Solid dispersion product of N-aryl urea-based drugs

Many potent drugs belong to the class of compounds of N-aryl ureas and compounds of related structural types. Unfortunately, the crystalline forms of most N-aryl urea-based active agents are characterized by poor solubility in aqueous liquids.

Drugs of low water solubility, for example those classified as "practically insoluble" or "insoluble" according to United States Pharmacopeia (USP) 24 (2000), p. 10, i. e., having a solubility of less than about 1 part per 10,000 parts water (less than about 100 µg/ml) are notoriously difficult to formulate for oral delivery. Among other problems, bioavailability of such drugs, when administered by the oral route, tends to be very low.

A specific illustrative small-molecule drug of low water solubility is the compound N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea (ABT-869), a multi-targeted protein tyrosine kinase (PTK) inhibitor. This compound, which has a molecular weight of 375.4 g/mol, is disclosed in International Patent Publication No. WO 2004/113304 of Abbott Laboratories.

For a variety of reasons, such as patient compliance and taste masking, a solid dosage form is usually preferred over a liquid dosage form. In most instances, however, oral solid dosage forms of a drug provide a lower bioavailability than oral solutions of the drug.

There remains a need in the pharmaceutical art for a novel solid formulation of N-aryl urea-based active agents of low water solubility such as ABT-869 that is suitable for oral administration. More particularly and without limitation, there is a need for such a formulation having at least one of the following features, advantages or benefits: acceptably high concentration of the drug; and acceptable bioavailability when administered orally.

The invention relates to a solid dispersion product comprising at least one pharmaceutically active agent, obtained by

a) preparing a liquid mixture containing the at least one active agent, at least one pharmaceutically acceptable matrix-forming agent, at least one pharmaceutically acceptable surfactant and at least one solvent, and
b) removing the solvent(s) from the liquid mixture to obtain the solid dispersion product.

The invention is particularly useful for water-insoluble or poorly water-soluble (or ''hydrophobic'' or "lipophilic") compounds. Compounds are considered water-insoluble or poorly water-soluble when their solubility in water at 25 °C is less than 1 g/100 ml, especially less than 0,1 g/100 ml.

In the dosage forms of the invention, the active agent is present as a solid dispersion or, preferably, as a solid solution. The term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed evenly throughout the other component or components. For example, the active agent or combination of active agents is dispersed in a matrix comprised of the matrix-forming agent(s) and pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles, typically of less than 1 μm in diameter, of one phase dispersed in another phase. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called a "solid solution" or a "glassy solution". A glassy solution is a homogeneous, glassy system in which a solute is dissolved in a glassy solvent. Glassy solutions and solid solutions are preferred physical systems. These systems do not contain any significant amounts of active agents in their crystalline or microcrystalline state, as evidenced by thermal analysis (DSC) or X-ray diffraction analysis (WAXS).

In an embodiment of the invention, at least one filler is added to the liquid mixture before removing the solvent(s). It was found that incorporation of a filler into the liquid mixture before removing the solvent(s) increases the brittleness of the solid dispersion product obtained. This allows the solid dispersion product to be subjected to a direct tabletting process.

Preferably, the filler is essentially insoluble in the liquid mixture.

The choice of fillers is not particularly restricted. The filler may be suitably selected from inorganic particulate materials such as silica, calcium carbonate, calcium phosphates, titanium dioxide; natural and pre-gelatinized starches such as corn starch, cereal starch, potato starch; or the like.

However, the filler is preferably water-soluble. Useful fillers to that end may be selected from sugars such as lactose, sucrose; sugar alcohols such as mannitol, sorbitol, xylitol; or sugar alcohol derivatives.

The relative amounts of active agent, pharmaceutically acceptable matrix-forming agent and pharmaceutically acceptable surfactant are chosen with the following conditions in mind: (1) Essentially all of the active agent should be dispersed evenly throughout the matrix comprised of the matrix-forming agent(s) and pharmaceutically acceptable surfactant(s). (2) The matrix should have sufficient mechanical integrity and stability; in particular, the matrix should not exhibit cold flow. Generally, the mass ratio of active agent and pharmaceutically acceptable matrix-forming agent is from 0.01:1 to 1:3, preferably 0.05:1 to 0.2:1; generally the mass ratio of active agent and pharmaceutically acceptable surfactant(s) is from 0.1:1 to 1:7, preferably 1:4 to 1:6.5.

Generally, the solid dispersion product comprises

from about 1 to 30 % by weight, preferably from about 4 to 15 % by weight, of said at least one pharmaceutically active agent,
from about 15 to 70 % by weight, preferably from about 20 to 55 % by weight, of said at least one pharmaceutically acceptable matrix-forming agent,
from about 2 to 70 % by weight, preferably from about 5 to 55 % by weight, of said at least one surfactant, and
from about 0 to 80 % by weight, preferably from about 0 to 60 % by weight, of additives such as fillers.

The matrix-forming agent may be any agent capable of embedding an active agent and/or being loaded with an active agent and stabilizing an essentially amorphous state of the active agent. Mixtures of matrix-forming agents can, of course, be used.

The pharmaceutically acceptable matrix-forming agent is suitably selected from the group consisting of cyclodextrines, pharmaceutically acceptable polymers, lipids or combinations of two or more thereof.

Cyclodextrins for the purpose of the invention are cyclic oligo- or polysaccharides, for example so-called cycloamyloses or cycloglucans, and analogous cyclic carbohydrates which are described, for example, in Angew. Chem. 92 (1980) p. 343 or F. Vögtle, Supramolekulare Chemie, 2nd Edition, (1992). Suitable and preferred are those cyclodextrins which have a structure suitable for interactions with active agent molecules, in particular in the sense of host-guest systems. Particularly suitable cyclodextrins are those consisting of 6, 7, 8 or 9 α-1,4-glycosidically linked glucose units, which are called α-, β-, γ- or δ-cyclodextrins. Higher structures analogous to cyclodextrins and composed of a larger number of glucoses or similar sugars are also conceivable and suitable.

Also suitable as cyclodextrins are modified cyclodextrins such as, for example, products which can be prepared by reacting cyclodextrins with alkylene oxides, alkyl halides, acid chlorides, epihalohydrins, isocyanates or halogenated carboxylic acids. Thus, suitable examples are products of the reaction of cyclodextrins with alkylene oxides such as ethylene oxide, propylene oxide, butylene oxide or styrene oxide. One, more than one or all hydroxyl groups in the cyclodextrin polyethers formed in this way may be substituted. Depending on the degree of substitution or the chain lengths of the polyether units, the average molar degree of substitution, that is to say the number of moles of alkylene oxide with which one mole of cyclodextrin is reacted, is usually between 3 and 20,000, but there is in principle no upper limit. Particularly suitable examples are the products of the reaction of cyclodextrins with alkylating agents such as C_1-C_{22}-alkyl halides, for example methyl chloride, ethyl chloride, isopropyl chloride, n-butyl chloride, isobutyl chloride, benzyl chloride, lauryl chloride, stearyl chloride, methyl bromide, ethyl bromide, n-butyl bromide and dialkyl sulfates such as, for example, dimethyl sulfate or diethyl sulfate. Reaction with alkylating reagents leads to cyclodextrin ethers in which one, more than one or all hydroxyl groups are substituted by alkyl ether groups. With the cyclodextrins composed of glucose units, the average degree of eth-

erification per glucose unit is usually in the range from 0.5 to 3, preferably in the range from 0.1 to 2.5 and particularly preferably in the range from 1 to 2. Particular preference is given to methylated, ethylated or propylated α-, β-, γ-cyclodextrins with an average degree of etherification of from 1.5 to 2.2. Also suitable are cyclodextrin esters which are obtainable by reacting cyclodextrins with acid chlorides such as carbonyl or sulfonyl chlorides. Particularly suitable are carbonyl chlorides such as acetyl chloride, acryloyl chloride, methacryloyl chloride or benzoyl chloride.

Also suitable are polymer-modified cyclodextrins, that is to say cyclodextrins which are incorporated into the main chain of polymers and/or cyclodextrins which have been attached to side chains of polymers or are themselves side chains of polymers. Polymer-modified cyclodextrins in which the cyclodextrin units are arranged in the main chain of the polymer can be obtained, for example, by reacting cyclodextrins with or in the presence of suitable coupling or crosslinking reagents, for example as described in Helv. Chim. Acta, Vol. 48, (1965), p. 1225. Polymer-modified cyclodextrins in which the cyclodextrin units are side chain constituents or act as side chains can be obtained, for example, by cyclodextrins modified with polymerizable groups being polymerized with other comonomers, for example by polymerizing cyclodextrin (meth)acrylates in the presence of other ethylenically unsaturated monomers or by free-radical grafting of cyclodextrin (meth)acrylates onto polymers with free hydroxyl groups such as, for example, polyvinyl alcohol. Another possibility for preparing polymer-modified cyclodextrins with the cyclodextrin units on side groups or as side groups of polymers is to react cyclodextrins, deprotonated cyclodextrins or their alkali metal salts with polymers which have complementary reactive groups such as, for example, anhydride, isocyanate, acid halide or epoxy groups or halogens.

Preferred cyclodextrines are hydroxyalkyl-cyclodextrines, such as hydroxypropyl-β-cyclodextrin.

Suitable lipids may be selected from waxes, tri-, di-, and monoglycerides and phospholipids.

The preferred matrix-forming agents are pharmaceutically acceptable polymers.

The pharmaceutically acceptable polymers may be selected from water-soluble polymers, water-dispersible polymers or water-swellable polymers or any mixture thereof. Polymers are considered water-soluble if they form a clear homogeneous solution in water. When dissolved at 20 °C in an aqueous solution at 2 % (w/v), the water-soluble polymer preferably has an apparent viscosity of 1 to 5000 mPa.s, more preferably of 1 to 700 mPa.s, and most preferably of 5 to 100 mPa.s. Water-dispersible polymers are those that, when contacted with water, form colloidal dispersions rather than a clear solution. Upon contact with water or aqueous solutions, water-swellable polymers typically form a rubbery gel. Water-soluble polymers are preferred.

Preferably, the pharmaceutically acceptable polymer employed in the invention has a Tg of at least 40°C, preferably at least +50°C, most preferably from 80 ° to 180. °C. "Tg" means glass transition temperature. Methods for determining Tg values of the organic polymers are described in "Introduction to Physical Polymer Science", 2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992. The Tg value can be calculated as the weighted sum of the Tg values for homopolymers derived from each of the individual monomers, i, that make up the polymer: $Tg = \Sigma W_i X_i$ where W is the weight percent of monomer i in the organic polymer, and X is the Tg value for the homopolymer derived from monomer i. Tg values for the homopolymers may be taken from "Polymer Handbook", 2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975.

Various additives contained in the solid dispersion product or even the active ingredient(s) itself may exert a plasticizing effect on the polymer and thus depress the Tg of the polymer such that the final solid dispersion product has a somewhat lower Tg than the starting polymer used for its preparation. In general, the final solid dispersion product has a Tg of 10 °C or higher, preferably 15 °C or higher, more preferably 20 °C or higher and most preferred 30 °C or higher.

For example, preferred pharmaceutically acceptable polymers can be selected from the group comprising

homopolymers and copolymers of N-vinyl lactams, especially homopolymers and copolymers of N-vinyl pyrrolidone, e.g. polyvinylpyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate,

cellulose esters and cellulose ethers, in particular methylcellulose and ethylcellulose, hydroxyalkylcelluloses, in particular hydroxypropylcellulose, hydroxyalkylalkylcelluloses, in particular hydroxypropylmethylcellulose, cellulose phthalates or succinates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate or hydroxypropylmethylcellulose acetate succinate;

high molecular polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide,

polyvinyl alcohol-polyethylene glycol-graft copolymers (available as Kollicoat® IR from BASF AG, Ludwigshafen, Germany);

polyacrylates and polymethacrylates such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates),

polyacrylamides,

vinyl acetate polymers such as copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"),

polyvinyl alcohol,

oligo- and polysaccharides such as carrageenans, galactomannans and xanthan gum, or mixtures of one or more thereof.

Among these, homopolymers or copolymers of N-vinyl pyrrolidone, in particular a copolymer of N-vinyl pyrrolidone and vinyl acetate, are preferred. A particularly preferred polymer is a copolymer of 60 % by weight of the copolymer, N-vinyl pyrrolidone and 40 % by weight of the copolymer, vinyl acetate.

A further polymer which can be suitably used is Kollidon® SR (available from BASF AG, Ludwigshafen, Germany) which comprises a mixture of PVP and polyvinylacetate.

The term “pharmaceutically acceptable surfactant” as used herein refers to a pharmaceutically acceptable non-ionic surfactant. The surfactant may effectuate an instantaneous emulsification of the active agent released from the dosage form and/or prevent precipitation of the active ingredient in the aqueous fluids of the gastrointestinal tract. A single surfactant as well as combinations of surfactants may be used. According to an embodiment of the invention, the solid dispersion product comprises a combination of two or more pharmaceutically acceptable surfactants.

Preferred surfactants are selected from sorbitan fatty acid esters, polyalkoxylated fatty acid esters such as, for example, polyalkoxylated glycerides, polyalkoxylated sorbitan fatty acid esters or fatty acid esters of polyalkylene glycols, polyalkoxylated ethers of fatty alcohols, tocopheryl compounds or mixtures of two or more thereof. A fatty acid chain in these compounds ordinarily comprises from 8 to 22 carbon atoms. The polyalkylene oxide blocks comprise on average from 4 to 50 alkylene oxide units, preferably ethylene oxide units, per molecule.

Suitable sorbitan fatty acid esters are sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate (Span® 60), sorbitan monooleate (Span® 80), sorbitan tristearate, sorbitan trioleate, sorbitan monostearate, sorbitan monolaurate or sorbitan monooleate.

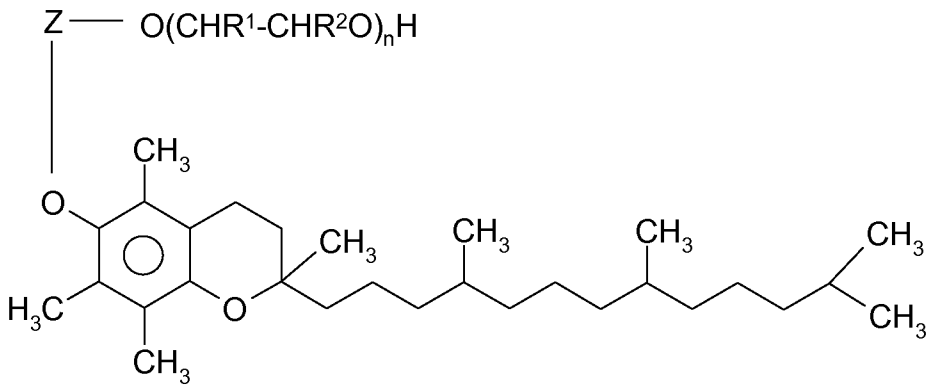
Examples of suitable polyalkoxylated sorbitan fatty acid esters are polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan tristearate (Tween® 65), polyoxyethylene (20) sorbitan trioleate (Tween® 85), polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (4) sorbitan monolaurate or polyoxyethylene (4) sorbitan monooleate.

Suitable polyalkoxylated glycerides are obtained for example by alkoxylation of natural or hydrogenated glycerides or by transesterification of natural or hydrogenated glycerides with polyalkylene glycols. Commercially available examples are polyoxyethylene glycerol ricinoleate 35, polyoxyethylene glycerol trihydroxystearate 40 (Cremophor® RH40, BASF AG) and polyalkoxylated glycerides like those obtainable under the proprietary names Gelucire® and Labrafil® from Gattefosse, e.g. Gelucire® 44/14 (lauroyl macrogol 32 glycerides prepared by transesterification of hydrogenated palm kernel oil with PEG 1500), Gelucire® 50/13 (stearoyl macrogol 32 glycerides, prepared by transesterification of hydrogenated palm oil with PEG 1500) or Labrafil M1944 CS (oleoyl macrogol 6 glycerides prepared by transesterification of apricot kernel oil with PEG 300).

A suitable fatty acid ester of polyalkylene glycols is, for example, PEG 660 hydroxystearic acid (polyglycol ester of 12-hydroxystearic acid (70 mol%) with 30 mol% ethylene glycol).

Suitable polyalkoxylated ethers of fatty alcohols are, for example, PEG (2) stearyl ether (Brij® 72), macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether.

In general, the tocopheryl compound corresponds to the formula below



wherein Z is a linking group, R^1 and R^2 are, independently of one another, hydrogen or C_1-C_4 alkyl and n is an integer from 5 to 100, preferably 10 to 50. Typically, Z is the residue of an aliphatic dibasic acid such as glutaric, succinic, or adipic acid. Preferably, both R^1 and R^2 are hydrogen.

The preferred tocopheryl compound is alpha tocopheryl polyethylene glycol succinate, which is commonly abbreviated as vitamin E TPGS. Vitamin E TPGS is a water-soluble form of natural-source vitamin E prepared by esterifying d-alpha-tocopheryl acid succinate with polyethylene glycol 1000. Vitamin E TPGS is available from Eastman Chemical Company, Kingsport, TN, USA and is listed in the US pharmacopoeia (NF).

It was found that surfactants or combination of surfactants having a defined HLB (hydrophilic lipophilic balance) value are preferred over other solubilizers.

The HLB system (Fiedler, H.B., Encyclopedia of Excipients, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values und hydrophilic substances receiving higher HLB values.

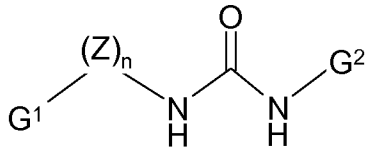
In preferred embodiments, the pharmaceutically acceptable surfactant comprises at least one surfactant having an HLB value of 10 or more.

Solubilizers having an HLB value of 10 or more may be selected from Gelucire® 44/14 (HLB 14), Cremophor® RH40 (HLB 13), Tween® 65 (HLB 10.5), Tween® 85 (HLB 11). Preferred high HLB solubilizers are tocopheryl compounds having a polyalkylene glycol moiety.

In a preferred embodiment, a combination of solubilizers is used which comprises (i) at least one tocopheryl compound having a polyalkylene glycol moiety, preferably alpha tocopheryl polyethylene glycol succinate, and (ii) at least one polyalkoxylated polyol fatty acid ester. The tocopheryl compound preferably is alpha tocopheryl polyethylene glycol succinate. The polyalkoxylated polyol fatty acid ester preferably is a polyalkoxylated glyceride. The mass ratio of tocopheryl compound and polyalkoxylated polyol fatty acid ester preferably is in the range of from 0.2:1 to 1:1.

In an embodiment, the active agent is a N-aryl urea-based active agent. N-aryl urea-based active agents are biologically active compounds which comprise at least one urea moiety in their molecular structure wherein one or both nitrogen atoms are substituted by an aryl group, and which exert a local physiological effect, as well as those which exert a systemic effect, after oral administration. The aryl group may be a carbocyclic or heterocyclic aromatic group or a fused carbocyclic or heterocyclic aromatic group. Attachment to the nitrogen atom is usually via a carbon atom of the aryl group. A fused aromatic group may be linked to the nitrogen atom via an aromatic or non-aromatic carbon atom. The aryl group may, of course, be substituted by further substituents.

Generally, the N-aryl urea-based active agent is represented by the general formula



wherein

G^1 and G^2 are, independently from one another, a carbocyclic ring selected from phenyl, naphthyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl, benzocycloheptenyl, indanyl and indenyl;

a ring system selected from benzoxazinyl, benzimidazolyl, indazolyl, benzothiazolyl, benzooxazolyl, benzisoxazolyl, benzofuranyl, benzopyranyl, benzodioxolyl, quinaldinyl, quinazolinyl, quinoxalinyl, isoquinolinyl, quinolinyl, indolyl, isoindolyl, indolinyl, purinyl, tetrahydroquinolinyl, indazolyl, imidazo-pyridinyl, pyrazolo-pyridinyl, pyrazolo-pyrimidinyl, pyrrolo-pyrimidinyl, pyrrolo-pyridinyl, pyridopyrazinyl, pyrido-pyrimidinyl, pyrido-oxazinyl, pyrido-thiazinyl, pyrido-oxazolyl, pyrido-thioxazolyl, pyrimido-pyrimidine, pteridinyl, cinnolinyl and naphthyridinyl;

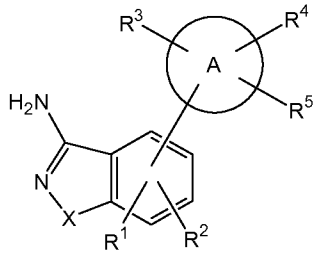
wherein G^1 or G^2 or both may be substituted by one or more substituents selected from the group consisting of C_{1-6} branched or unbranched alkyl, C_{1-6} haloalkyl, C_{1-6} branched or unbranched acyl, C_{1-6} branched or unbranched alkoxy, halogen, C_{1-6} branched or unbranched alkyloxycarbonyl, hydroxy, amino, mono- or di-(C_{1-4} alkyl)amino, mono- or di-(C_{1-4} alkyl)amino-SO_2, cyano, nitro or H_2NSO_2,

Z is 1,4-phenylene, and

n is 0 or1,

or the pharmaceutically acceptable salts, esters, isomers, hydrates or solvates thereof

In an embodiment, the active agent is represented by the formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

A is selected from the group consisting of indolyl, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, and thienyl;

X is selected from the group consisting of O, S, and NR^9;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^aR^b)alkoxy, (NR^aR^b)alkenyl, (NR^aR^b)alkyl, (NR^aR^b)alkynyl, (NR^aR^b)carbonylalkenyl, and (NR^aR^b)carbonylalkyl;

R^3, R^4, and R^5 are each independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, haloalkoxy, haloalkyl, hydroxy, and LR^6; provided that at least two of R^3, R^4, and R^5 are other than LR^6;

L is selected from the group consisting of $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$ and $CH_2C(O)NR^7$, wherein m and n are independently 0 or 1, and wherein each group is drawn with its left end attached to A;

R^6 is selected from the group consisting of hydrogen, aryl, cycloalkyl, heterocyclyl, and 1,3-benzodioxolyl wherein the 1,3-benzodioxolyl can be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl;

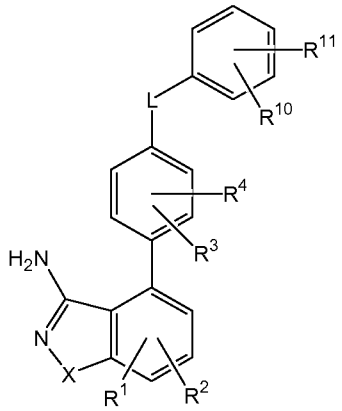
R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl;

R^9 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylcarbonyl, aryl, heterocyclylalkyl, hydroxyalkyl, and (NR^aR^b)alkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkyl, arylcarbonyl, arylsulfonyl, haloalkylsulfonyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylsulfonyl; and

R^c and R^d are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

In another embodiment, the active agent is a compound of formula (II)



(II),

or a therapeutically acceptable salt thereof, wherein

X is selected from the group consisting of O, S, and NR^9;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^aR^b)alkoxy, (NR^aR^b)alkenyl, (NR^aR^b)alkyl, (NR^aR^b)carbonylalkenyl, and (NR^aR^b)carbonylalkyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkoxy, haloalkyl, and hydroxy;

L is selected from the group consisting of $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$ and $CH_2C(O)NR^7$, wherein m and n are independently 0 or 1, and wherein each group is drawn with its left end attached to the ring substituted with R^3 and R^4;

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl;

R^9 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylcarbonyl, aryl, heterocyclylalkyl, hydroxyalkyl, and (NR^aR^b)alkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^cR^d$;

R^a and R^b are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; and

R^c and R^d are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein X is O and A, R^1, R^2, R^3, R^4, and R^5 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is 1,3-benzodioxolyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, and R^8 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is 1,3-benzodioxolyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; R^3, R^4, R^7, and R^8 are hydrogen; and R^c and R^d are selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is 1,3-benzodioxolyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; and R^3, R^4, R^7, and R^8 are hydrogen.

In another embodiment, the present invention provides a compound of formula (I) wherein X is S and A, R^1, R^2, R^3, R^4, and R^5 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is 1,3-benzodioxolyl optionally substituted

with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, and R^8 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is 1,3-benzodioxolyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; R^3, R^4, R^7, and R^8 are hydrogen; and R^c and R^d are selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is 1,3-benzodioxolyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; and R^3, R^4, R^7, and R^8 are hydrogen.

In another embodiment, the present invention provides a compound of formula (I) wherein X is NR^9; and A, R^1, R^2, R^3, R^4, R^5, and R^9 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is 1,3-benzodioxolyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, R^8, and R^9 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is 1,3-benzodioxolyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; R^3, R^4, R^7, and R^8 are hydrogen; R^9 is selected from the group consisting of hydrogen and alkyl; and R^c and R^d are selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is 1,3-benzodioxolyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; R^3, R^4, R^7, and R^8 are hydrogen; and R^9 is selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is cycloalkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, and R^8 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is cycloalkyl wherein the cycloalkyl is selected from the group consisting of cyclobutyl, cyclopentyl, and cyclohexyl, wherein the cycloalkyl is optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, hydroxy, (NR^aR^b)alkoxy, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkenyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkoxy, halo, haloalkoxy, and hydroxy; R^7 and R^8 are hydrogen; R^a and R^b are independently selected from the group consisting of hydrogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is cycloalkyl wherein the cycloalkyl is cyclopentyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; and R^3, R^4, R^7, and R^8 are hydrogen.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is cycloalkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, and R^8 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is cycloalkyl wherein the cycloalkyl is selected from the group consisting of cyclobutyl, cyclopentyl, and cyclohexyl, wherein the cycloalkyl is optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, hydroxy, (NR^aR^b)alkoxy, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkenyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkoxy, halo, haloalkoxy, and hydroxy; R^7 and R^8 are hydrogen; R^a and R^b are independently selected from the group consisting of hy-

drogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is cycloalkyl wherein the cycloalkyl is cyclopentyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; and R^3, R^4, R^7, and R^8 are hydrogen.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is cycloalkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, R^8, and R^9 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is cycloalkyl wherein the cycloalkyl is selected from the group consisting of cyclobutyl, cyclopentyl, and cyclohexyl, wherein the cycloalkyl is optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, hydroxy, (NR^aR^b)alkoxy, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkenyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkoxy, halo, haloalkoxy, and hydroxy; R^7 and R^8 are hydrogen; R^9 is selected from the group consisting of hydrogen and alkyl; R^a and R^b are independently selected from the group consisting of hydrogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is cycloalkyl wherein the cycloalkyl is cyclopentyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; R^3, R^4, R^7, and R^8 are hydrogen; and R^9 is selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is heterocyclyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, and R^8 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is heterocyclyl wherein the heterocyclyl is selected from the group consisting of furyl, isoxazolyl, isothiazolyl, oxazolyl, pyridinyl, thiazolyl, and thienyl, wherein the heterocyclyl is optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy,

alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, hydroxy, (NR^aR^b)alkoxy, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkenyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkoxy, halo, haloalkoxy, and hydroxy; R^7 and R^8 are hydrogen; R^a and R^b are independently selected from the group consisting of hydrogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is O; R^5 is LR^6; R^6 is heterocyclyl wherein the heterocyclyl is thienyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; and R^3, R^4, R^7, and R^8 are hydrogen.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is heterocyclyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, and R^8 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is heterocyclyl wherein the heterocyclyl is selected from the group consisting of furyl, isoxazolyl, isothiazolyl, oxazolyl, pyridinyl, thiazolyl, and thienyl, wherein the heterocyclyl is optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, hydroxy, (NR^aR^b)alkoxy, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkenyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkoxy, halo, haloalkoxy, and hydroxy; R^7 and R^8 are hydrogen; R^a and R^b are independently selected from the group consisting of hydrogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is S; R^5 is LR^6; R^6 is heterocyclyl wherein the heterocyclyl is thienyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; and R^3, R^4, R^7, and R^8 are hydrogen.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is heterocyclyl optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkyl, and oxo; L is

$(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^c, R^d, R^1, R^2, R^3, R^4, R^7, R^8, and R^9 are as defined in formula (I).

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is heterocyclyl wherein the heterocyclyl is selected from the group consisting of furyl, isoxazolyl, isothiazolyl, oxazolyl, pyridinyl, thiazolyl, and thienyl, wherein the heterocyclyl is optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, hydroxy, (NR^aR^b)alkoxy, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkenyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkoxy, halo, haloalkoxy, and hydroxy; R^7 and R^8 are hydrogen; R^9 is selected from the group consisting of hydrogen and alkyl; R^a and R^b are independently selected from the group consisting of hydrogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein A is phenyl; X is NR^9; R^5 is LR^6; R^6 is heterocyclyl wherein the heterocyclyl is thienyl; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 and R^2 are independently selected from the group consisting of hydrogen and alkoxy; R^3, R^4, R^7, and R^8 are hydrogen; and R^9 is selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a therapeutically acceptable salt thereof, in combination with a therapeutically acceptable carrier.

In another embodiment, the present invention provides a method for inhibiting protein kinase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of formula (I), or a therapeutically acceptable salt thereof.

In another embodiment, the present invention provides a method for treating cancer in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of formula (I), or a therapeutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (II) wherein L is $CH_2C(O)NR^7$; and X, R^1, R^2, R^3, R^4, R^7, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $CH_2C(O)NR^7$; and R^1, R^2, R^3, R^4, R^7, R^9, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $CH_2C(O)NR^7$; and R^1, R^2, R^3, R^4, R^7, R^9, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $CH_2C(O)NR^7$; R^1, R^2, R^3, R^4, and R^7 are hydrogen; R^9 is selected from the group consisting of hydrogen and alkyl; R^{10} and R^{11} are as defined in

formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $CH_2C(O)NR^7$; R^1, R^2, R^3, R^4, and R^7 are hydrogen; R^9 is selected from the group consisting of hydrogen and alkyl; R^{10} and R^{11} independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $CH_2C(O)NR^7$; R^1, R^2, R^3, R^4, and R^7 are hydrogen; R^9 is selected from the group consisting of hydrogen and alkyl; R^{10} and R^{11} independently selected from the group consisting of hydrogen, alkyl, halo, and haloalkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, X, R^1, R^2, R^3, R^4, R^7, R^8, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula(II) wherein X is NR^9; and L, R^1, R^2, R^3, R^4, R^9, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is selected from the group consisting of alkoxyalkyl, alkyl, alkylcarbonyl, aryl, heterocyclylalkyl, hydroxyalkyl, and (NR^aR^b)alkyl; and R^a, R^b, R^1, R^2, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; and R^1, R^2, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is selected from the group consisting of hydrogen and halo and the other is selected from the group consisting of hydroxy, hydroxyalkyl, and (NR^aR^b)alkyl; and R^a, R^b, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is selected from the group consisting of hydrogen and halo and the other is selected from the group consisting of hydroxy, hydroxyalkyl, and (NR^aR^b)alkyl; one of R^3 and R^4 is hydrogen and the other is selected from the group consisting of alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^cR^d$; R^a and R^b are independently se-

lected from the group consisting of hydrogen and alkyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^7, R^8, and R^9 are hydrogen; R^4 is selected from the group consisting of hydrogen and halo; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^cR^d$; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^7, R^8, and R^9 are hydrogen; R^4 is selected from the group consisting of hydrogen and halo; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^7, R^8, and R^9 are hydrogen; R^4 is selected from the group consisting of hydrogen and halo; and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, halo, and haloalkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^7, and R^8 are hydrogen; R^9 is alkyl; R^4 is selected from the group consisting of hydrogen and halo; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^cR^d$; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^7, and R^8 are hydrogen; R^9 is alkyl; R^4 is selected from the group consisting of hydrogen and halo; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^7, and R^8 are hydrogen; R^9 is alkyl; R^4 is selected from the group consisting of hydrogen and halo; and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, halo, and haloalkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is halo; and R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is halo; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9, L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$, m and n are 0, R^7 and R^8 are hydrogen, R^9 is hydrogen, one of R^1 and R^2 is hydrogen and the other is heterocyclylalkoxy; and R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9, L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$, m and n are 0, R^7 and R^8 are hydrogen, R^9 is hydrogen, one of R^1 and R^2 is hydrogen and the other is heterocyclylalkoxy; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9, L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$, m and n are 0, R^7 and R^8 are hydrogen, R^9 is hydrogen, one of R^1 and R^2 is hydrogen and the other is heterocyclylalkoxy wherein the heterocyclyl is selected from the group consisting of morpholinyl, piperidinyl, pyridinyl, pyrrolyl, pyrrolidinyl optionally substituted with oxo, and 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of (NR^aR^b)carbonylalkenyl and (NR^aR^b)alkoxy; and R^a, R^b, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of (NR^aR^b)carbonylalkenyl and (NR^aR^b)alkoxy; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; R^a and R^b are

independently selected from the group consisting of hydrogen, alkyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of (NR^aR^b)carbonylalkenyl and (NR^aR^b)alkoxy; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; R^a and R^b are independently selected from the group consisting of hydrogen, alkyl, alkylsulfonyl, arylsulfonyl wherein the aryl is phenyl, haloalkylsulfonyl, and heterocyclylsulfonyl wherein the heterocyclyl is thienyl; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of aryloxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclyloxyalkyl; and R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of aryloxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclyloxyalkyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is aryloxyalkyl wherein the aryl is phenyl optionally substituted with halo; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is heterocyclyl wherein the heterocyclyl is selected from the group consisting of pyridinyl and thienyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the

group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, -NR^cR^d, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is heterocyclylalkyl wherein the heterocyclyl is selected from the group consisting of morpholinyl and piperazinyl wherein the piperazinyl is optionally substituted with alkyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, -NR^cR^d, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is heterocyclyloxyalkyl wherein the heterocyclyl is pyridinyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, -NR^cR^d, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of alkoxy, alkoxyalkoxy, and alkyl; and R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; one of R^1 and R^2 is hydrogen and the other is selected from the group consisting of alkoxy, alkoxyalkoxy, and alkyl; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, -NR^cR^d, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; R^1 and R^2 are hydrogen; and R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; R^1 and R^2 are hydrogen; one of R^3 and R^4 is hydrogen and

the other is selected from the group consisting of alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; and R^{10} and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; R^1 and R^2 are hydrogen; one of R^3 and R^4 is hydrogen and the other is selected from the group consisting of alkoxyalkoxy, alkyl, halo, haloalkoxy, and hydroxy; and R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; R^1 and R^2 are hydrogen; R^3 and R^4 are hydrogen; and R^{10} and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; R^1 and R^2 are hydrogen; R^3 and R^4 are hydrogen; and R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is NR^9; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^7 and R^8 are hydrogen; R^9 is hydrogen; R^1 and R^2 are hydrogen; R^3 and R^4 are alkyl; and R^{10} and R^{11} are selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and aryloxy wherein the aryloxy is phenoxy; and R^c and R^d are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^aR^b)alkoxy, (NR^aR^b)alkenyl, (NR^aR^b)alkyl, (NR^aR^b)carbonylalkenyl, and (NR^aR^b)carbonylalkyl; and X, L, R^a, R^b, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula(II) wherein X is O and L, R^1, R^2, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is O; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^1, R^2, R^3, R^4, R^7, R^8, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is O; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^aR^b$; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is O; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^aR^b$, and aryloxy wherein the aryloxy is phenoxy; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is O; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 is heterocyclylalkoxy; R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^aR^b$; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is O; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 is heterocyclylalkoxy wherein the heterocyclyl is morpholinyl; R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^aR^b$, and aryloxy wherein the aryloxy is phenoxy; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is O; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 is selected from the group consisting of alkoxy, alkyl, halo, and haloalkoxy; R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^aR^b$, and aryloxy wherein the aryloxy is phenoxy; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula(II) wherein X is S and L, R^1, R^2, R^3, R^4, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; and m, n, R^1, R^2, R^3, R^4, R^7, R^8, R^{10}, and R^{11} are as defined in formula (II).

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^aR^b$; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^aR^b$, and aryloxy wherein the aryloxy is phenoxy; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl..

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1, R^2, R^3, R^4, R^7, and R^8 are hydrogen; and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, halo, and haloalkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 is heterocyclylalkoxy; R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^aR^b$; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 is heterocyclylalkoxy wherein the heterocyclyl is morpholinyl; R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^aR^b$, and aryloxy wherein the aryloxy is phenoxy; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a compound of formula (II) wherein X is S; L is $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$; m and n are 0; R^1 is selected from the group consisting of alkoxy, alkyl, halo, and haloalkoxy; R^2, R^3, R^4, R^7, and R^8 are hydrogen; R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxycarbonyl, alkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^aR^b$, and aryloxy wherein the aryloxy is phenoxy; and R^a and R^b are independently selected from the group consisting of hydrogen and alkyl.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (II), or a therapeutically acceptable salt thereof, in combination with a therapeutically acceptable carrier.

In another embodiment, the present invention provides a method for inhibiting protein kinase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of formula (II), or a therapeutically acceptable salt thereof.

In another embodiment, the present invention provides a method for treating cancer in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of formula (II), or a therapeutically acceptable salt thereof.

As used in the present specification the following terms have the meanings indicated:

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group attached to the parent molecular moiety through another alkoxy group.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with at least one alkoxy group.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon of one to six carbon atoms. Preferred alkyl groups of the present invention are of one to three carbon atoms. Most preferred alkyl groups are methyl and ethyl.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic or tricyclic fused ring system wherein one or more of the fused rings is a phenyl group. Bicyclic fused ring systems are exemplified by a phenyl group fused to a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, or another phenyl group. Tricyclic fused ring systems are exemplified by a bicyclic fused ring system fused to a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, or another phenyl group. Aryl groups include, but are not limited to, anthracenyl, azulenyl, fluorenyl, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; wherein the second aryl group, the aryl part of the arylalkoxy, the arylalkyl, and the aryloxy, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl can be further optionally substituted with one, two, three, four, or five groups independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and oxo.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with at least one aryl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aryloxyalkyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through an alkyl group.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkenyl," as used herein, refers to a non-aromatic cyclic or bicyclic ring system having three to ten carbon atoms and one to three rings, wherein each five-membered ring has one double bond, each six-membered ring has one or two double bonds, each seven- and eight-membered ring has one to three double bonds, and each nine-to ten-membered ring has one to four double bonds. Examples of cycloalkenyl groups include, but are not limited to, cyclohexenyl, octahydronaphthalenyl, and norbornylenyl.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, bicyclic, or tricyclic hydrocarbon ring system having three to twelve carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[3.1.1]heptyl, and adamantyl.

The cycloalkyl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo.

The terms "halo," and "halogen," as used herein, refer to F, Cl, Br, and I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term "haloalkylsulfonyl," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "heterocyclyl," as used herein, represents a monocyclic, bicyclic, or tricyclic ring system wherein one or more rings is a four-, five-, six-, or seven-membered ring containing one, two, or three heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. Monocyclic ring systems are exemplified by any 3- or 4-membered ring containing a heteroatom independently selected from the group consisting of oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms wherein the heteroatoms are independently selected from the group consisting of nitrogen, oxygen and sulfur. The 3- and 4-membered rings have no double bonds, the 5-membered ring has from 0-2 double bonds and the 6- and 7-membered rings have from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, and trithiane. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to phenyl ring, a monocyclic cycloalkyl group as defined herein, a monocyclic cycloalkenyl group, as defined herein, or another monocyclic heterocyclyl ring system. Representative examples of

bicyclic ring systems include but are not limited to, benzimidazole, benzothiazole, benzothiophene, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxine, 1,3-benzodioxole, cinnoline, dihydrobenzimidazole, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, and thiopyranopyridine. Tricyclic rings systems are exemplified by any of the above bicyclic ring systems fused to a phenyl ring, a monocyclic cycloalkyl group as defined herein, a monocyclic cycloalkenyl group as defined herein, or another monocyclic heterocyclyl ring system. Representative examples of tricyclic ring systems include, but are not limited to, acridine, carbazole, carboline, dibenzofuran, dibenzothiophene, naphthofuran, naphthothiophene, oxanthrene, phenazine, phenoxathin, phenoxazine, phenothiazine, thianthrene, thioxanthene, and xanthene. Heterocyclyl groups can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the group.

The heterocyclyl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, (NR^cR^d)alkyl, and oxo; wherein the aryl, the aryl part of the arylalkoxy, the arylalkyl, and the aryloxy, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl can be further optionally substituted with one, two, three, four, or five groups independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and oxo.

The term "heterocyclylalkenyl," as used herein, refers to an alkenyl group substituted with at least one heterocyclyl group.

The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with at least one heterocyclyl group.

The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

The term "heterocyclyloxyalkyl," as used herein, refers to an alkyl group substituted with at least one heterocyclyloxy group.

The term "heterocyclylsulfonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a sulfonyl group.

The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkoxy," as used herein, refers to a hydroxy group attached to the parent molecular moiety through an alkoxy group.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with at least one hydroxy group.

The term "nitro," as used herein, refers to $-NO_2$.

The term "$-NR^aR^b$," as used herein, represents two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcar-

bonyl, alkylsulfonyl, aryl, arylalkyl, arylcarbonyl, arylsulfonyl, haloalkylsulfonyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylsulfonyl, wherein the aryl, the aryl part of the arylalkyl and the arylcarbonyl, the heterocyclyl, the heterocyclyl part of the heterocyclylalkyl and the heterocyclylsulfonyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkyl, cyano, halo, haloalkyl, haloalkoxy, nitro, and oxo.

The term "(NR^aR^b)alkenyl," as used herein, represents an alkenyl group substituted with at least one -NR^aR^b group.

The term "(NR^aR^b)alkoxy," as used herein, represents an -NR^aR^b group attached to the parent molecular moiety through an alkoxy group.

The term "(NR^aR^b)alkyl," as used herein, represents an alkyl group substituted with at least one -NR^aR^b group.

The term "(NR^aR^b)alkynyl," as used herein, represents an alkynyl group substituted with at least one -NR^aR^b group.

The term "(NR^aR^b)carbonyl," as used herein, represents an (NR^aR^b) group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^aR^b)carbonylalkenyl," as used herein, represents an alkenyl group substituted with at least one (NR^aR^b)carbonyl group.

The term "(NR^aR^b)carbonylalkyl," as used herein, represents an alkyl group substituted with at least one (NR^aR^b)carbonyl group.

The term "-NR^cR^d," as used herein, represents two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein the aryl, the aryl part of the arylalkyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkyl, cyano, halo, haloalkyl, haloalkoxy, nitro, and oxo.

The term "(NR^cR^d)alkyl," as used herein, represents an alkyl group substituted with at least one -NR^cR^d group.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to -SO_2.

The compounds of the present invention can exist as therapeutically acceptable salts. The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible, which are suitable for treatment of diseases without undue toxicity, irritation, and allergic response; which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting an -NR^aR^b group with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate,

persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Also, -NR^aR^b groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

The present compounds can also exist as therapeutically acceptable prodrugs. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The term "prodrug," refers to compounds which are rapidly transformed in vivo to parent compounds of formula (I) or (II) for example, by hydrolysis in blood.

Representative compounds of formulas (I) and (II) are:
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3,5-dimethoxyphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-bromo-4-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-ethylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-phenylurea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-fluoro-4-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(4-fluorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1H-indazol-4-yl]phenyl}-N'-(3-fluorophenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1H-indazol-4-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1H-indazol-4-yl]phenyl}-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1H-indazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[(4-methyl-1-piperazinyl)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[(4-methyl-1-piperazinyl)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;

N-(4-{3-amino-7-[(4-methyl-1-piperazinyl)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-7-[(4-methyl-1-piperazinyl)methyl]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[(4-methyl-1-piperazinyl)methyl]-1H-indazol-4-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[(4-methyl-1-piperazinyl)methyl]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-cyanophenyl)urea;
N-(4-{3-amino-7-[(dimethylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[(dimethylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[(dimethylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-phenylurea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(2-methylphenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(4-methylphenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(3-methoxyphenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-fluorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3,5-dimethylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-ethylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-chloro-4-fluorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-fluoro-4-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-bromo-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-{4-[3-amino-1-(2-hydroxyethyl)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
2-[4-(3-amino-1H-indazol-4-yl)phenyl]-N-phenylacetamide;
2-[4-(3-amino-1H-indazol-4-yl)phenyl]-N-(3-chlorophenyl)acetamide;
2-[4-(3-amino-1H-indazol-4-yl)phenyl]-N-(4-fluoro-3-methylphenyl)acetamide;
2-[4-(3-amino-1H-indazol-4-yl)phenyl]-N-[3-(trifluoromethyl)phenyl]acetamide;
2-[4-(3-amino-1H-indazol-4-yl)phenyl]-N-(3-methylphenyl)acetamide;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;

N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-phenylurea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-(3-ethylphenyl)urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-(3-fluoro-4-methylphenyl)urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1H-indazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-phenylurea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-(3-fluorophenyl)urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-(3-bromophenyl)urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-phenylurea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-bromophenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-ethylphenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
(2E)-3-{3-amino-4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}-N,N-dimethylacrylamide;
(2E)-3-{3-amino-4-[4-({[(3-chlorophenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}-N,N-dimethylacrylamide;
(2E)-3-(3-amino-4-{4-[({[3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-1H-indazol-7-yl)-N,N-dimethylacrylamide;
N-(4-{3-amino-7-[2-(dimethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-phenylurea;

N-(4-{3-amino-7-[2-(dimethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-bromophenyl)urea;
N-(4-{3-amino-7-[2-(dimethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[2-(dimethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[2-(2-oxo-1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
2-[4-(3-amino-1-methyl-1H-indazol-4-yl)phenyl]-N-(3-methylphenyl)acetamide.
N-[4-(3-amino-1H-indazol-4-yl)-2-methylphenyl]-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[2-(2-oxo-1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[2-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3,5-dimethylphenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3-phenoxyphenyl)urea;
N-{4-[3-amino-7-(4-morpholinylmethyl)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3-bromophenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1,2-benzisoxazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1,2-benzisoxazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;

N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1,2-benzisoxazol-4-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1,2-benzisoxazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(2-methoxyethoxy)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[2-(4-morpholinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-(methoxymethoxy)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-(3-ethylphenyl)urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-hydroxy-1H-indazol-4-yl)phenyl]-N'-phenylurea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-phenylurea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-bromophenyl)urea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[2-(1-pyrrolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-phenylurea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-bromophenyl)urea;

N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[2-(diethylamino)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-ethylphenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-ethylphenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-fluoro-6-(hydroxymethyl)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-fluoro-6-(hydroxymethyl)-1H-indazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-fluoro-6-(hydroxymethyl)-1H-indazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;
N-{4-[3-amino-7-fluoro-6-(hydroxymethyl)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-fluoro-6-(hydroxymethyl)-1H-indazol-4-yl]phenyl}-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-6-[(diethylamino)methyl]-7-fluoro-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-6-[(diethylamino)methyl]-7-fluoro-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-6-[(diethylamino)methyl]-7-fluoro-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-6-[(diethylamino)methyl]-7-fluoro-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[(3-pyridinyloxy)methyl]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-1-[2-(4-morpholinyl)ethyl]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-1-[2-(4-morpholinyl)ethyl]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-1-[2-(4-morpholinyl)ethyl]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-1-[2-(4-morpholinyl)ethyl]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(4-{3-amino-1-[2-(4-morpholinyl)ethyl]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-[4-(3-amino-6-bromo-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-4-bromo-1H-indazol-6-yl)phenyl]-N'-(3-methylphenyl)urea;
N-(4-{3-amino-1-[2-(dimethylamino)ethyl]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-1-[2-(dimethylamino)ethyl]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-[2-({3-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]methanesulfonamide;
4-(1H-indol-5-yl)-1H-indazol-3-amine;
N-{4-[3-amino-1-(2-methoxyethyl)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethoxy]-1H-indazol-4-yl}phenyl)-N'-(3,5-dimethylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2,6-dimethylphenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2,6-dimethylphenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-hydroxyphenyl)urea;
N-[2-({3-amino-4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]methanesulfonamide;
N-{2-[(3-amino-4-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-1H-indazol-7-yl)oxy]ethyl}methanesulfonamide;
N-[2-({3-amino-4-[4-({[(3-chlorophenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]methanesulfonamide;
N-{2-[(3-amino-4-{4-[({[3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-1H-indazol-7-yl)oxy]ethyl}methanesulfonamide;
N-[3-(3-amino-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-methyl-1H-indazol-4-yl)phenyl]-N'-(3-cyanophenyl)urea
N-[4-(3-amino-1H-indazol-4-yl)-2-(trifluoromethoxy)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(4-fluorophenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(2-fluorophenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-fluoro-4-methylphenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-phenylurea;
N-[2-({3-amino-4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]-1,1,1-trifluoromethanesulfonamide;
N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(4-bromo-2-fluorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(5-fluoro-2-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(4-fluoro-3-methylphenyl)urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-phenylurea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-fluorophenyl)urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;
N-[2-({3-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]-1,1,1-trifluoromethanesulfonamide;
N-[2-({3-amino-4-[4-({[(3-fluorophenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]-1,1,1-trifluoromethanesulfonamide;
N-[2-({3-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]benzenesulfonamide;
N-{2-[(3-amino-4-{4-[({[3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-1H-indazol-7-yl)oxy]ethyl}benzenesulfonamide;
N-[2-({3-amino-4-[4-({[(3-fluorophenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]benzenesulfonamide;
N-[2-({3-amino-4-[4-({[(3-chlorophenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]benzenesulfonamide;
N-(4-{3-amino-7-[(isopropylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;

N-(4-{3-amino-7-[(isopropylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;

N-(4-{3-amino-7-[(isopropylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(4-{3-amino-7-[(isopropylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;

N-(4-{3-amino-7-[(isopropylamino)methyl]-1H-indazol-4-yl}phenyl)-N'-(4-fluoro-3-methylphenyl)urea;

N-(4-{3-amino-7-[(4-chlorophenoxy)methyl]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;

N-(4-{3-amino-7-[(4-chlorophenoxy)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;

N-(4-{3-amino-7-[(4-chlorophenoxy)methyl]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(4-{3-amino-7-[(4-chlorophenoxy)methyl]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;

N-(4-{3-amino-7-[(4-chlorophenoxy)methyl]-1H-indazol-4-yl}phenyl)-N'-(4-fluoro-3-methylphenyl)urea;

N-(4-{3-amino-7-[3-(1H-pyrrol-1-yl)propoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;

4-(1H-indol-5-yl)-7-[3-(1H-pyrrol-1-yl)propoxy]-1H-indazol-3-amine;

N-(4-{3-amino-7-[3-(1H-pyrrol-1-yl)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;

N-(4-{3-amino-7-[3-(1H-pyrrol-1-yl)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;

N-[2-({3-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]thiophene-2-sulfonamide;

N-[2-({3-amino-4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]thiophene-2-sulfonamide;

N-(2-{[3-amino-4-(1H-indol-5-yl)-1H-indazol-7-yl]oxy}ethyl)thiophene-2-sulfonamide

N-(4-{3-amino-7-[3-(diethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;

N-(4-{3-amino-7-[3-(diethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;

N-(4-{3-amino-7-[3-(diethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(4-{3-amino-7-[3-(diethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;

N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-[3-(trifluoromethyl)-phenyl]urea;

N-[4-(3-amino-1H-indazol-4-yl)-2-fluorophenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-pyridin-3-yl-1H-indazol-4-yl)phenyl]-N'-(4-fluoro-3-methylphenyl)urea;

N-[4-(3-amino-7-pyridin-3-yl-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-pyridin-3-yl-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-pyridin-3-yl-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-pyridin-3-yl-1H-indazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-fluorophenyl)urea;
N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-(4-fluoro-3-methylphenyl)urea;
N-{4-[3-amino-7-(3-morpholin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-bromophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-3-fluorophenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-3-fluorophenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-3-fluorophenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-3-fluorophenyl]-N'-(4-fluoro-3-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-3-fluorophenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1H-indazol-4-yl)-3-fluorophenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3,5-dimethylphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-phenylurea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(4-methylphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-cyanophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-ethylphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-fluoro-4-methylphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3,5-difluorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methoxyphenyl)urea;

N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(4-methoxyphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-nitrophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(4-fluorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(2-fluorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chloro-4-fluorophenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chloro-4-methoxyphenyl)urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-(dimethylamino)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-1,3-benzodioxol-5-ylurea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[2-(trifluoromethoxy)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-[3,5-bis(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chloro-4-methylphenyl)urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-[3,5-bis(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methoxyphenyl)urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3,5-difluorophenyl)-urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(4-methylphenyl)-urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-bromophenyl)-urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(3,5-dimethylphenyl)urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-(dimethylamino)-phenyl]urea;
N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-1,3-benzodioxol-5-ylurea
N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)-phenyl]urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3,5-dimethylphenyl)urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-ethylphenyl)urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(4-methylphenyl)urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-fluoro-4-methylphenyl)urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methoxyphenyl)-urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-phenylurea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-[3,5-bis(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;

N-[4-(3-amino-7-methyl-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-fluorophenyl)urea;

N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-methoxy-1,2-benzisoxazol-4-yl)phenyl]-N'-(4-fluoro-3-methylphenyl)urea;

N-[4-(3-amino-7-fluoro-1,2-benzisoxazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)-phenyl]urea;

N-[4-(3-amino-7-fluoro-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;

N-[4-(3-amino-7-fluoro-1,2-benzisoxazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-fluoro-1,2-benzisoxazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;

N-[4-(3-amino-7-fluoro-1,2-benzisoxazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-fluoro-1,2-benzisoxazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-(3-bromophenyl)urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-{4-[3-amino-7-(trifluoromethoxy)-1,2-benzisoxazol-4-yl]phenyl}-N'-(4-fluoro-3-methylphenyl)urea;

N-[4-(3-amino-1,2-benzisothiazol-4-yl)phenyl]-N'-(3,5-dimethylphenyl)urea;

N-[4-(3-amino-1,2-benzisothiazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;

N-[4-(3-amino-1,2-benzisothiazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1,2-benzisothiazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(3-amino-1,2-benzisothiazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)-2-fluorophenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)-2-fluorophenyl]-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[(1-methylpiperidin-4-yl)methoxy]-1H-indazol-4-yl}-2-fluorophenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{3-amino-7-[(1-methylpiperidin-4-yl)methoxy]-1H-indazol-4-yl}phenyl)-N'-(3-methylphenyl)urea;
N-(4-{3-amino-7-[(1-methylpiperidin-4-yl)methoxy]-1H-indazol-4-yl}phenyl)-N'-(3-chlorophenyl)urea;
N-(4-{3-amino-7-[(1-methylpiperidin-4-yl)methoxy]-1H-indazol-4-yl}phenyl)-N'-(4-fluoro-3-methylphenyl)urea;
N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;
N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(4-fluoro-3-methylphenyl)urea;
N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-chloro-4-fluorophenyl)urea;
N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;
N-{4-[3-amino-7-(3-pyridin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-{4-[3-amino-7-(3-pyridin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-methylphenyl)urea;
N-{4-[3-amino-7-(3-pyridin-4-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(3-chlorophenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-(methoxymethoxy)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)-2-hydroxyphenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(hydroxymethyl)phenyl]urea;
N-[4-(3-amino-7-thien-3-yl-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;
N-[4-(3-amino-7-thien-3-yl-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;
N-[4-(3-amino-7-pyridin-4-yl-1H-indazol-4-yl)phenyl]-N'-(4-fluoro-3-methylphenyl)urea;

N-[4-(3-amino-7-pyridin-4-yl-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-pyridin-4-yl-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;

N-[4-(3-amino-7-pyridin-4-yl-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;

N-[4-(3-amino-7-pyridin-4-yl-1H-indazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-7-pyridin-4-yl-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-bromophenyl)urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-methylphenyl)urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-phenylurea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-[2-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-chlorophenyl)urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-(4-fluoro-3-methylphenyl)urea;

N-[4-(3-amino-5-fluoro-1H-indazol-4-yl)phenyl]-N'-(3-chloro-4-fluorophenyl)urea;

N-[4-(3-amino-7-bromo-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;

3-[({[4-(3-amino-1H-indazol-4-yl)phenyl]amino}carbonyl)amino]-4-fluorobenzoic acid;

methyl 3-[({[4-(3-amino-1H-indazol-4-yl)phenyl]amino}carbonyl)amino]-4-fluorobenzoate;

N-[4-(3-amino-1H-indazol-6-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea

N-[2-({3-amino-4-[4-({[(3-fluorophenyl)amino]carbonyl}amino)phenyl]-1H-indazol-7-yl}oxy)ethyl]methanesulfonamide; and

N-(4-{3-amino-7-[3-(dimethylamino)propoxy]-1H-indazol-4-yl}phenyl)-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-(1-acetyl-3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;

N-[4-(3-amino-7-fluoro-1H-indazol-4-yl)phenyl]-N'-(4-bromo-3-methylphenyl)urea;

N-[4-(3-amino-1-phenyl-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea;

N-{4-[3-amino-7-(3-pyridin-3-ylpropoxy)-1H-indazol-4-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;

N-[4-(3-amino-1H-indazol-6-yl)phenyl]-N'-phenylurea;

N-[4-(3-amino-1H-indazol-6-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea;

N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-thien-3-ylurea; and
N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-cyclopentylurea.

In an embodiment of the invention, the active agent is N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea (ABT869) or salts or hydrates or solvates thereof.

Compounds of formula (I) or (II) are useful for inhibiting protein tyrosine kinases. The solid dispersion product or dosage forms containing the solid dispersion product of the invention are used in a method for treating cancer in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound.

The solid dispersion product is prepared by a process which comprises

a) preparing a liquid mixture containing the at least one active agent, at least one pharmaceutically acceptable matrix-forming agent, at least one pharmaceutically acceptable surfactant and at least one solvent, and
b) removing the solvent(s) from the liquid mixture to obtain the solid dispersion product.

As described above, at least one filler may advantageously be added to the liquid mixture before removing the solvent(s).

Suitable solvents are those which are capable of dissolving or solubilising the matrix-forming agent. Any such solvent may be used, however, pharmaceutically acceptable solvents are preferred because traces of solvent may remain in the dried solid dispersion product. Suitably, the solvent may be selected from the group consisting of alkanols, such as methanol, ethanol, isopropanol, n-propanol, isobutanol, n-butanol; hydrocarbons, such as pentane, hexane, cyclohexane, methylcyclohexane, toluene, xylene; halogenated hydrocarbons, such as dichloromethane, trichloromethane, dichloroethane, chlorobenzene; ketones, such as acetone; esters, such as ethyl acetate; ethers, such as dioxane, tetrahydrofurane; and combinations of two or more thereof. Ethanol is particularly preferred due to its availability, dissolving power and pharmaceutical safeness.

The liquid mixture may be prepared by any suitable method of contacting the essential ingredients thereof, i. e. the pharmaceutically acceptable matrix-forming agent, active agent, the pharmaceutically acceptable surfactant and the solvent or combination of solvents. In an embodiment, the liquid mixture is prepared by dissolving the pharmaceutically acceptable matrix-forming agent to obtain a matrix-forming agent solution, and adding the active agent and the pharmaceutically acceptable surfactant to the solution. The dissolved matrix-forming agent may exert an solubility-enhancing effect on the active agent; thus, the solubility of the active agent in the matrix-forming agent solu-

tion may be several times higher than its solubility in the solvent alone. Preferably, the active agent is essentially completely dissolved in the liquid mixture.

The liquid mixture has a dry matter content of up to 90 % by weight, for example 0.5 to 90 % by weight, in most instances 2 to 60 % by weight, relative to the total weight of the liquid mixture.

The solvent(s) may be removed by any suitable method known in the art, such as spray-drying, drum drying, belt drying, tray drying, fluid-bed drying or combinations of two or more thereof. For example, the primary solid dispersion powder obtained by spray-drying may be further dried by tray drying (optionally under vacuum) or fluid-bed drying (optionally under vacuum). In an embodiment, removal of the solvent comprises a spray-drying step, optionally in combination with one or more drying steps other than spray-drying.

The residual solvent content in the final solid dispersion product is preferably 5% by weight or less, more preferably 1% by weight or less.

In spray-drying, the liquid to be dried is suspended in a gas flow, e. g., air, i. e. the liquid is converted into a fog-like mist (atomized), providing a large surface area. The atomized liquid is exposed to a flow of hot gas in a drying chamber. The moisture evaporates quickly and the solids are recovered as a powder consisting of fine, hollow spherical particles. Gas inlet temperatures of up to 250 °C or even higher may be used, due to the evaporation the gas temperature drops very rapidly to a temperature of about 30 to 150 °C (outlet temperature of the gas).

The principle of the drum drying process (roller drying) is that a thin film of material is applied to the smooth surface of a continuously rotating, heated metal drum. The film of dried material is continuously scraped off by a stationary knife located opposite the point of application of the liquid material. The dryer consists of a single drum or a pair of drums with or without “satellite” rollers. The drum(s) may be located in a vacuum chamber. Conveniently, the solvent vapours are collected and the solvent is recovered and recycled.

In a belt dryer, the liquid is spread or sprayed onto a belt which passes over several heated plates underneath the belt. The material is heated by steam-heated or electrically heated plates. The evaporation of the solvent can additionally be fostered by infrared radiators or microwave radiators located over the belt. Belt drying may be carried out in a vacuum chamber.

In tray drying, the liquid mixture (or a dispersion product that has been pre-dried by any other method) is distributed over a number of trays. These are placed in an oven, usually in a stream of hot gas, e. g. air. Vacuum may be applied additionally.

The dried solid dispersion product may then be grinded and/or classified (sieved).

The dried solid dispersion product may then be filled into capsules or may be compacted. Compacting means a process whereby a powder mass comprising the solid dispersion product is densified under high pressure in order to obtain a compact with low porosity, e.g. a tablet. Compression of the powder mass is usually done in a tablet press, more specifically in a steel die between two moving punches.

At least one additive selected from flow regulators, disintegrants, bulking agents and lubricants is preferably used in compacting the granules. Disintegrants promote a rapid disintegration of the compact in the stomach and keep the liberated granules separate from one another. Suitable disintegrants are crosslinked polymers such as crosslinked polyvinyl pyrrolidone and crosslinked sodium carboxymethyl cellulose. Suitable bulking agents are selected from lactose, calcium hydrogenphosphate, microcrystalline cellulose (Avicel®), magnesium oxide, natural or pre-gelatinized potato or corn starch, polyvinyl alcohol.

Suitable flow regulators are selected from highly dispersed silica (Aerosil®), and animal or vegetable fats or waxes.

A lubricant is preferably used in compacting the granules. Suitable lubricants are selected from polyethylene glycol (e.g., having a Mw of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, talc, and the like.

Various other additives may be used, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, or stabilizers against microbial attack.

In order to facilitate the intake of such a dosage form by a mammal, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. If desired, the film coat may be an enteric coat. The film coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. a Tween® type, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. The film coat usually accounts for less than about 5 % by weight of the dosage form.

The following examples will serve to further illustrate the invention without limiting it.

Example 1: Preparation of Solid Dispersion Products

Solid dispersion products wherein the matrix-forming agent is PVP are prepared according to the following protocol:

(1) Dissolve PVP in ethanol. For PVP K30 prepare a 30 % (w/w) solution, for PVP K12 prepare a 50 % (w/w) solution.
(2) Melt surfactants at 60 °C in an oven and mix in the ratio indicated.
(3) Weigh PVP solution into amber glass bottle.
(4) Weigh active agent (ABT 869) and add to PVP solution; stir until dissolved.
(5) Add surfactant and mix. If surfactant solidifies partially, warm again.
(6) If solution is still turbid after one hour, add further ethanol and homogenize.

Solid dispersion products wherein the matrix-forming agent is hydroxypropyl-β-cyclodextrin (HP-β-CD) are prepared according to the following protocol:

(1) Weigh 8.5 g HP-β-CD and dissolve in 60 g ethanol (anhydrous).
(2) Weigh active agent and dissolve in (1).
(3) Melt surfactant and add to (2).
(4) If surfactant solidifies partially, warm again until a clear solution is obtained.

Spray drying was performed using a Büchi B-191 lab scale spray dryer. The equipment was pre-heated before the spray cycle was started. After spraying a final drying was conducted for 10-20 minutes before the cooling cycle was initiated. For atomization of the liquid a two-component nozzle (liquid plus air for atomization) has been used.

Protocol for the oral bioavailability studies

For bioavailability evaluation, solid dispersion powder as obtained in example were screened and filled into capsules or compressed to tablets.

The studies were run in a randomized cross-over study design.

Dogs (beagle dogs, mixed sexes, weighing approximately 10 kg) received a balanced diet with 27 % fat and were permitted water ad libitum (non-fasted) or were left without diet overnight and water ad libitum (fasted). Each dog received a 100 µg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. A single dose of ABT 869 was administered to each dog. The dose was followed by approximately 10 milliliters of water. Blood samples were obtained from each animal prior to dosing and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after drug administration. The plasma was separated from the red cells by centrifugation and frozen (-30 °C) until analysis. Concentrations of active ingredient were determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The area under the curve (AUC) was calculated by the trapezoidal method over the time

course of the study. Each dosage form was evaluated in a group containing 3-6 dogs; the values reported are averages for each group of dogs.

Following the procedures above, an ABT 869 solid dispersion product having the following composition was prepared: 6% ABT-869: 54.8% K30: 23.4% Gelucire 44/14: 15.6% Vitamin E TPGS.

Bioavailability was tested as described above with 20 mg/dog. The studies were run with liquid clinical formulation as reference (4.0 % by weight ABT 869 in ethanol-surfactant solution) in a crossover study design. Each dosage form was evaluated in a group containing 5 dogs; the values reported are averages for each group of dogs.

	C_{max} (µg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (µg•hr/ml)	C_{max} Pt. est.	AUC Pt. est.
Clinical Reference	0.35	1.2	0.7	0.62		
Solid Dispersion	0.42	0.9	0.8	0.74	1.07	1.04

Example 2:

Following the procedures of Example 1 above, a liquid mixture is prepared, containing 56.13 % by weight of ethanol, 15.36 % of PVP K30, 3.56 % of Gelucire 44/14, 1.92 % of Vitamin E TPGS, 21.94 % of maltitol and 1.10 % of ABT-869.

The liquid mixture is fed to a twin-drum dryer. This dryer comprises a pair of drums which are rotated in the opposite direction to each other. The drums are heated to a temperature of about 60 °C by circulating thermal oil. The space between the drums forms a liquid pool into which the liquid mixture is introduced. The liquid mixture is being spread on the circumferential faces of the respective drums; the adjustable gap between the two drums acts as a means to control the film thickness. After travelling part of a revolution, the dried material is removed in the form of thin sheets by scraper knifes.

The drying drums are positioned in a vacuum chamber which is maintained at a pressure of 50mbar (absolute pressure). The ethanol vapours are drawn off and condensed.

We claim:

1. A solid dispersion product comprising at least one pharmaceutically active agent, obtained by

   a) preparing a liquid mixture containing the at least one active agent, at least one pharmaceutically acceptable matrix-forming agent, at least one pharmaceutically acceptable surfactant and at least one solvent, and
   b) removing the solvent(s) from the liquid mixture to obtain the solid dispersion product.

2. The solid dispersion product of claim 1, wherein at least one filler is added to the liquid mixture before removing the solvent(s).

3. The solid dispersion product of claim 1, wherein the mass ratio of active agent and pharmaceutically acceptable matrix-forming agent is from 0.01:1 to 1:3.

4. The solid dispersion product of claim 1, wherein the mass ratio of active agent and pharmaceutically acceptable surfactant is from 0.1:1 to 1:7.

5. The solid dispersion product of claim 1, wherein the pharmaceutically acceptable matrix-forming agent is selected from the group consisting of cyclodextrines, pharmaceutically acceptable polymers, lipids or combinations of two or more thereof.

6. The solid dispersion product of claim 1, wherein said pharmaceutically acceptable matrix-forming agent is selected from the group consisting of cellulose esters, cellulose ethers, maltodextrines, N-vinyl pyrrolidone homopolymers, N-vinyl pyrrolidone copolymers and combinations of two or more thereof.

7. The solid dispersion product of claim 1, wherein said pharmaceutically acceptable matrix-forming agent is selected from the group consisting of poly N-vinylpyrrolidones, copolymers of N-vinyl pyrrolidone and vinyl acetate and combinations thereof.

8. The solid dispersion product of claim 1, wherein the pharmaceutically acceptable surfactant is selected from the group consisting of polyol fatty acid esters, polyalkoxylated polyol fatty acid esters, polyalkoxylated fatty alcohol ethers, tocopheryl compounds or combinations of two or more thereof.

9. The solid dispersion product of claim 1, wherein the pharmaceutically acceptable surfactant comprises a combination of two or more pharmaceutically acceptable surfactants.

10. The solid dispersion product dispersion product of claim 1, wherein the pharmaceutically acceptable surfactant comprises at least one surfactant having an HLB value of 10 or more.

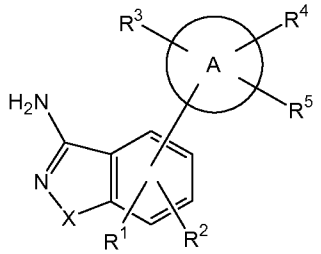
11. The solid dispersion product of claim 9 wherein the combination of pharmaceutically acceptable surfactants comprises (i) at least one tocopheryl compound having a polyalkylene glycol moiety and (ii) at least one polyalkoxylated polyol fatty acid ester.

12. The solid dispersion product of claim 11, wherein the tocopheryl compound is alpha tocopheryl polyethylene glycol succinate.

13. The solid dispersion product of claim 11, wherein the polyalkoxylated polyol fatty acid ester is a polyalkoxylated glyceride.

14. The solid dispersion product of claim 11, wherein the mass ratio of tocopheryl compound and polyalkoxylated polyol fatty acid ester is in the range of from 0.2:1 to 1:1 .

15. The solid dispersion product of claim 1, wherein the active agent is represented by the formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

A is selected from the group consisting of indolyl, phenyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, and thienyl;

X is selected from the group consisting of O, S, and NR^9;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^aR^b)alkoxy, (NR^aR^b)alkenyl, (NR^aR^b)alkyl, (NR^aR^b)alkynyl, (NR^aR^b)carbonylalkenyl, and (NR^aR^b)carbonylalkyl;

R^3, R^4, and R^5 are each independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkyl, halo, haloalkoxy, haloalkyl, hydroxy, and LR^6; provided that at least two of R^3, R^4, and R^5 are other than LR^6;

L is selected from the group consisting of $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$ and $CH_2C(O)NR^7$, wherein m and n are independently 0 or 1, and wherein each group is drawn with its left end attached to A;

R^6 is selected from the group consisting of hydrogen, aryl, cycloalkyl, heterocyclyl, and 1,3-benzodioxolyl wherein the 1,3-benzodioxolyl can be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxy, arylalkyl, aryloxy, carboxy, cyano, cycloalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, $-NR^cR^d$, and (NR^cR^d)alkyl;

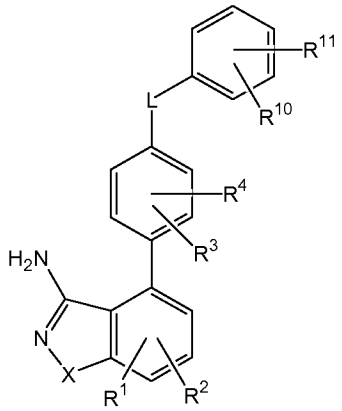
R^7 and R^8 are independently selected from the group consising of hydrogen and alkyl;

R^9 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylcarbonyl, aryl, heterocyclylalkyl, hydroxyalkyl, and (NR^aR^b)alkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkyl, arylcarbonyl, arylsulfonyl, haloalkylsulfonyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylsulfonyl; and

R^c and R^d are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, and heterocyclyl.

16. The solid dispersion product of claim 15, wherein the active agent is represented by the formula (II)



(II),

or a therapeutically acceptable salt thereof, wherein

X is selected from the group consisting of O, S, and NR^9;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^aR^b)alkoxy, (NR^aR^b)alkenyl, (NR^aR^b)alkyl, (NR^aR^b)carbonylalkenyl, and (NR^aR^b)carbonylalkyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkoxy, alkyl, halo, haloalkoxy, haloalkyl, and hydroxy;

L is selected from the group consisting of $(CH_2)_mN(R^7)C(O)N(R^8)(CH_2)_n$ and $CH_2C(O)NR^7$, wherein m and n are independently 0 or 1, and wherein each group is drawn with its left end attached to the ring substituted with R^3 and R^4;

R^7 and R^8 are independently selected from the group consising of hydrogen and alkyl;

R^9 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylcarbonyl, aryl, heterocyclylalkyl, hydroxyalkyl, and (NR^aR^b)alkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $-NR^cR^d$;

R^a and R^b are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; and

R^c and R^d are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

17. The solid dispersion product of claim 1, wherein the active agent is selected from the group consisting of N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea (ABT869) or salts or hydrates or solvates thereof.

18. A pharmaceutical dosage form, comprising the solid dispersion product of claim 1.

19. A process for preparing a solid dispersion product comprising at least one pharmaceutically active agent, which process comprises

a) preparing a liquid mixture containing the at least one active agent, at least one pharmaceutically acceptable matrix-forming agent, at least one pharmaceutically acceptable surfactant and at least one solvent, and
b) removing the solvent(s) from the liquid mixture to obtain the solid dispersion product.

20. The process of claim 19, wherein the liquid mixture is prepared by dissolving the pharmaceutically acceptable matrix-forming agent to obtain a matrix-forming agent solution, and adding the active agent and the pharmaceutically acceptable surfactant to the solution.

21. The process of claim 19, wherein the liquid mixture has a dry matter content of up to 90 % by weight.

22. The process of claim 19, wherein removing of the solvent is carried out by spray-drying, drum drying, belt drying, tray drying or combinations of two or more thereof.

23. The process of claim 19, wherein the solvent is selected from the group consisting of alkanols, hydrocarbons, halogenated hydrocarbons, ketons, esters, ethers and combinations of two or more thereof.

24. The process of claim 19, further comprising compressing the solid dispersion product to obtain a tablet.

25. The process of claim 24, wherein at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants is added before compressing.

26. The process of claim 19, further comprising filling the solid dispersion product into capsules.

27. The process of claim 19, wherein at least one filler is added to the liquid mixture before removing the solvent(s).

28. The process of claim 19, wherein the mass ratio of active agent and pharmaceutically acceptable matrix-forming agent is from 0.01:1 to 1:3.

29. The process of claim 19, wherein the mass ratio of active agent and pharmaceutically acceptable surfactant is from 0.1:1 to 1:7.

30. The process of claim 19, wherein the pharmaceutically acceptable matrix-forming agent is selected from the group consisting of cyclodextrines, pharmaceutically acceptable polymers, lipids or combinations of two or more thereof.

31. The process of claim 19, wherein said pharmaceutically acceptable matrix-forming agent is selected from the group consisting of cellulose esters, cellulose ethers, maltodextrines, N-vinyl pyrrolidone homopolymers, N-vinyl pyrrolidone copolymers and combinations of two or more thereof.

32. The process of claim 19, wherein said pharmaceutically acceptable matrix-forming agent is selected from the group consisting of poly N-vinylpyrrolidones, copolymers of N-vinyl pyrrolidone and vinyl acetate and combinations thereof.

33. The process of claim 19, wherein the pharmaceutically acceptable surfactant is selected from the group consisting of polyol fatty acid esters, polyalkoxylated polyol fatty acid esters, polyalkoxylated fatty alcohol ethers, tocopheryl compounds or combinations of two or more thereof.

34. The process of claim 19, wherein the pharmaceutically acceptable surfactant comprises a combination of two or more pharmaceutically acceptable surfactants.

35. The process dispersion product of claim 19, wherein the pharmaceutically acceptable surfactant comprises at least one surfactant having an HLB value of 10 or more.

36. The process of claim 34 wherein the combination of pharmaceutically acceptable surfactants comprises (i) at least one tocopheryl compound having a polyalkylene glycol moiety and (ii) at least one polyalkoxylated polyol fatty acid ester.

37. The process of claim 36, wherein the tocopheryl compound is alpha tocopheryl polyethylene glycol succinate.

38. The process of claim 36, wherein the polyalkoxylated polyol fatty acid ester is a polyalkoxylated glyceride.

39. The process of claim 36, wherein the mass ratio of tocopheryl compound and polyalkoxylated polyol fatty acid ester is in the range of from 0.2:1 to 1:1 .