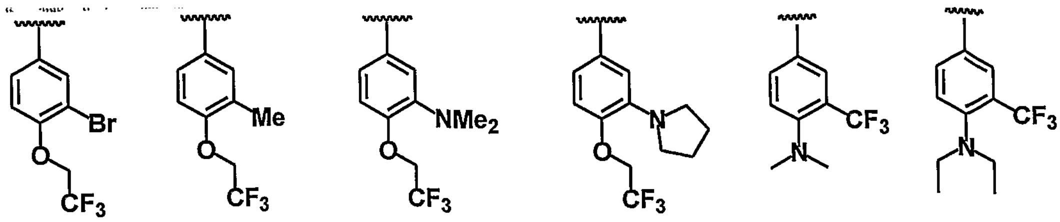


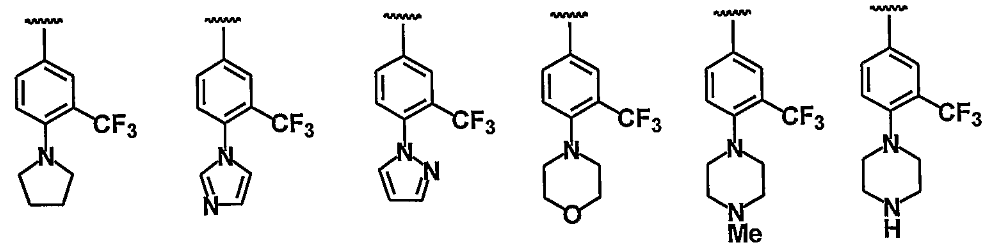


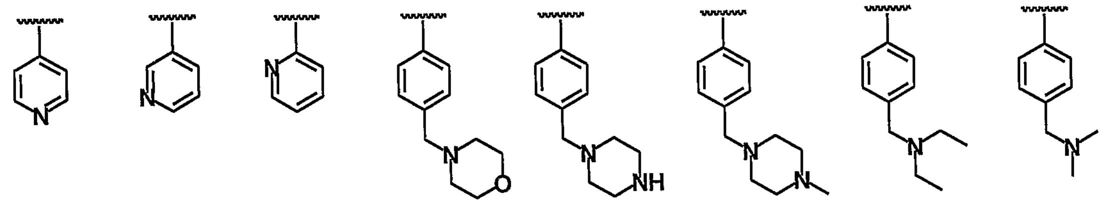


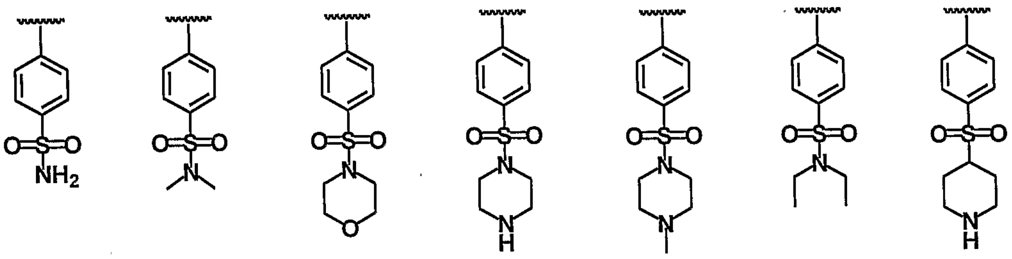


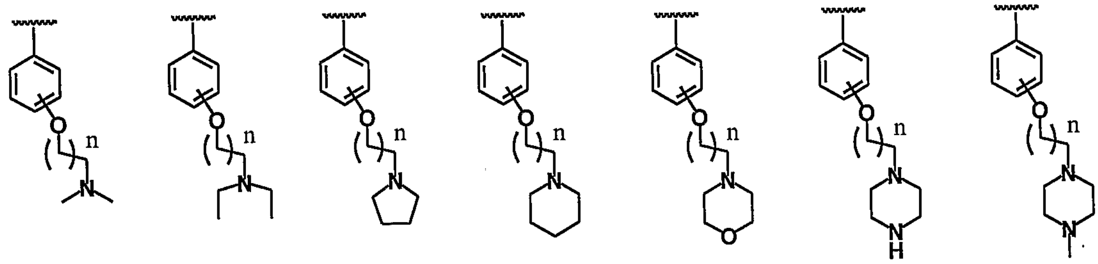


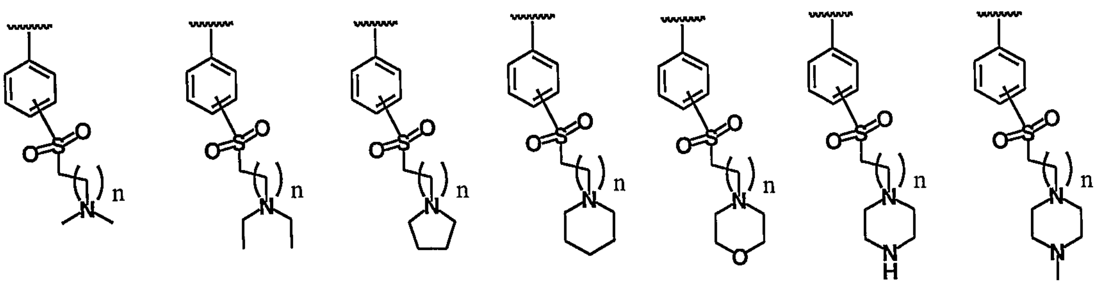


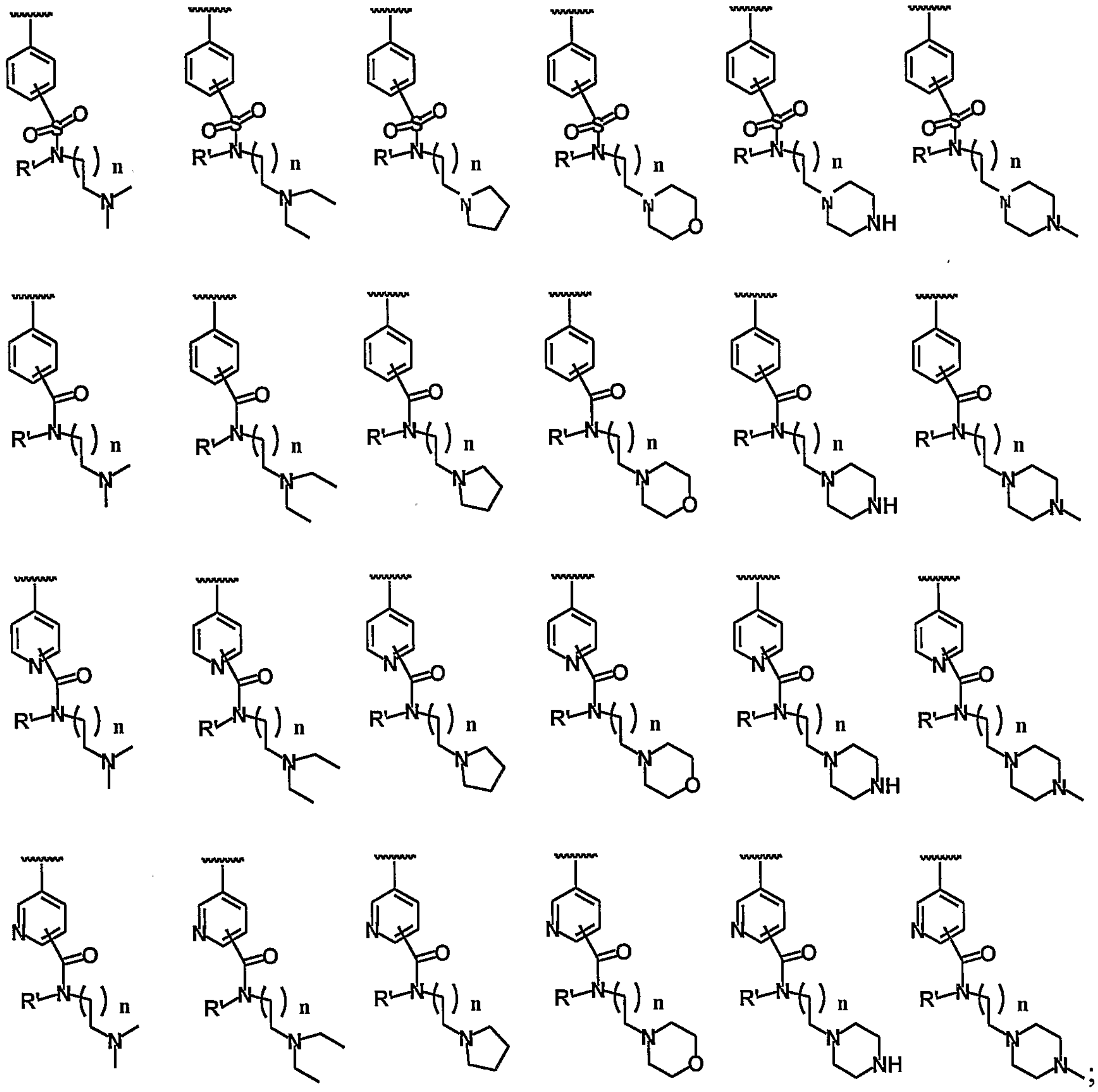








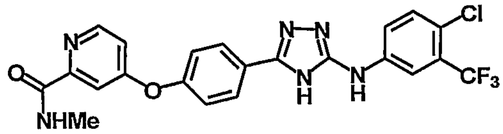




n is an integer selected from a group consisting of 0, 1, 2, and 3, and

R′ is selected from a group consisting of hydrogen, a C_1-C_{18} alkyl, and a substituted C_1-C_{18} alkyl.

20. The compound of claim 18, wherein the compound having structure (B) is selected from a group consisting of compounds having formulae (17)-(35):



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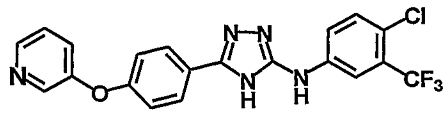
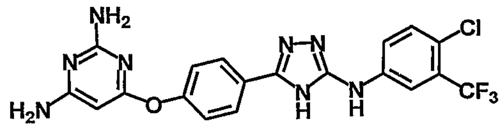


(18)



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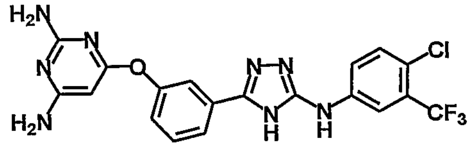
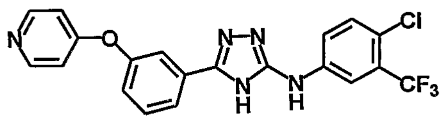


(20)



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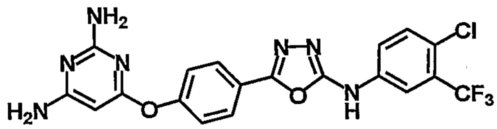
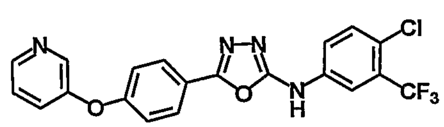


(22)



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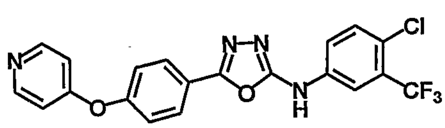

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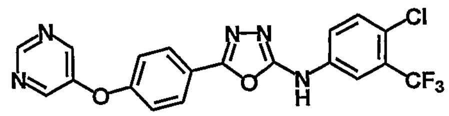

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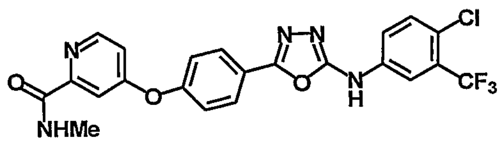

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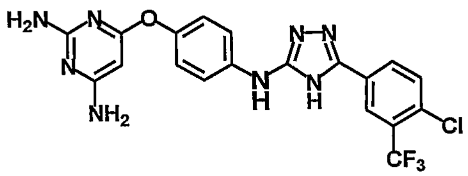

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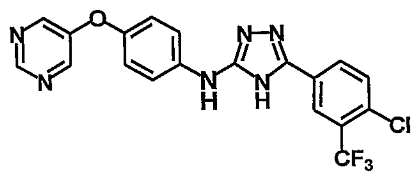

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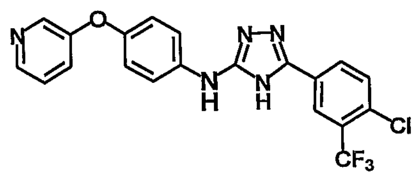
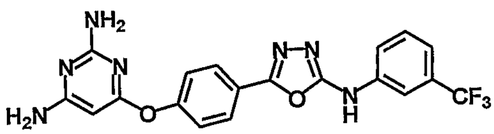
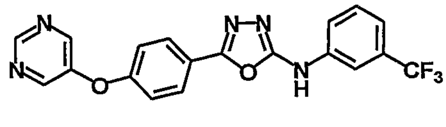


(29)



(30)



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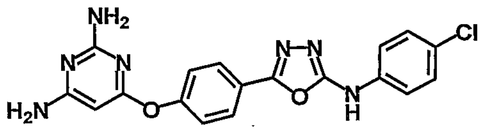
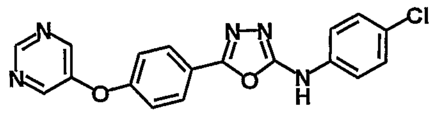


(32)



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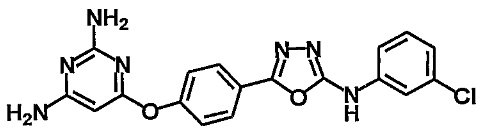
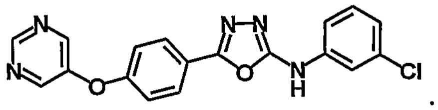
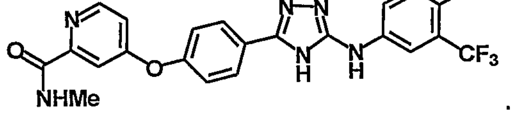


(34)

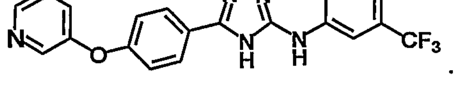


(35)

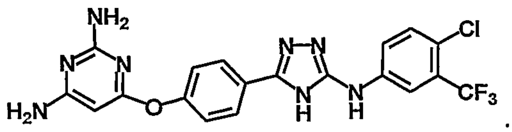
21. The compound of claim 20, wherein the compound has the formula:



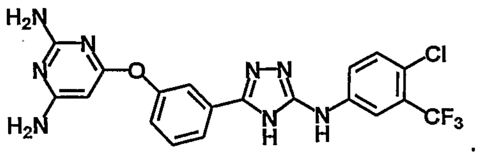
22. The compound of claim 20, wherein the compound has the formula:



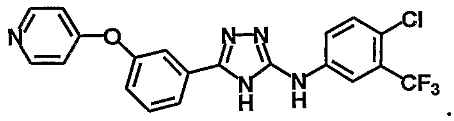
23. The compound of claim 20, wherein the compound has the formula:



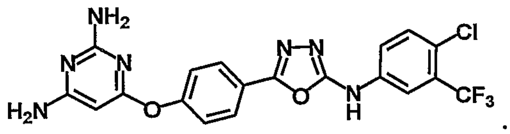
24. The compound of claim 20, wherein the compound has the formula:



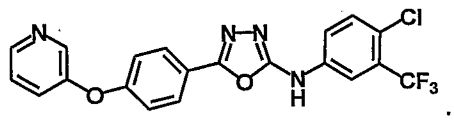
25. The compound of claim 20, wherein the compound has the formula:



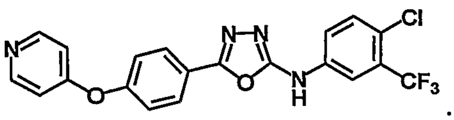
26. The compound of claim 20, wherein the compound has the formula:



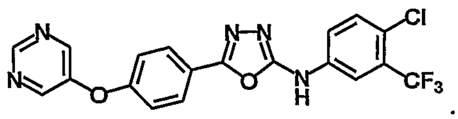
27. The compound of claim 20, wherein the compound has the formula:



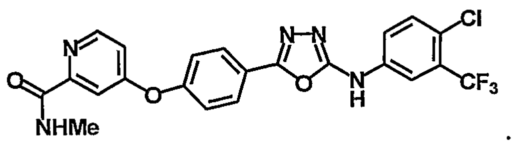
28. The compound of claim 20, wherein the compound has the formula:



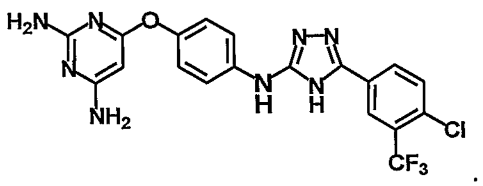
29. The compound of claim 20, wherein the compound has the formula:



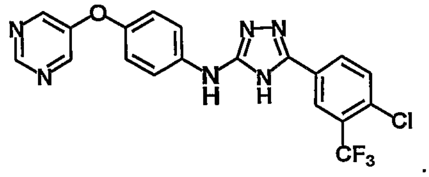
30. The compound of claim 20, wherein the compound has the formula:



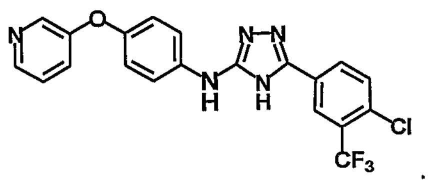
31. The compound of claim 20, wherein the compound has the formula:



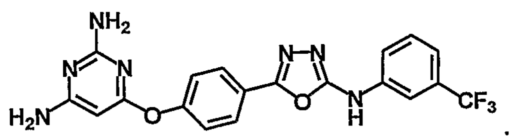
32. The compound of claim 20, wherein the compound has the formula:



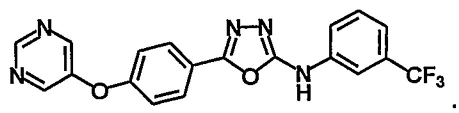
33. The compound of claim 20, wherein the compound has the formula:



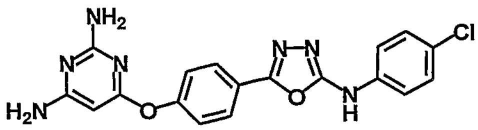
34. The compound of claim 20, wherein the compound has the formula:



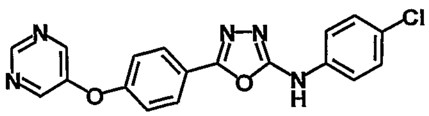
35. The compound of claim 20, wherein the compound has the formula:



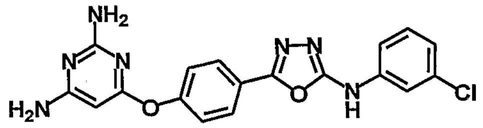
36. The compound of claim 20, wherein the compound has the formula:


.

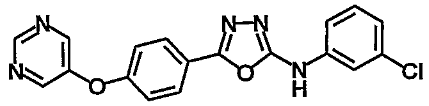
37. The compound of claim 20, wherein the compound has the formula:


.

38. The compound of claim 20, wherein the compound has the formula:


.

39. The compound of claim 20, wherein the compound has the formula:


.

40. A compound comprising a derivative of benzotriazine, the compound including a benzotriazine moiety having at least a first substituent attached to the benzene ring of benzotriazine and a second substitutent attached to the triazine ring of the benzotriazine, wherein:

(a) the first substitutent includes a substituted phenyl, substituted pyridyl or substituted pyrimidyl group; and

(b) the second substitutent is selected from a secondary amino group, a substituted amide group, and a substituted sulfonylamino group.

41. The compound of claim 40, wherein the substitutent in the substituted pyridyl group comprises an amido moiety, an aminoalkyl group, carboxyl group or a carboxylate group.

42. The compound of claim 41, wherein the nitrogen in the amido moiety additionally carries a third substitutent selected from an alkyl, an alkylaminoalkyl, a pyridyl, an alkyl pyrrolidine, an alkyl morpholine, and an alkyl piperazine groups.

43. The compound of claim 40, wherein the second substitutent includes a group derived from a compound selected from benzene, pyridine, thiophene, and isoxazole.

44. The compound of claim 43, wherein the group derived from benzene is selected from *tert*-butyl phenyl, trifluoromethoxyphenyl, methoxyphenyl, dimethylamino, dimethylaminophenyl, aminophenyl, trifluoroethoxyphenyl, trifluoromethoxychlorophenyl, trifluoromethoxybromophenyl, trifluoroethoxychlorophenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchloro phenyl, chlorotoluyl, N-phenylacetamide, N,N-alkyl-benzamide, isopropoxyphenyl, alkoxyphenyl, dialkoxyphenyl, acetylphenyl.

45. A compound comprising a benzene derived moiety bridged to a heterocyclic moiety, wherein:

(a) the benzene-derived moiety includes a molecule of benzene having a substitutent selected from:

a pyridyl group connected to the benzene molecule via an oxygen link, and

a sulfonyl group; and

(b) the heterocyclic moiety is selected from triazine, triazole, oxadiazole, pyridazine, pyrimidine, pyridine, oxazole, pyrazol, pyrrole, imidazole, thiadiazole.

46. The compound of claim 45, wherein the pyridyl group includes a first substitutent comprising an amido moiety, an alkylamino group, or a carboxyl group.

47. The compound of claim 46, wherein the nitrogen in the amido moiety additionally carries a second substituent selected from an alkyl, an alkylamino alkyl, a pyridyl, an alkyl pyrrolidine, an alkyl morpholine, and an alkyl piperazine groups.

48. The compound of claim 45, wherein the heterocyclic moiety optionally includes a third substituent connected to the heterocyclic moiety, wherein the third substituent is selected from a secondary amino group, a substituted amide group, and a substituted sulfonylamino group.

49. The compound of claim 48, wherein the third substitutent includes a group derived from a compound selected from benzene, thiophene, and isoxazole.

50. The compound of claim 49, wherein the group derived from benzene is selected from *tert*-butyl phenyl, trifluoromethoxyphenyl, methoxyphenyl, dimethylamino, dimethylaminophenyl, aminophenyl, trifluoroethoxyphenyl, trifluoromethoxychlorophenyl, trifluoromethoxybromophenyl, trifluoroethoxychlorophenyl, chlorophenyl, dichlorophenyl, trifluoromethyl phenyl, trifluoromethylchloro phenyl, chlorotoluyl, N-phenylacetamide, N,N-alkyl-benzamide, isopropoxyphenyl, alkoxyphenyl,dialkoxyphenyl, acetylphenyl.

51. The compound of claim 45, wherein the bridge between the benzene derived moiety and the heterocyclic moiety includes a single bond or a nitrogen atom.

52. A method for treating a disorder comprising administering to a subject in need thereof an effective amount of a compound, wherein the compound is set forth in Structures (A), (B) or a combination thereof.

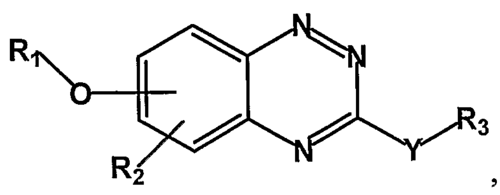
53. The method of claim 52, wherein the disorder is selected from a group consisting of cancer, eye disease, inflammation, psoriasis, and a viral infection.

54. The method of claim 53, wherein the cancer is an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

55. The method of claim 52, wherein the disorder is associated with a kinase.

56. The method of claim 55, wherein disorder is associated with a MAPK kinase pathway.

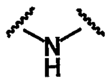
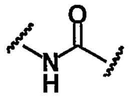
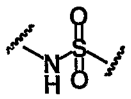
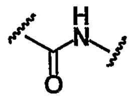
57. A method for treating a disorder, comprising administering to a subject in need thereof an effective amount of a compound having the structure (A):



(A)

wherein:

Y is absent or is a moiety selected from a group consisting of:

 ;  ;  ;  ;

R_1 is a substituent selected from a group consisting of an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl;

R_2 is a substituent selected from a group consisting of hydrogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkylamino, halogen, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, and $-C{\equiv}N$; and

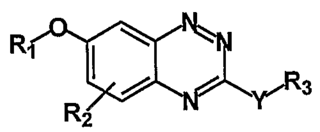
R_3 is a substituent selected from a group consisting of an aryl, a substituted aryl, a heterocycle, a heteroaryl, a substituted heterocycle, and a substituted heteroaryl.

58. The method of claim 57, wherein:

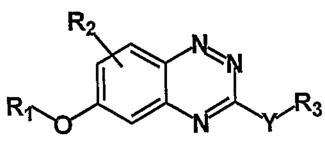
R_1 is selected from a group consisting of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from N, S, and O, substituted C_6-C_{12} aryl, substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl;

R_3 is selected from a group consisting of C_6-C_{12} aryl; C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from N, S, and O, substituted C_6-C_{12} aryl, substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from N, S and O, C_7-C_{24} aralkyl; C_7-C_{24} alkylaryl; substituted C_7-C_{24} aralkyl; and substituted C_7-C_{24} alkaryl.

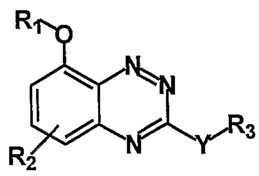
59. The method of claim 57, wherein the compound having the structure (A) is selected from the group of compounds having the structures (A1), (A2), (A3), and (A4):



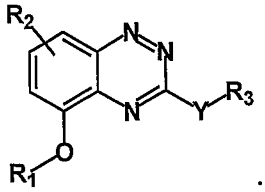
(A1)



(A2)

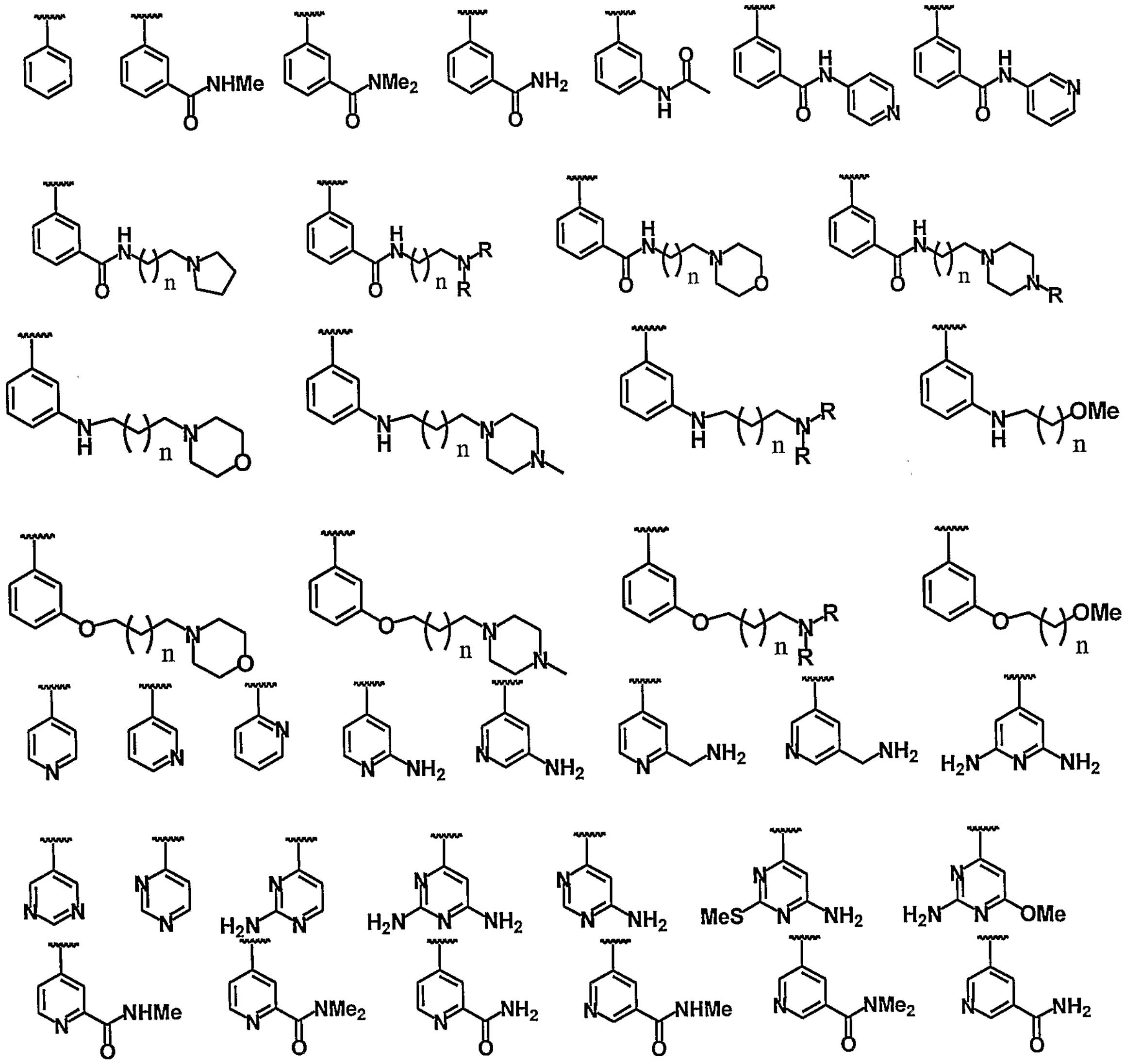


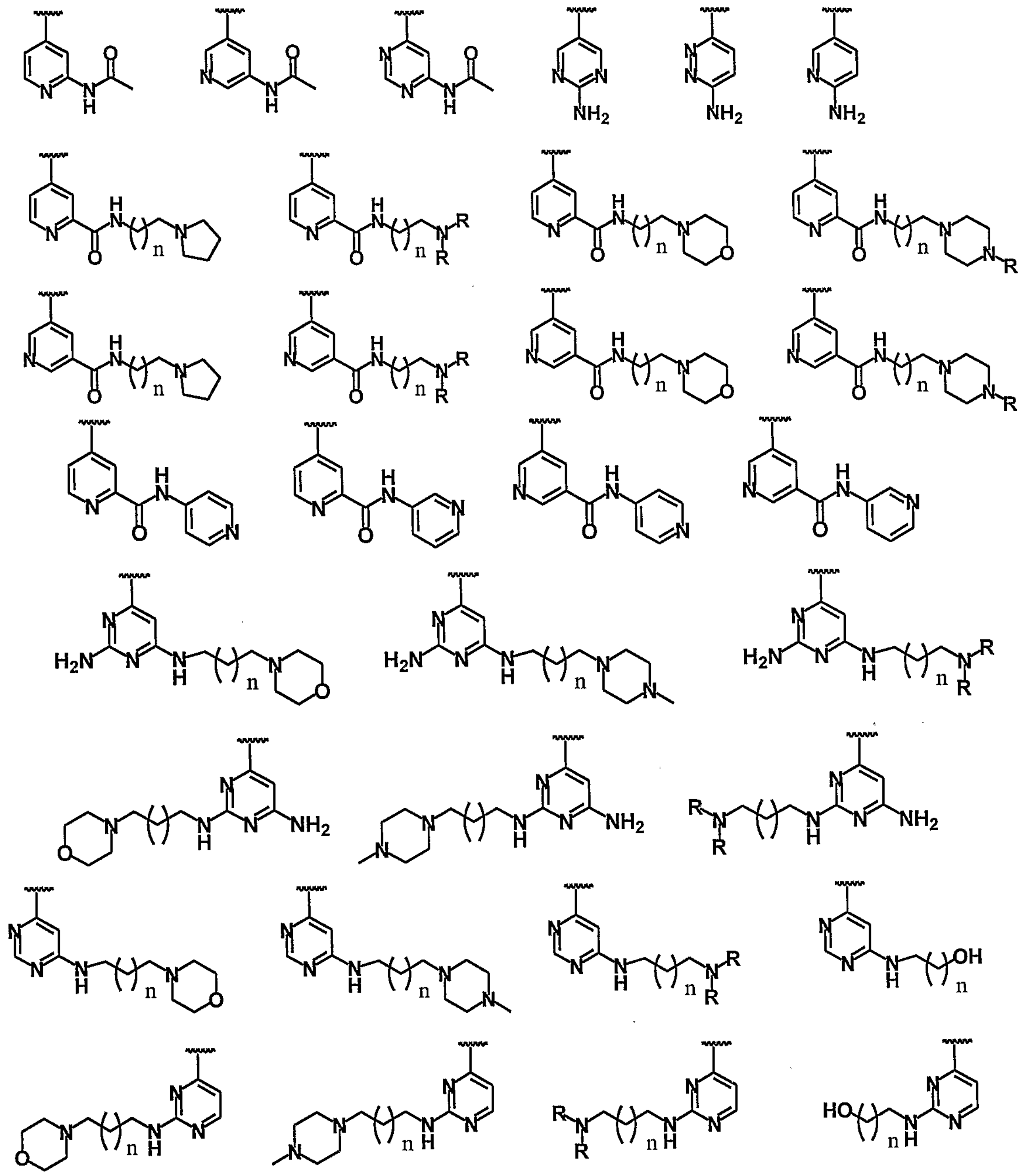
(A3)

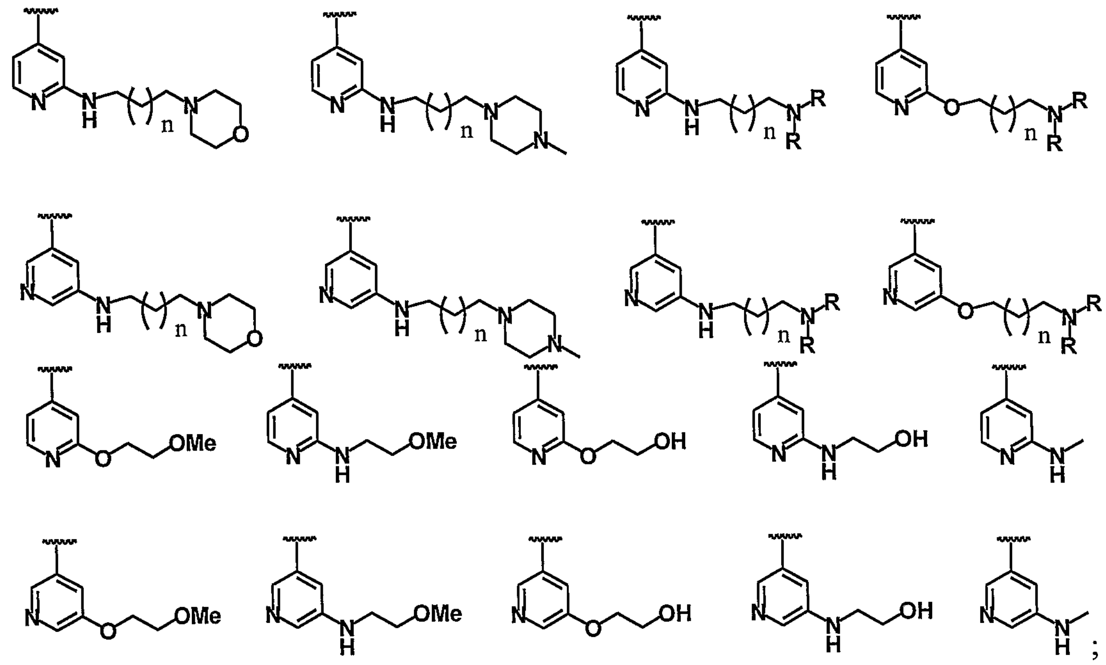


(A4)

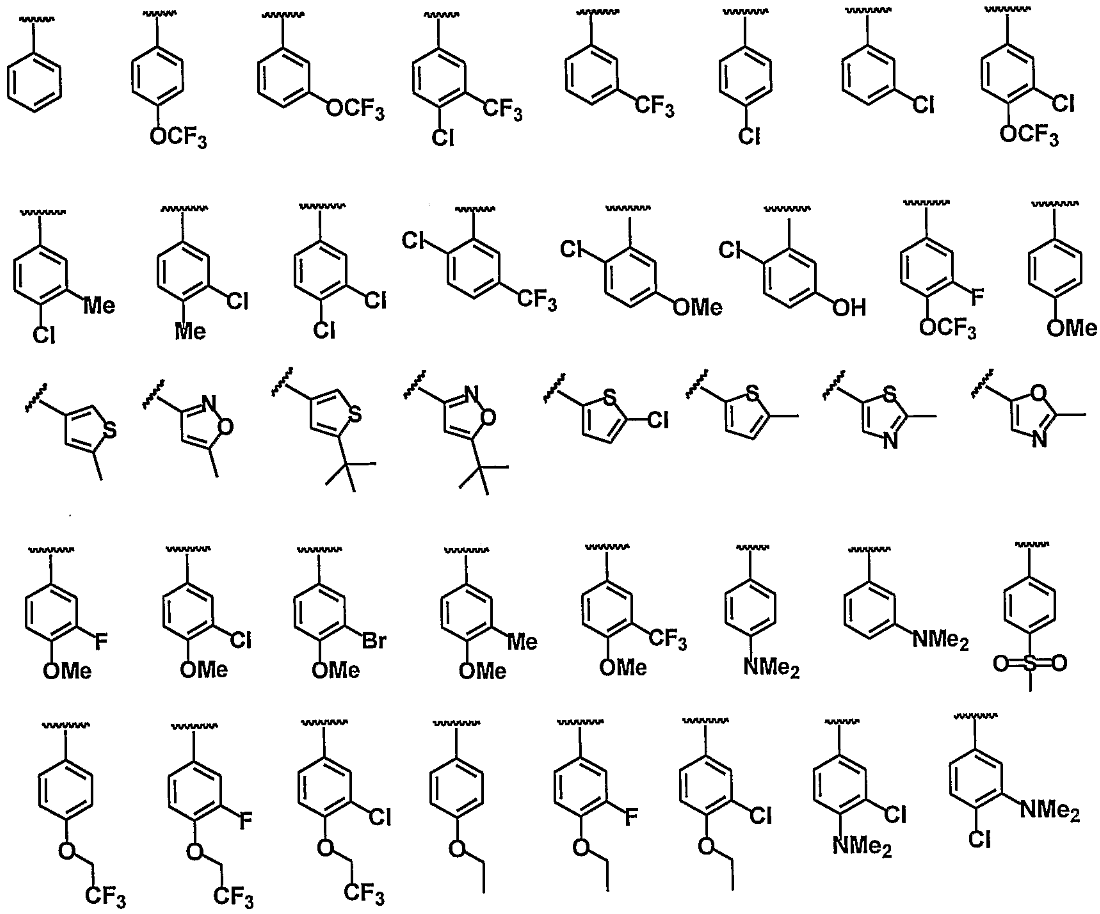
60. The method of claim 57, wherein: R_1 is selected from a group consisting of

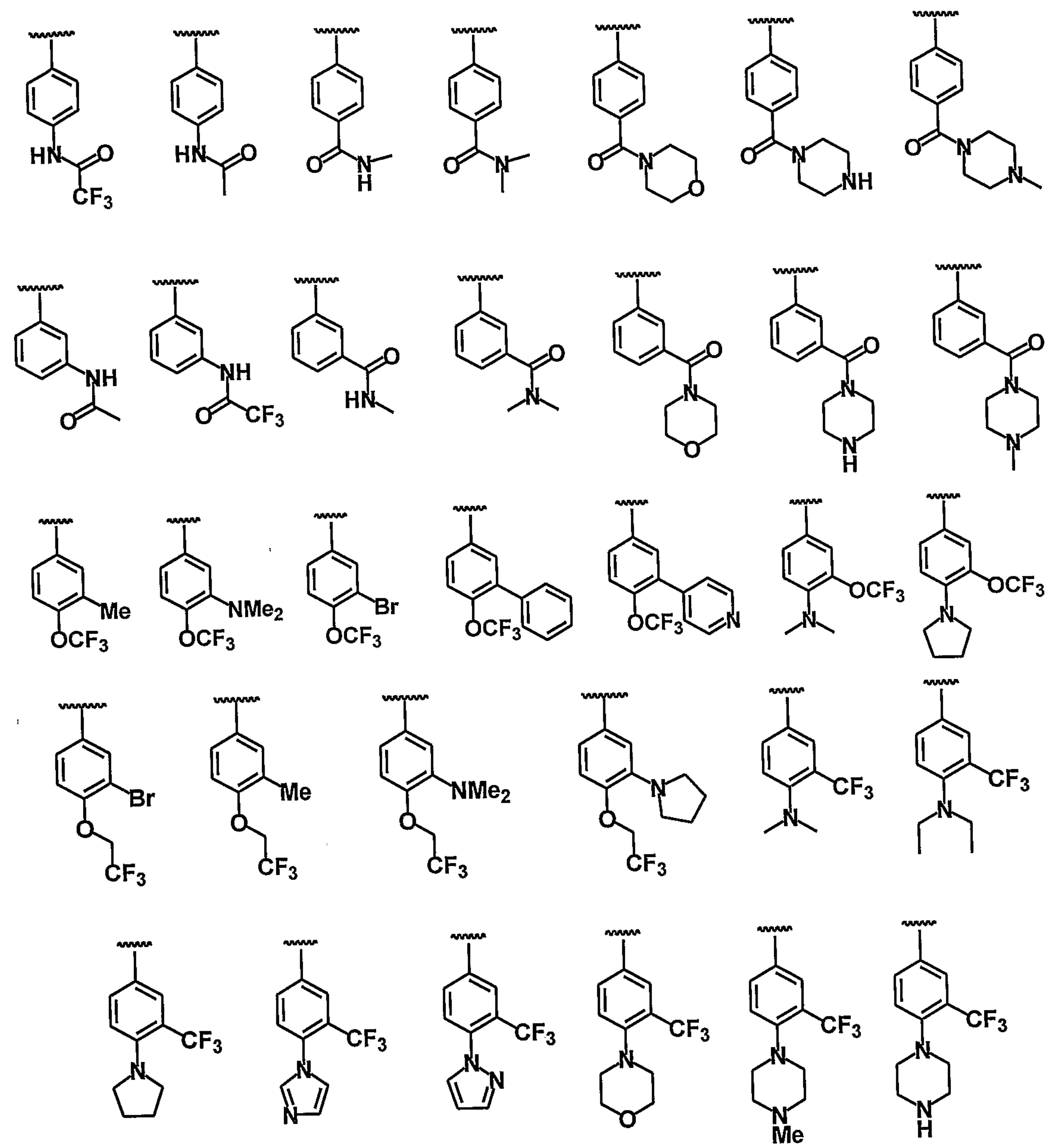


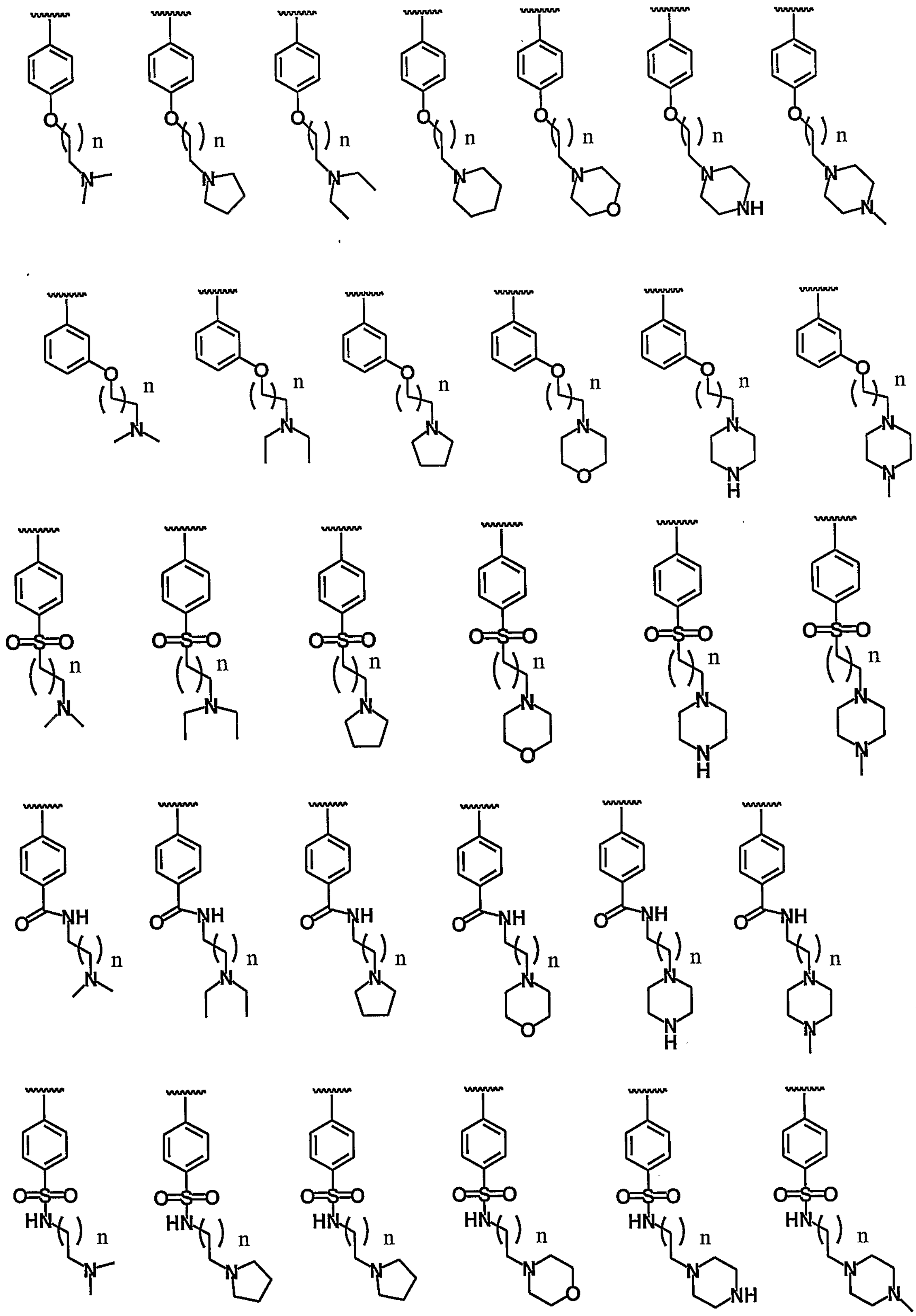


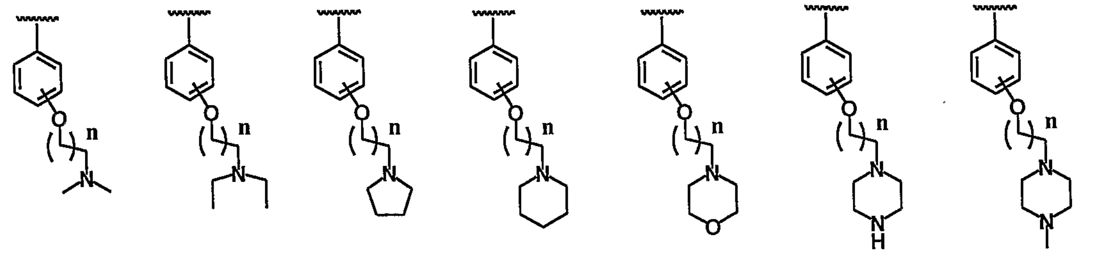


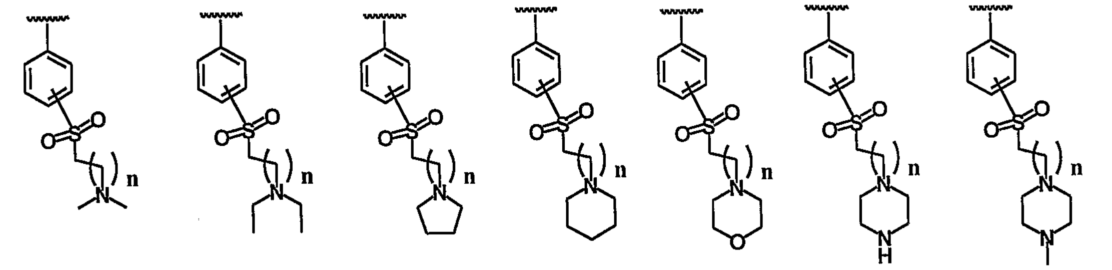
R_3 is selected from a group consisting of:

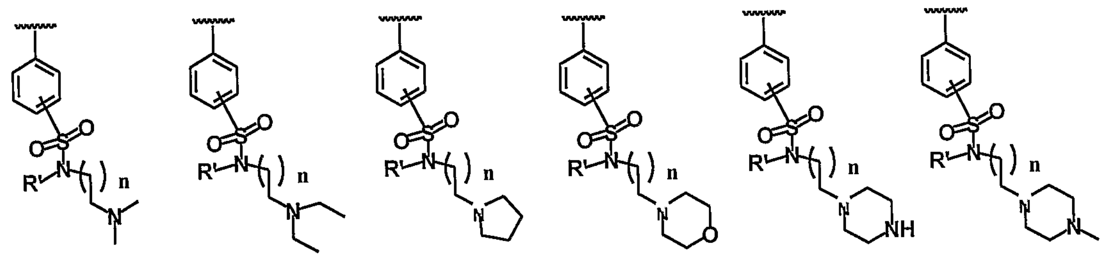


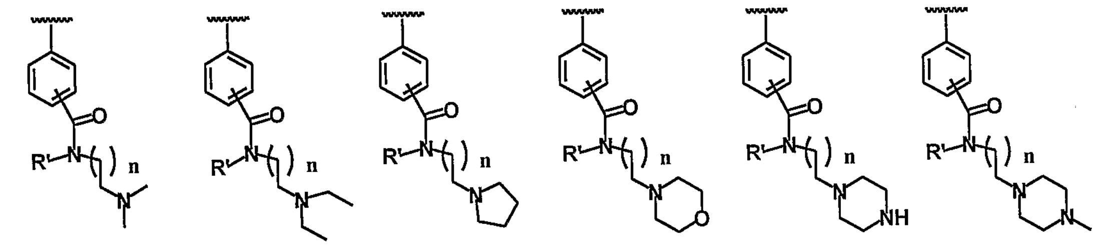


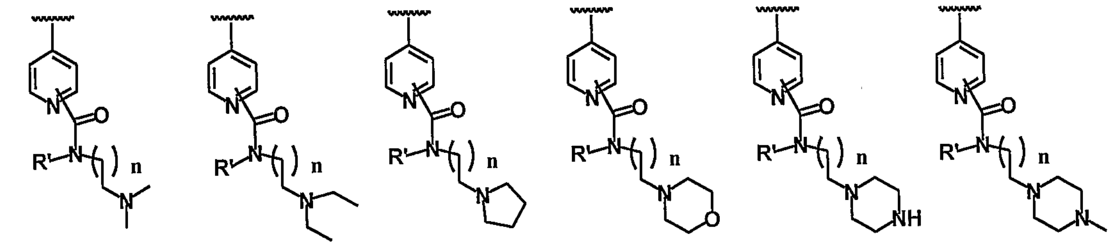

n
N
NH
O
O=S=O
HN

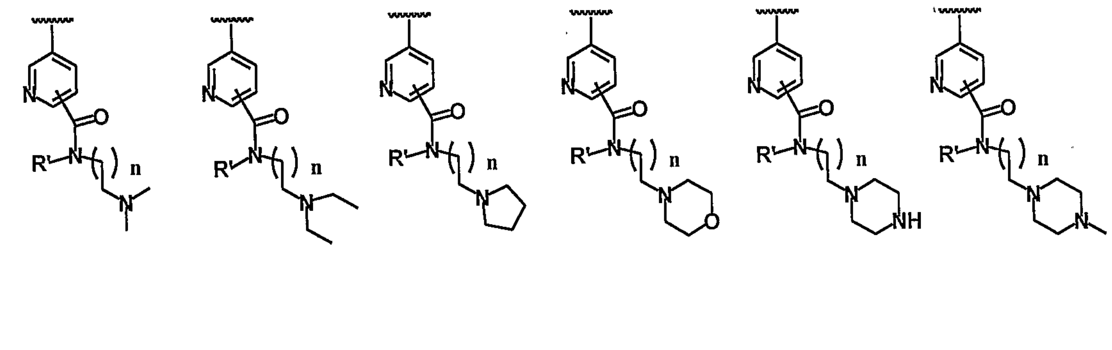


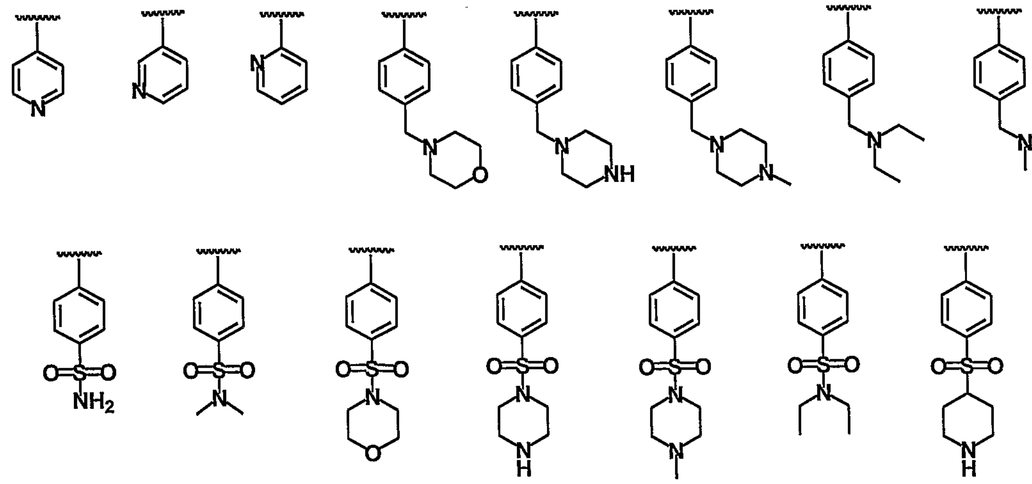








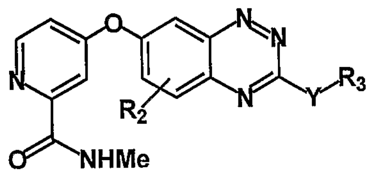




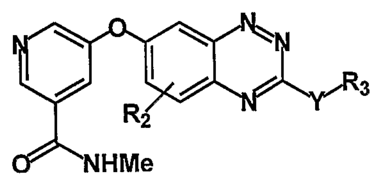
; and

n is an integer selected from a group consisting of 0, 1, 2, and 3.

61. The method of claim 59, wherein the compound having the structure (A1) is selected from a group consisting of compounds having structures (1) and (2):

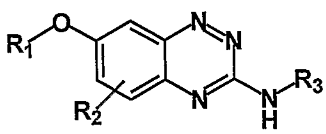


(1)

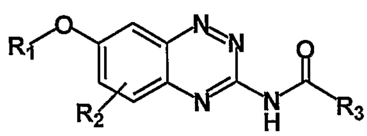


(2)

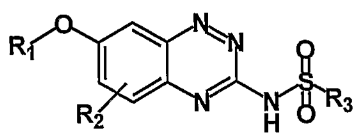
62. The method of claim 59, wherein the compound having structure (A1) is selected from a group consisting of compounds having the structures (3), (4), (5) and (6):



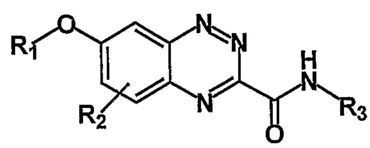
(3)



(4)

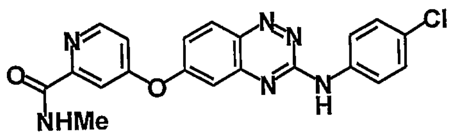


(5)

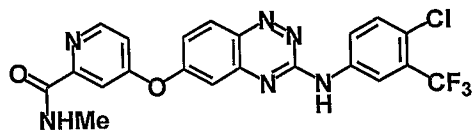


(6)

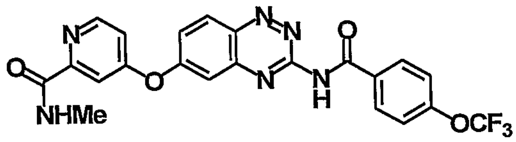
63. The method of claim 62, wherein the compound having structure (A1) is selected from a group consisting of compounds having the structures (7)-(16):



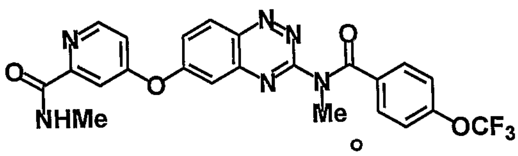
(7)



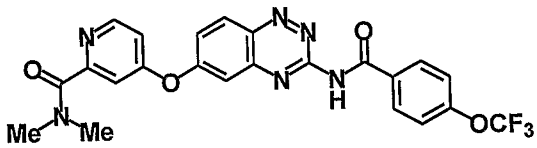
(8)



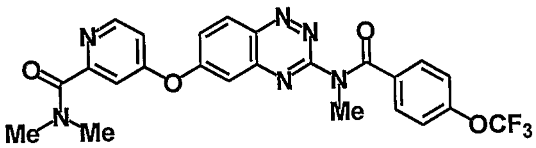
(9)



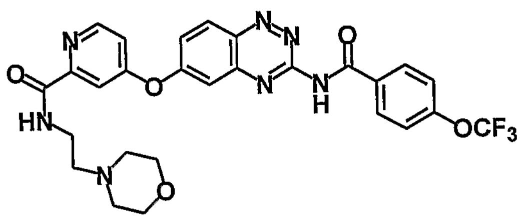
(10)



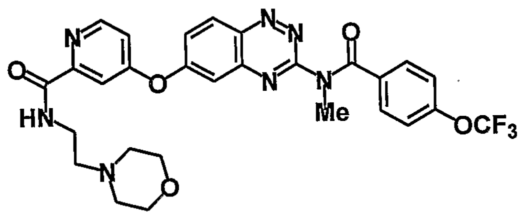
(11)



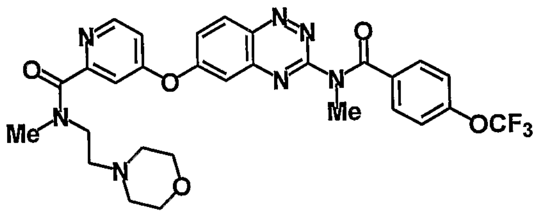
(12)



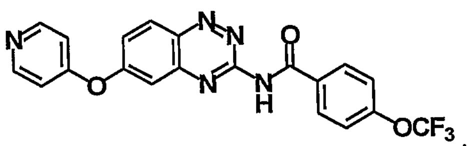
(13)



(14)

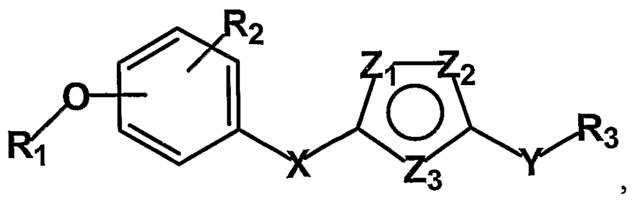


(15)



(16)

64. A method for treating a disorder, comprising administering to a subject in need thereof an effective amount of a compound having the structure (B):



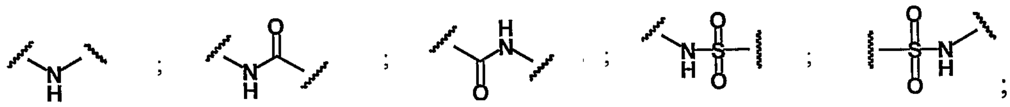
(B)

wherein:

each of Z_1, Z_2 and Z_3 is independently selected from a group consisting of N, CH, N=CH, O, S and N-R^4, wherein R^4 is hydrogen or lower alkyl, with the further proviso that at least one of Z_1, Z_2 and Z_3 is not CH;

X is absent or is NH; and

Y is absent or is selected from a group consisting of the following moieties:



R_1 is an unsubstituted or a substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms;

R_2 is selected from a group consisting of of hydrogen, halogen, C_1-C_{18} alkyl, -OH, -NO_2, -CN, C_1-C_{18} alkoxy, -$NHSO_2R^5$, -SO_2NHR^5, -$NHCOR^5$, -NH_2, -NR^5R^6 , -S(O)R^5, -S(O)$_2R^5$, -CO_2R^5, -$CONR^5R^6$, wherein R^5 and R^6 are independently selected from a group consisting of hydrogen, a C_1-C_{18} alkyl, and a substituted C_1-C_{12} alkyl; and

R_3 is selected from a group consisting of hydrogen, a C_1-C_{18} alkyl, a substituted C_1-C_{12} alkyl, a C_1-C_{12} cycloalkyl, a substituted C_1-C_{12} cycloalkyl, a substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms, an C_6-C_{12} aryl, a substituted C_6-C_{12} aryl, a heterocycle, a substituted heterocycle, a C_3-C_{12} heteroaryl having 1-3 heteroatoms, a substituted C_3-C_{12} heteroaryl having 1-3 heteroatoms, a C_7-C_{24} aralkyl, a substituted C_7-C_{24} aralkyl, a C_7-C_{24} alkylaryl, and a substituted C_7-C_{24} alkaryl.

65 The method of claim 64, wherein R_1 is selected from the group consisting of:

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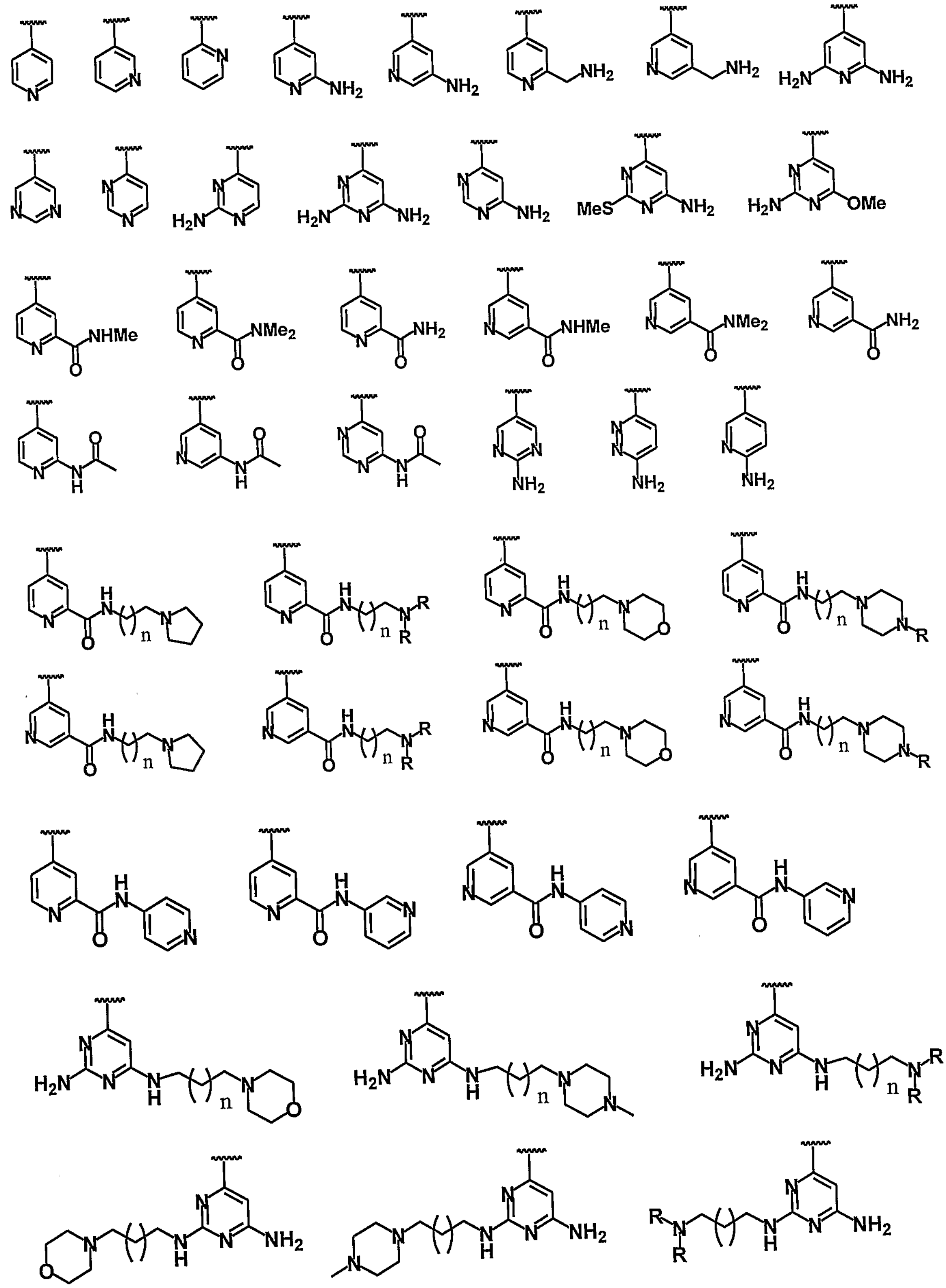
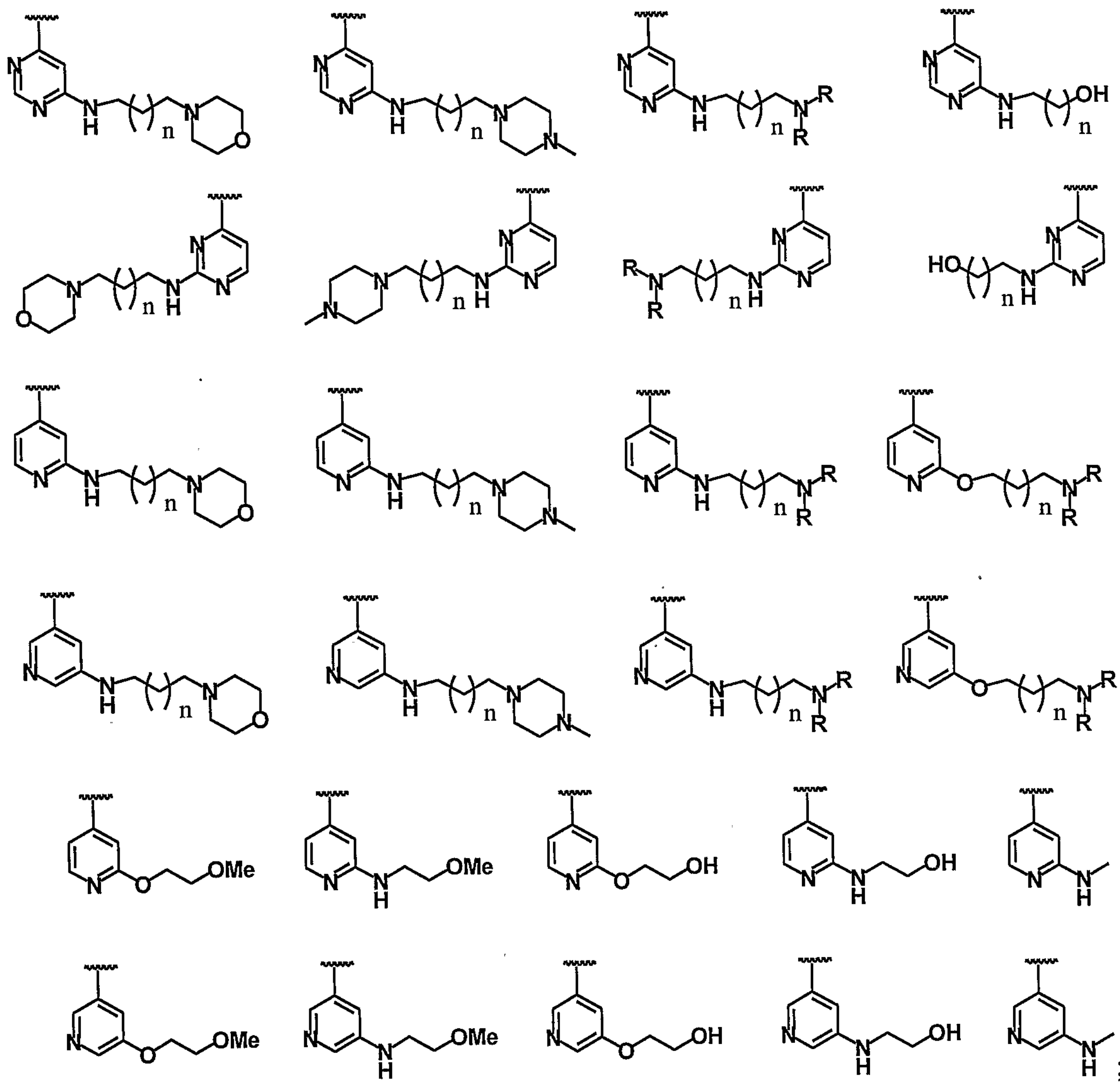
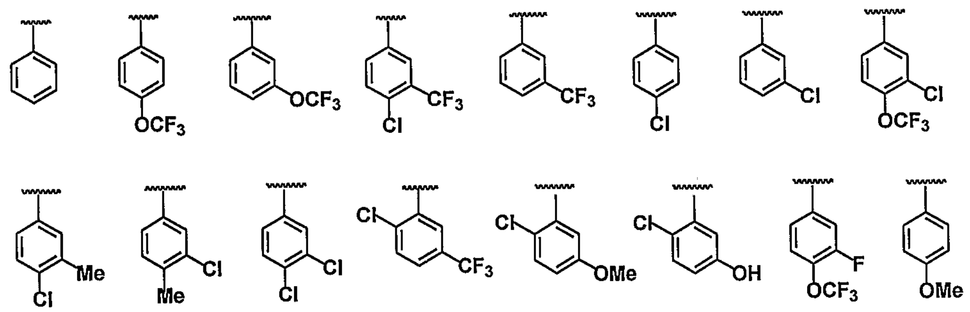
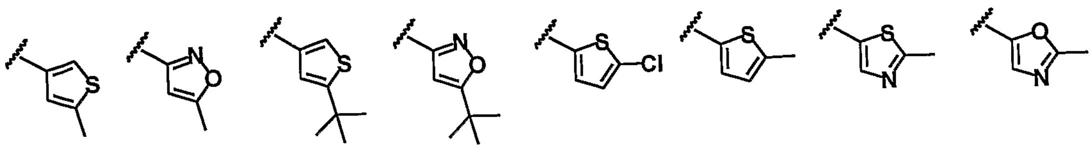


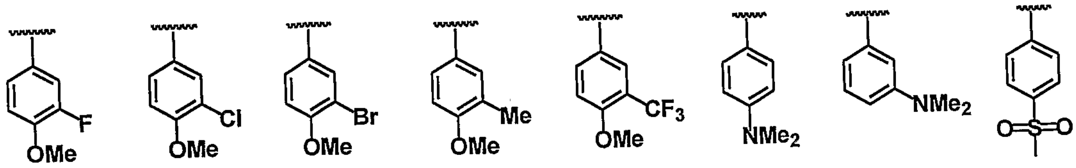


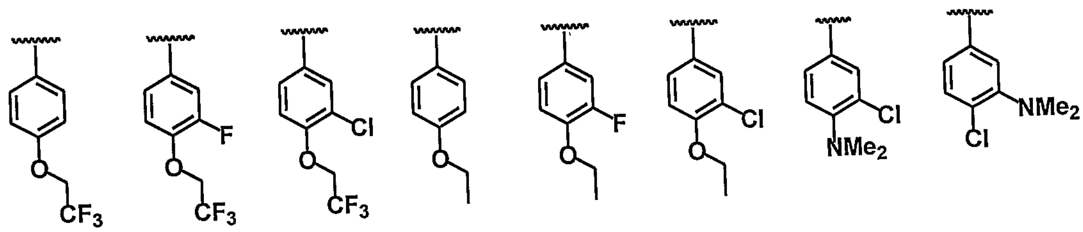
;

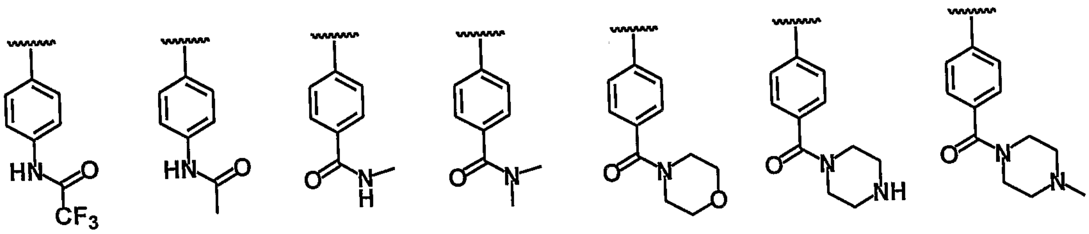
R_3 is selected from the group consisting of:

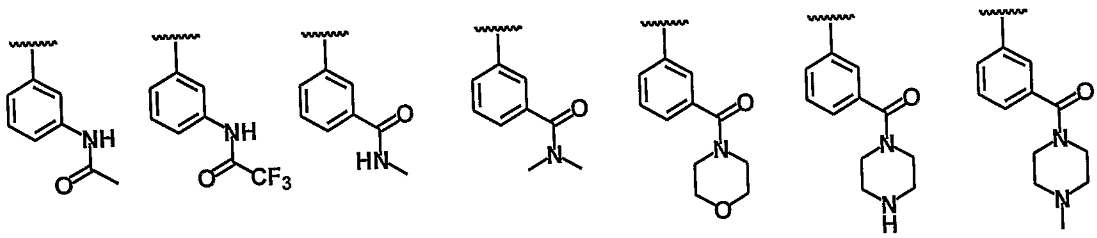


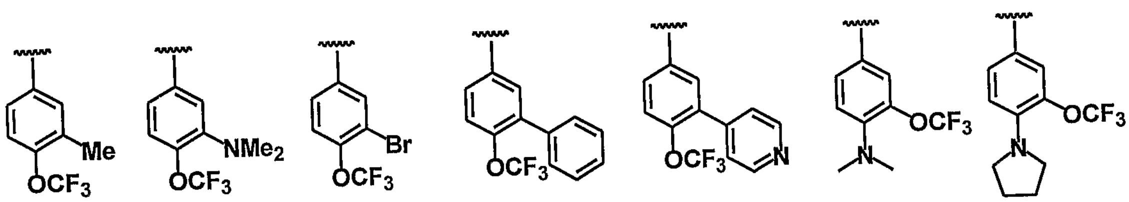


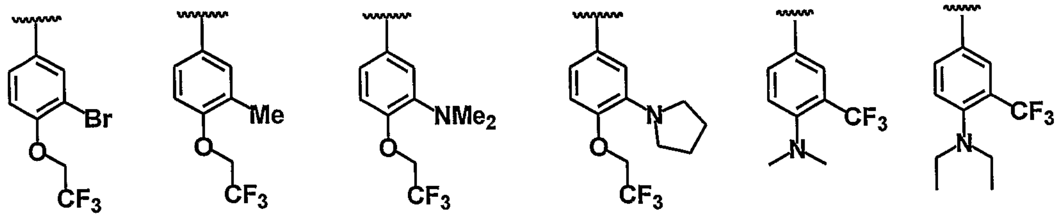


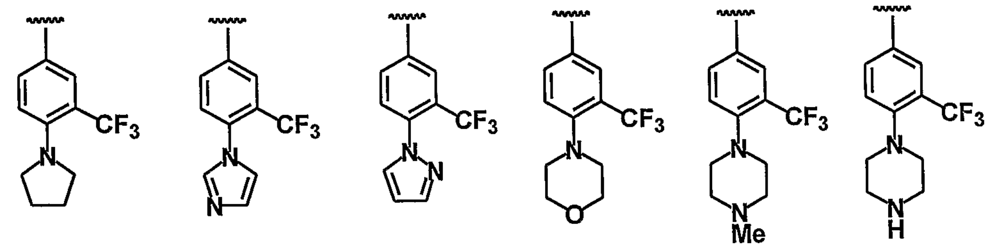


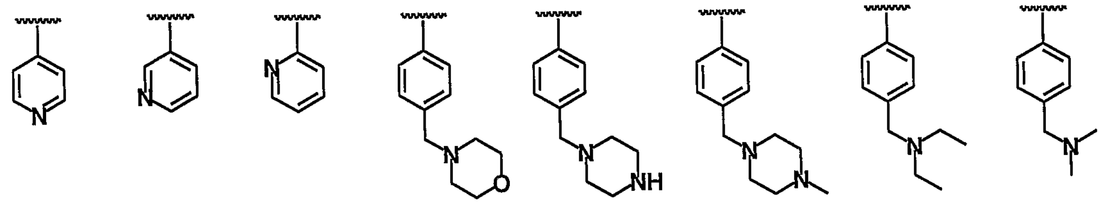


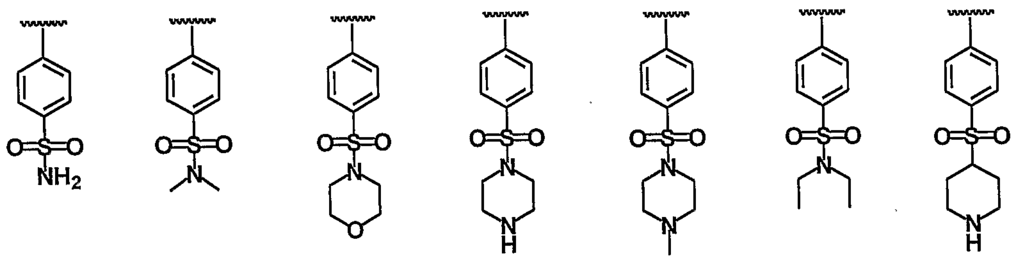


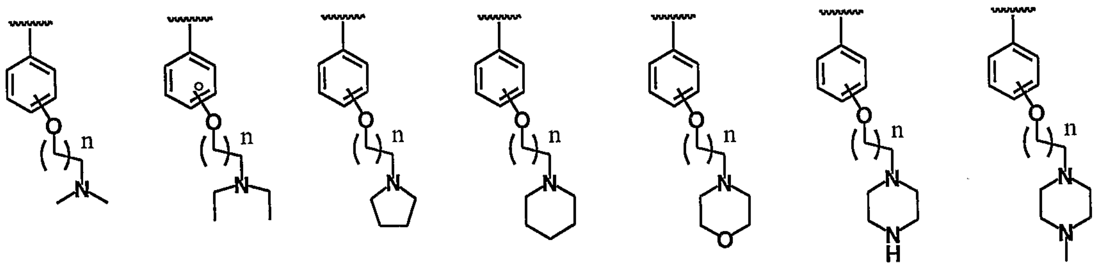


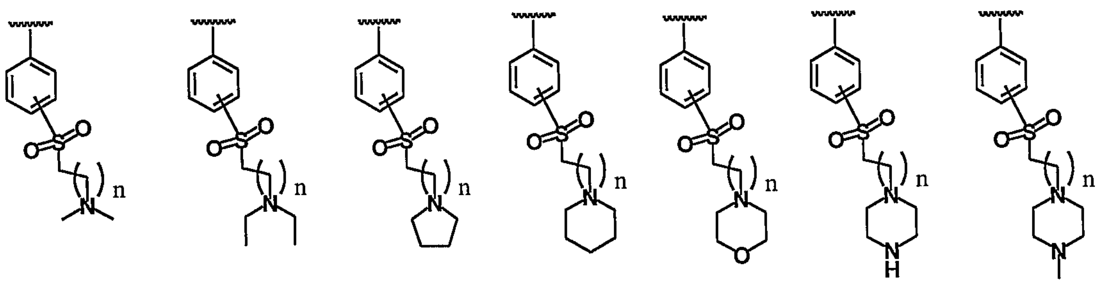


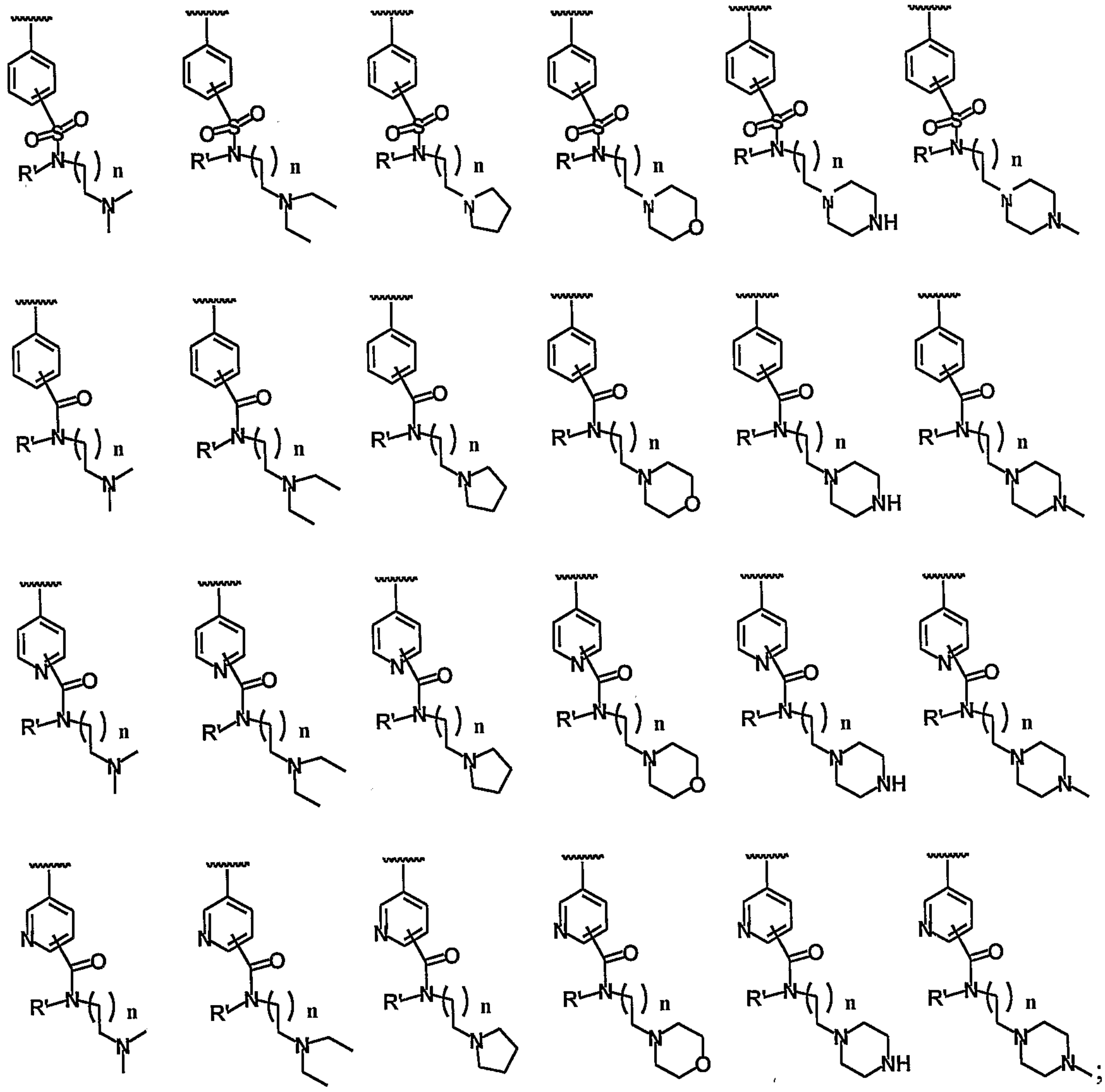








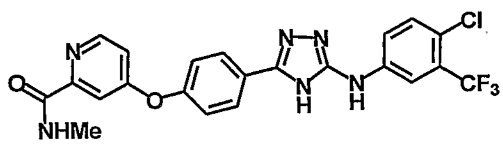




n is an integer selected from a group consisting of 0, 1, 2, and 3, and

R′ is selected from a group consisting of hydrogen, a C_1-C_{18} alkyl, and a substituted C_1-C_{18} alkyl.

66. The method of claim 64, wherein the compound having structure (B) is selected from a group consisting of compounds having formulae (17)-(35):



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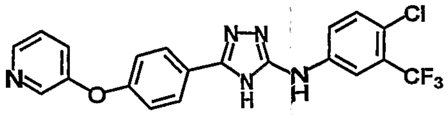

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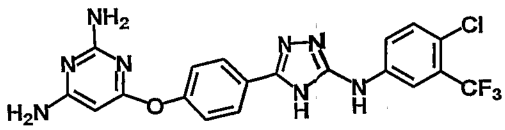

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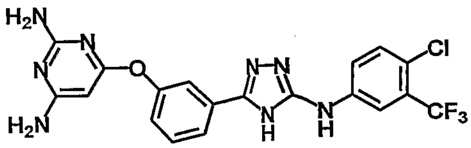

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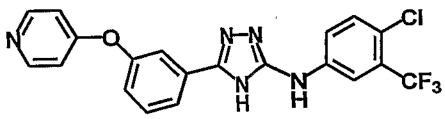

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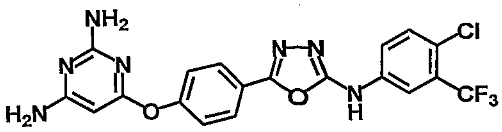

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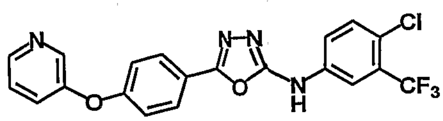

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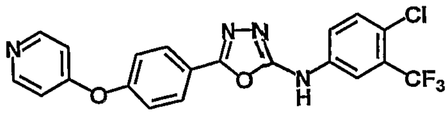

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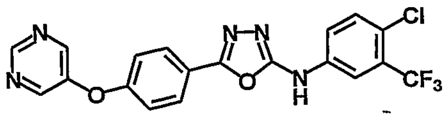

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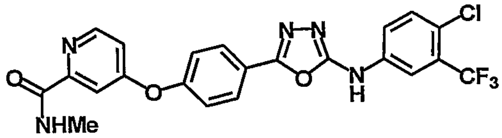

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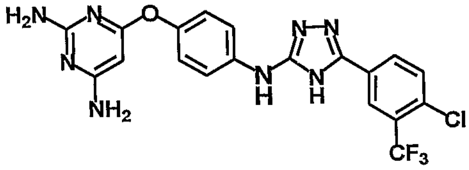

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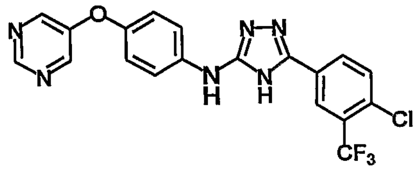

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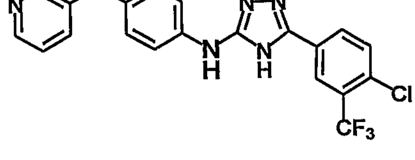

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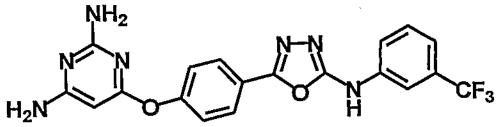

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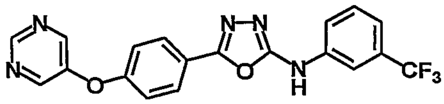

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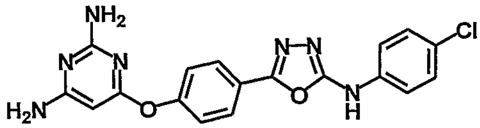

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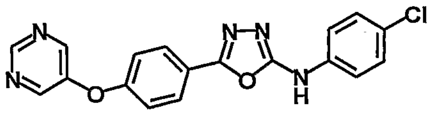

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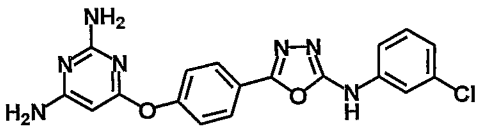

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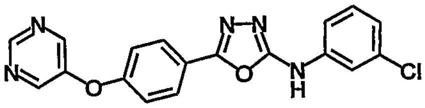


(35)

67. The method of claim 57 or 64, wherein the disorder is selected from a group consisting of cancer, eye disease, inflammation, psoriasis, and a viral infection.

68. The method of claim 67, wherein the cancer is an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate

cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

69. A pharmaceutical composition comprising a compound set forth in structures (A), (B) or any combination thereof, in a pharmaceutically acceptable carrier.

70. An article of manufacture comprising packaging material and a pharmaceutical composition contained within the packaging material, wherein the packaging material comprises a label which indicates that the pharmaceutical composition can be used for treatment of disorders and wherein said pharmaceutical composition comprises a compound set forth in structures (A), (B) or any combination thereof.

71. An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for treatment of cancer and wherein said pharmaceutical composition comprises a compound set forth in structures (A), (B) or any combination thereof.

72. A method of treating a disorder, comprising the administration of a therapeutically effective amount of at least one compound set forth in structures (A), (B) or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, to a subject in need of such treatment.

73. The method of claim 72, wherein the disorder is selected from a group consisting of cancer, eye disease, inflammation, psoriasis, and a viral infection.

74. The method of claim 73, wherein the cancer is an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

75. A method of treating a disorder comprising the administration of a therapeutically effective amount of at least one compound as set forth in structures (A), (B) or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, in combination with a chemotherapeutic agent, immunomodulatory agent, therapeutic antibody or a protein kinase inhibitor, to a subject in need of such treatment.

76. A method of treating a subject having cancer comprising administering to the subject a therapeutically effective amount of a compound as set forth in structures (A), (B) or any combination thereof, thereby treating the subject.

77. A process for making a pharmaceutical composition comprising combining a combination of a compound set forth in structures (A), (B) or any combination thereof or its pharmaceutically acceptable salts, hydrates, solvates, crystal forms salts and individual diastereomers thereof, and a pharmaceutically acceptable carrier.

78. A pharmaceutical composition comprising a compound as set forth in Structure (A1) in a pharmaceutically acceptable carrier.

79. A pharmaceutical composition comprising a compound as set forth in Structure (A2) in a pharmaceutically acceptable carrier.

80. A pharmaceutical composition comprising a compound as set forth in Structure (A3) in a pharmaceutically acceptable carrier.

81. A pharmaceutical composition comprising a compound as set forth in Structure (A4) in a pharmaceutically acceptable carrier.

82. A pharmaceutical composition comprising a compound as set forth in Structure (B) in a pharmaceutically acceptable carrier.

83. A method for treating cancer or a tumor in a subject, comprising administering to a subject in need thereof an effective amount of a therapeutic antibody, chemotherapeutic agent or immunotoxic agents, in combination with a compound set forth in Structures (A), (B) or any combination thereof, thereby treating the cancer or tumor in the subject.

84. A pharmaceutical composition comprising a therapeutic agent and at least one compound as set forth in Structures (A1), (A2), (A3), (A4) or any combination thereof, in a concentration effective to treat cancer in a subject.

85. The composition of claim 84, wherein the cancer is an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

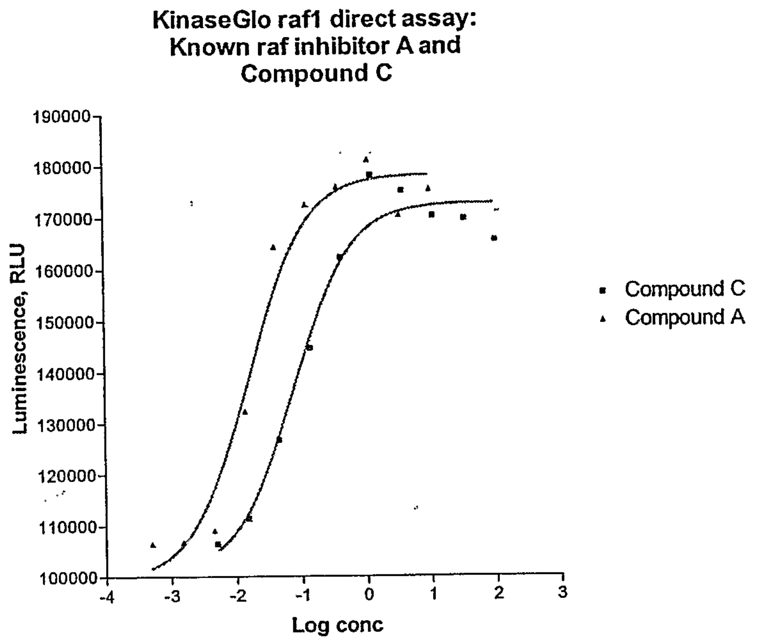
86. The composition of claim 85, wherein the cancer is colon cancer or lung cancer.

87. The method of claim 84, wherein the therapeutic agent is an antimetabolite; a DNA cross-linking agent; alkylating agent; topoisomerase I inhibitor; microtubule inhibitors, a vinca alkaloid, mitomycin-type antibiotic, and a bleomycin-type antibiotic.

88. The method of claim 84, wherein the therapeutic agent is methotrexate, cisplatin/carboplatin; canbusil; dactinomicin; taxol (paclitaxel), antifolate, colchicine, demecoline, etoposide, taxane/taxol, docetaxel, doxorubicin, anthracycline antibiotic, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-dimethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate or adriamycin-14-naphthaleneacetate, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, trastuzumab.

89. The method of claim 88, wherein the therapeutic agent is doxorubicin, docetaxol, or taxol.

90. The method of claim 84, wherein the therapeutic agent is trastuzumab, bevacizumab, OSI-774, or Vitaxin.



	Bottom	Top	LOG IC50	IC50 (µM)
Compound A	99213	178380	-1.797	0.01597
Compound C	100504	172817	-1.114	0.07685

FIG. 1

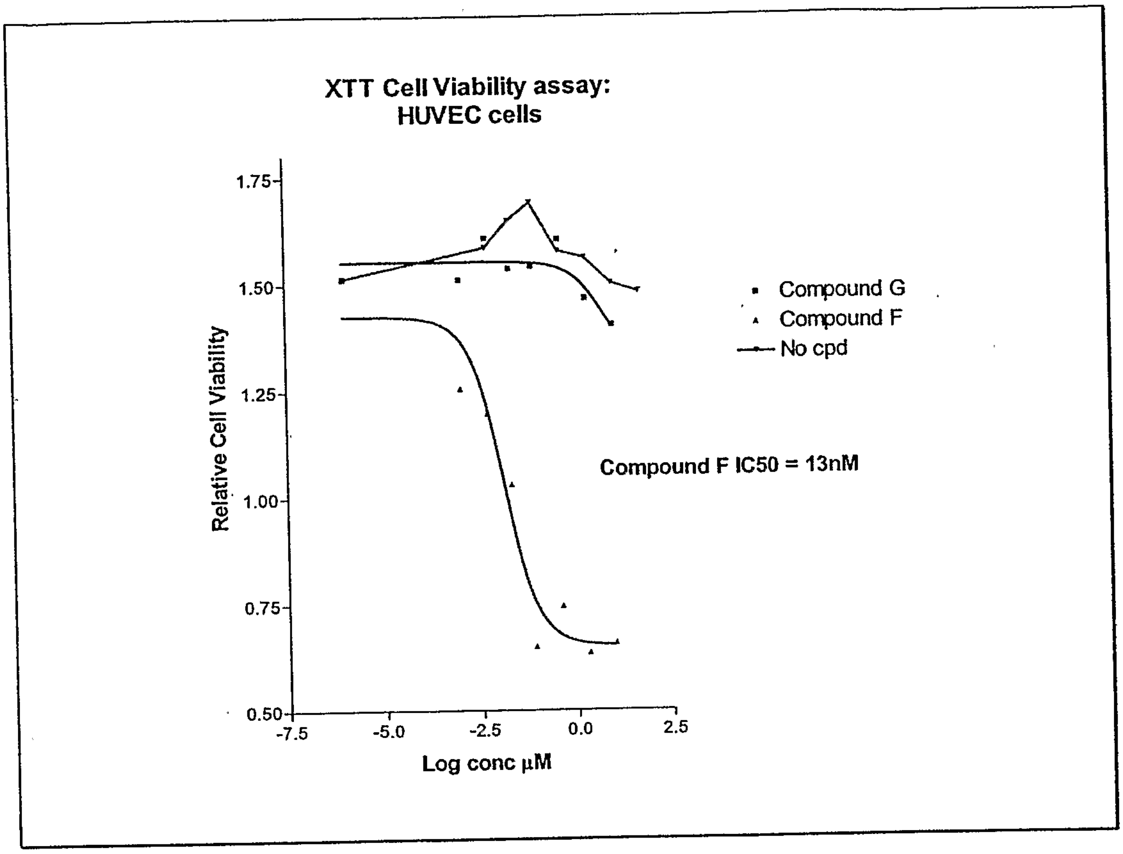

XTT Cell Viability assay:
HUVEC cells
Relative Cell Viability
1.75
1.50
1.25
1.00
0.75
0.50
-7.5
-5.0
-2.5
0.0
2.5
Log conc µM
Compound G
Compound F
No cpd
Compound F IC50 = 13nM

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/30614

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 253/10, 241/02, 237/02, 213/02; A61K 31/53, 31/506, 31/495, 31/44; A61P 35/00, 31/12, 19/02

US CL : 544/183, 238, 242, 336; 546/268.1; 514/243, 247, 256, 277

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/183, 238, 242, 336; 546/268.1; 514/243, 247, 256, 277

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE , EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,309,211 (SERBAN et al) 05 January 1982 (05.01.1982), see entire document, espeically formula I and examples 1-5.	1-51
X	US 4,160,833 (DIEL) 10 July 1979 (10.07.1979), see entire document esepecially formula I and examples 1-5, compounds 1-23.	1-51, 69-71 and 77-82.
X	US 5,849,738 A (LEE et al) 15 December 1998 (15.12.1998), see entire documetn especially formula I and examples 1-22.	1-90

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 January 2006 (06.01.2006)	27 JAN 2006

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Venkataraman Balasubramanian Telephone No. (571) 272-1600