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(54) **FUNGICIDAL COMPOUNDS AND MIXTURES**

FUNGIZIDE VERBINDUNGEN UND MISCHUNGEN

COMPOSES ET MELANGES FONGICIDES

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(56) References cited:
WO-A1-01/34150
WO-A2-2007/014290
WO-A2-2008/013622
WO-A2-2008/013925
WO-A2-2008/091580
WO-A2-2008/091594
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Description

FIELD OF THE INVENTION

[0001] This invention relates to fungicidal mixtures of a certain carboxamide derivative, its *N*-oxides and salts, and to compositions comprising such mixtures and methods for using such mixtures as fungicides.

BACKGROUND OF THE INVENTION

[0002] The control of plant diseases caused by fungal plant pathogens is extremely important in achieving high crop efficiency. Plant disease damage to ornamental, vegetable, field, cereal and fruit crops can cause significant reduction in productivity and thereby result in increased costs to the consumer. In addition to often being highly destructive, plant diseases can be difficult to control and may develop resistance to commercial fungicides. Combinations of fungicides are often used to facilitate disease control, to broaden spectrum of control and to retard resistance development. Furthermore, certain rare combinations of fungicides demonstrate a greater-than-additive (i.e. synergistic) effect to provide commercially important levels of plant disease control. The advantages of particular fungicide combinations are recognized in the art to vary, depending on such factors as the particular plant species and plant disease to be treated, and whether the plants are treated before or after infection with the fungal plant pathogen. Accordingly new advantageous combinations are needed to provide a variety of options to best satisfy particular plant disease control needs. Remarkably advantageous combinations have now been discovered. WO 2007/014290 discloses fungicidal carboxamides. WO 01/34150 discloses aliphatic amine substituted piperidyl diaryl pyrrole derivatives as antiprotozoal agents. WO2008/091580 discloses fungicidal amides. WO 2008/013622 discloses fungicidal azocyclic amides. WO2008/013925 (prior art according to Article 54(3) EPC) discloses fungicidal azocyclic amides. WO 2008/091594 discloses fungicidal mixtures. WO 2009/094407 (prior art according to Article 54(3) EPC) discloses fungicidal amides.

SUMMARY OF THE INVENTION

[0003] This invention relates to a fungicidal combination (e.g., composition) comprising

(a) at least one compound selected from 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone, its enantiomer or a mixture thereof, *N*-oxides, and salts thereof; and
(b) at least one additional fungicidal compound selected from amisulbrom, azoxystrobin, benthiavalicarb, boscalid, chlorothalonil, copper hydroxide, copper oxychloride, copper sulfate, cyazofamid, cymoxanil, cyproconazole, dithianon, difenoconazole, dimethomorph, ethaboxam, epoxiconazole, famoxadone, fenamidone, fluazinam, fluopicolide, flusilazole, folpet, fosetyl-aluminum, iprovalicarb, kresoxim-methyl, mancozeb, mandipropamid, metalaxyl, metalaxyl-M, metconazole, metiram, penthiopyrad, phosphorous acid and salts, picoxystrobin, propamacarb, propiconazole, propineb, proquinazid, pyraclostrobin, quinoxyfen, tebuconazole, triadimenol, trifloxystrobin, valiphenal, and zoxamide.

[0004] This invention also relates to a method for controlling plant diseases caused by fungal plant pathogens comprising applying to the plant or portion thereof, or to the plant seed, a fungicidally effective amount of the aforesaid composition.

DETAILS OF THE INVENTION

[0005] As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having", "contains" or "containing" or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a composition, process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such composition, process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0006] Also, the indefinite articles "a" and "an" preceding an element or component of the invention are intended to be nonrestrictive regarding the number of instances (i.e. occurrences) of the element or component. Therefore "a" or "an" should be read to include one or at least one, and the singular word form of the element or component also includes the plural unless the number is obviously meant to be singular.

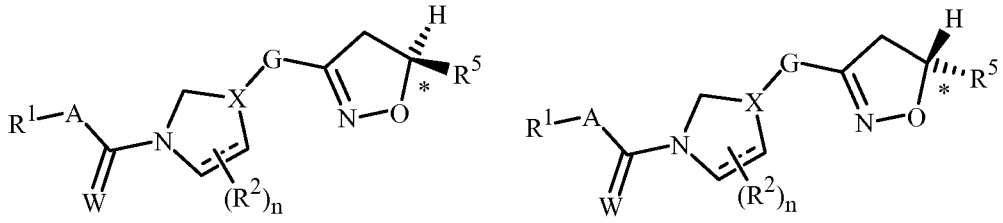
[0007] As referred to in the present disclosure and claims, "plant" includes members of Kingdom Plantae, particularly

seed plants (Spermatopsida), at all life stages, including young plants (e.g., germinating seeds developing into seedlings) and mature, reproductive stages (e.g., plants producing flowers and seeds). Portions of plants include geotropic members typically growing beneath the surface of the growing medium (e.g., soil), such as roots, tubers, bulbs and corms, and also members growing above the growing medium, such as foliage (including stems and leaves), flowers, fruits and seeds.

[0008] As referred to herein, the term "seedling", used either alone or in a combination of words means a young plant developing from the embryo of a seed or bud of a vegetative propagation unit such as tuber, corm or rhizome.

[0009] Naming of substituents in the present disclosure uses recognized terminology providing conciseness in precisely conveying to those skilled in the art the chemical structure. For sake of conciseness, locant descriptors may be omitted; "pyrazol-1-yl" means "1*H*-pyrazol-1-yl" according to the Chemical Abstracts system of nomenclature. The order of listing substituents may be different from the Chemical Abstracts system if the difference does not affect the meaning.

[0010] The compound 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (compound (a)) can exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, and/or to selectively prepare said stereoisomers. The compound (a) may be present as a mixture of stereoisomers, individual stereoisomers, or as an optically active form. For example, when J is isoxazolyl bonded at the 3-position to the remainder of the compound and the isoxazolyl has one R^5 substituent other than H at the 5-position, then the compound possesses a chiral center at the carbon atom to which R^5 is bonded. The two enantiomers are depicted as Formula **1'** and Formula **1"** with the chiral center identified with an asterisk (*).



1' **1"**

[0011] The compound (a) may comprise racemic mixtures, for example, equal amounts of the enantiomers of Formulae **1'** and **1".** In addition, compound (a) may include compounds that are enriched compared to the racemic mixture in an enantiomer. Also included are the essentially pure enantiomers of compounds of Formula **1,** for example, Formula **1'** and Formula **1".**

[0012] When enantiomerically enriched, one enantiomer is present in greater amounts than the other, and the extent of enrichment can be defined by an expression of enantiomeric excess ("ee"), which is defined as (2x-1)·100 %, where x is the mole fraction of the dominant enantiomer in the mixture (e.g., an ee of 20 % corresponds to a 60:40 ratio of enantiomers).

[0013] Preferably the compositions of this invention have at least a 50 % enantiomeric excess; more preferably at least a 75 % enantiomeric excess; still more preferably at least a 90 % enantiomeric excess; and the most preferably at least a 94 % enantiomeric excess of the more active isomer. Of particular note are enantiomerically pure embodiments of the more active isomer.

[0014] The compound (a) can exist as one or more conformational isomers due to restricted rotation about the amide bond (e.g., C(W)-N). Compound (a) comprises mixtures of conformational isomers. In addition, compound (a) includes compounds that are enriched in one conformer relative to others.

[0015] Some of the unsaturated rings and ring systems depicted herein can have an arrangement of single and double bonds between ring members different from that depicted. Such differing arrangements of bonds for a particular arrangement of ring atoms correspond to different tautomers. For these unsaturated rings and ring systems, the particular tautomer depicted is to be considered representative of all the tautomers possible for the arrangement of ring atoms shown. The tables listing particular compounds incorporating the ring and ring systems depicted herein may involve a tautomer different from the tautomer depicted herein.

[0016] The compound 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone typically exists in more than one form, and thus the claims include all crystalline and non-crystalline forms. Non-crystalline forms include embodiments which are solids such as waxes and gums as well as embodiments which are liquids such as solutions and melts. Crystalline forms include embodiments which represent essentially a single crystal type and embodiments which represent a mixture of polymorphs (i.e. different

crystalline types). The term "polymorph" refers to a particular crystalline form of a chemical compound that can crystallize in different crystalline forms, these forms having different arrangements and/or conformations of the molecules in the crystal lattice. Although polymorphs can have the same chemical composition, they can also differ in composition due the presence or absence of co-crystallized water or other molecules, which can be weakly or strongly bound in the lattice. Polymorphs can differ in such chemical, physical and biological properties as crystal shape, density, hardness, color, chemical stability, melting point, hygroscopicity, suspensibility, dissolution rate and biological availability. One skilled in the art will appreciate that a polymorph of compound (a) can exhibit beneficial effects (e.g., suitability for preparation of useful formulations, improved biological performance) relative to another polymorph or a mixture of polymorphs of the same compound. Preparation and isolation of a particular polymorph of a compound can be achieved by methods known to those skilled in the art including, for example, crystallization using selected solvents and temperatures.

[0017] The compound 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone includes *N*-oxide derivatives. One skilled in the art will appreciate that not all nitrogen-containing heterocycles can form *N*-oxides since the nitrogen requires an available lone pair of electrons for oxidation to the oxide; one skilled in the art will recognize those nitrogen-containing heterocycles which can form *N*-oxides. One skilled in the art will also recognize that tertiary amines can form *N*-oxides. Synthetic methods for the preparation of *N*-oxides of heterocycles and tertiary amines are very well known by one skilled in the art including the oxidation of heterocycles and tertiary amines with peroxy acids such as peracetic and m-chloroperbenzoic acid (MCPBA), hydrogen peroxide, alkyl hydroperoxides such as *tert*-butyl hydroperoxide, sodium perborate, and dioxiranes such as dimethyldioxirane. These methods for the preparation of *N*-oxides have been extensively described and reviewed in the literature, see for example: T. L. Gilchrist in Comprehensive Organic Synthesis, vol. 7, pp 748-750, S. V. Ley, Ed., Pergamon Press; M. Tisler and B. Stanovnik in Comprehensive Heterocyclic Chemistry, vol. 3, pp 18-20, A. J. Boulton and A. McKillop, Eds., Pergamon Press; M. R. Grimmett and B. R. T. Keene in Advances in Heterocyclic Chemistry, vol. 43, pp 149-161, A. R. Katritzky, Ed., Academic Press; M. Tisler and B. Stanovnik in Advances in Heterocyclic Chemistry, vol. 9, pp 285-291, A. R. Katritzky and A. J. Boulton, Eds., Academic Press; and G. W. H. Cheeseman and E. S. G. Werstiuk in Advances in Heterocyclic Chemistry, vol. 22, pp 390-392, A. R. Katritzky and A. J. Boulton, Eds., Academic Press.

[0018] One skilled in the art recognizes that because in the environment and under physiological conditions salts of chemical compounds are in equilibrium with their corresponding nonsalt forms, salts share the biological utility of the nonsalt forms. When the compounds forming the present mixtures and compositions contain acidic or basic moieties, a wide variety of salts can be formed, and these salts are useful in the present mixtures and compositions for controlling plant diseases caused by fungal plant pathogens (i.e. are agriculturally suitable). When a compound contains a basic moiety such as an amine function, salts include acid-addition salts with inorganic or organic acids such as hydrobromic, hydrochloric, nitric, phosphoric, sulfuric, acetic, butyric, fumaric, lactic, maleic, malonic, oxalic, propionic, salicylic, tartaric, 4-toluenesulfonic or valeric acids. When a compound contains an acidic moiety such as a carboxylic acid or phenol, salts include those formed with organic or inorganic bases such as pyridine, triethylamine or ammonia, or amides, hydrides, hyroxides or carbonates of sodium, potassium, lithium, calcium, magnesium or barium.

[0019] Component (b) may be selected from the group consisting of
amisulbrom, azoxystrobin, benthiavalicarb, boscalid, chlorothalonil, copper hydroxide, copper oxychloride, copper sulfate, cyazofamid, cymoxanil, cyproconazole, dithianon, difenoconazole, dimethomorph, ethaboxam, epoxiconazole, famoxadone, fenamidone, fluazinam, fluopicolide, flusilazole, folpet, fosetyl-aluminum, iprovalicarb, kresoxim-methyl, mancozeb, mandipropamid, metalaxyl, metalaxyl-M, metconazole, metiram, penthiopyrad, phosphorous acid and salts, picoxystrobin, propamacarb, propiconazole, propineb, proquinazid, pyraclostrobin, quinoxyfen, tebuconazole, triadimenol, trifloxystrobin, valiphenal, and zoxamide.

[0020] Component (b) may comprise at least one fungicide from each of two different groups selected from (b1) through (b46).

[0021] "Demethylation inhibitor (DMI) fungicides (b3)" (Fungicide Resistance Action Committee (FRAC) code 3) inhibit C14-demethylase which plays a role in sterol production. Sterols, such as ergosterol, are needed for membrane structure and function, making them essential for the development of functional cell walls. Therefore, exposure to these fungicides result in abnormal growth and eventually death of sensitive fungi. DMI fungicides are divided between several chemical classes: azoles (including triazoles and imidazoles), pyrimidines, piperazines and pyridines. The triazoles include azaconazole, bitertanol, bromuconazole, cyproconazole, difenoconazole, diniconazole (including diniconazole-M), epoxiconazole, etaconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, hexaconazole, imibenconazole, ipconazole, metconazole, myclobutanil, penconazole, propiconazole, prothioconazole, quinconazole, simeconazole, tebuconazole, tetraconazole, triadimefon, triadimenol, triticonazole and uniconazole. The imidazoles include clotrimazole, econazole, imazalil, isoconazole, miconazole, oxpoconazole, prochloraz, pefurazoate and triflumizole. The pyrimidines include fenarimol, nuarimol and triarimol. The piperazines include triforine. The pyridines include buthiobate and pyrifenox. Biochemical investigations have shown that all of the above mentioned fungicides are DMI fungicides as described by K. H. Kuck et al. in Modern Selective Fungicides - Properties, Applications and Mechanisms of Action, H. Lyr (Ed.),

Gustav Fischer Verlag: New York, 1995, 205-258.

[0022] "Phenylamide fungicides (b4)" (Fungicide Resistance Action Committee (FRAC) code 4) are specific inhibitors of RNA polymerase in Oomycete fungi. Sensitive fungi exposed to these fungicides show a reduced capacity to incorporate uridine into rRNA. Growth and development in sensitive fungi is prevented by exposure to this class of fungicide. Phenylamide fungicides include acylalanine, oxazolidinone and butyrolactone fungicides. The acylalanines include benalaxyl, benalaxyl-M, furalaxyl, metalaxyl, metalaxyl-M/mefenoxam. The oxazolidinones include oxadixyl. The butyrolactones include ofurace.

[0023] "Carboxamide fungicides (b7)" (Fungicide Resistance Action Committee (FRAC) code 7) inhibit Complex II (succinate dehydrogenase) fungal respiration by disrupting a key enzyme in the Krebs Cycle (TCA cycle) named succinate dehydrogenase. Inhibiting respiration prevents the fungus from making ATP, and thus inhibits growth and reproduction. Carboxamide fungicides include benzamide, furan carboxamide, oxathiin carboxamide, thiazole carboxamide, pyrazole carboxamide and pyridine carboxamide. The Benzamides include benodanil, flutolanil and mepronil. The furan carboxamides include fenfuram. The oxathiin carboxamide include carboxin and oxycarboxin. The thiazole carboxamides include thifluzamide. The pyrazole carboxamides include furametpyr, penthiopyrad, bixafen, *N*-[2-(1*S*,2*R*)-[1,1'-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide and *N*-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide (PCT Patent Publication WO 2003/010149). The pyridine carboxamide include boscalid.

[0024] "Quinone outside inhibitor (QoI) fungicides (b11)" (Fungicide Resistance Action Committee (FRAC) code 11) inhibit Complex III mitochondrial respiration in fungi by affecting ubiquinol oxidase. Oxidation of ubiquinol is blocked at the "quinone outside" (Q_o) site of the cytochrome bc_1 complex, which is located in the inner mitochondrial membrane of fungi. Inhibiting mitochondrial respiration prevents normal fungal growth and development. Quinone outside inhibitor fungicides (also known as strobilurin fungicides) include methoxyacrylate, methoxycarbamate, oximinoacetate, oximinoacetamide, oxazolidinedione, dihydrodioxazine, imidazolinone and benzylcarbamate fungicides. The methoxyacrylates include azoxystrobin, enestroburin (SYP-Z071) and picoxystrobin. The methoxycarbamates include pyraclostrobin. The oximinoacetates include kresoxim-methyl and trifloxystrobin. The oximinoacetamides include dimoxystrobin, metominostrobin, orysastrobin and α-(methoxyimino)-*N*-methyl-2-[[[1-[3-(trifluoromethyl)phenyl]-ethoxy]imino]methyl]benzeneacetamide. The oxazolidinediones include famoxadone. The dihydrodioxazines include fluoxastrobin. The imidazolinones include fenamidone. The benzylcarbamates include pyribencarb.

[0025] "Quinoline fungicides (b13)" (Fungicide Resistance Action Committee (FRAC) code 13) are proposed to inhibit signal transduction by affecting G-proteins in early cell signaling. They have been shown to interfere with germination and/or appressorium formation in fungi that cause powder mildew diseases. Quinoxyfen is an example of this class of fungicide.

[0026] "Quinone inside inhibitor (QiI) fungicides (b21)" (Fungicide Resistance Action Committee (FRAC) code 21) inhibit Complex III mitochondrial respiration in fungi by affecting ubiquinol reductase. Reduction of ubiquinol is blocked at the "quinone inside" (Q_i) site of the cytochrome bc_1 complex, which is located in the inner mitochondrial membrane of fungi. Inhibiting mitochondrial respiration prevents normal fungal growth and development. Quinone inside inhibitor fungicides include cyanoimidazole and sulfamoyltriazole fungicides. The cyanoimidazoles include cyazofamid. The sulfamoyltriazoles include amisulbrom.

[0027] "Benzamide fungicides (b22)" (Fungicide Resistance Action Committee (FRAC) code 22) inhibit mitosis by binding to β-tubulin and disrupting microtubule assembly. Inhibition of microtubule assembly can disrupt cell division, transport within the cell and cell structure. Examples include zoxamide.

[0028] "Cyanoacetamideoxime fungicides (b27) (Fungicide Resistance Action Committee (FRAC) code 27) include cymoxanil.

[0029] "Carbamate fungicides (b28)" (Fungicide Resistance Action Committee (FRAC) code 28) are considered multisite inhibitors of fungal growth. They are proposed to interfere with the synthesis of fatty acids in cell membranes, which then disrupts cell membrane permeability. Propamacarb, iodocarb, and prothiocarb are examples of this fungicide class.

[0030] "Oxidative phosphorylation uncoupling fungicides (b29)" (Fungicide Resistance Action Committee (FRAC) code 29) inhibit fungal respiration by uncoupling oxidative phosphorylation. Inhibiting respiration prevents normal fungal growth and development. This class includes 2,6-dinitroanilines such as fluazinam, pyrimidonehydrazones such as ferimzone and dinitrophenyl crotonates such as dinocap, meptyldinocap and binapacryl.

[0031] "Phosphonate fungicides (b33)" (Fungicide Resistance Action Committee (FRAC) code 33) include phosphorous acid and its various salts, including fosetyl-aluminum.

[0032] "Carboxylic acid amide (CAA) fungicides (b40)" (Fungicide Resistance Action Committee (FRAC) code 40) are proposed to inhibit phospholipid biosynthesis and cell wall deposition. Inhibition of these processes prevents growth and leads to death of the target fungus. Carboxylic acid amide fungicides include cinnamic acid amide, valinamide carbamate and mandelic acid amide fungicides. The cinnamic acid amides include dimethomorph and flumorph. The valinamide carbamates include benthiavalicarb, benthiavalicarb-isopropyl, iprovalicarb and valiphenal. The mandelic acid amides include mandipropamid, *N*-[2-[4-[[3-(4-chlorophenyl)-2-propyn-1-yl]oxy]-3-methoxyphenyl]-ethyl]-3-methyl-2-[(methyl-

sulfonyl)amino]butanamide and *N*-[2-[4-[[3-(4-chlorophenyl)-2-propyn-1-yl]oxy]-3-methoxyphenyl]ethyl]-3-methyl-2-[(ethylsulfonyl)amino]-butanamide.

[0033] "Benzamide fungicides (b43)" (Fungicide Resistance Action Committee (FRAC) code 43) inhibit growth of fungi by delocalization of spectrin-like proteins. Examples include acylpicolide fungicides such as fluopicolide and fluopyram.

[0034] "Multi-site contact fungicides (b45)" inhibit fungal growth through multiple sites of action and have contact/preventive activity. This class of fungicides includes: "copper fungicides (b45.1) (Fungicide Resistance Action Committee (FRAC) code M1)", "sulfur fungicides (b45.2) (Fungicide Resistance Action Committee (FRAC) code M2)", "dithiocarbamate fungicides (b45.3) (Fungicide Resistance Action Committee (FRAC) code M3)", "phthalimide fungicides (b45.4) (Fungicide Resistance Action Committee (FRAC) code M4)", "chloronitrile fungicides (b45.5) (Fungicide Resistance Action Committee (FRAC) code M5)", "sulfamide fungicides (b45.6) (Fungicide Resistance Action Committee (FRAC) code M6)", "guanidine fungicides (b45.7) (Fungicide Resistance Action Committee (FRAC) code M7)" "triazines fungicides (b45.8) (Fungicide Resistance Action Committee (FRAC) code M8)" and "quinone fungicides (b45.9) (Fungicide Resistance Action Committee (FRAC) code M9)". "Copper fungicides" are inorganic compounds containing copper, typically in the copper(II) oxidation state; examples include copper oxychloride, copper sulfate and copper hydroxide, including compositions such as Bordeaux mixture (tribasic copper sulfate). "Sulfur fungicides" are inorganic chemicals containing rings or chains of sulfur atoms; examples include elemental sulfur. "Dithiocarbamate fungicides" contain a dithiocarbamate molecular moiety; examples include mancozeb, metiram, propineb, ferbam, maneb, thiram, zineb and ziram. "Phthalimide fungicides" contain a phthalimide molecular moiety; examples include folpet, captan and captafol. "Chloronitrile fungicides" contain an aromatic ring substituted with chloro and cyano; examples include chlorothalonil. "Sulfamide fungicides" include dichlofluanid and tolylfluanid. "Guanidine fungicides" include dodine, guazatine and iminoctadine. "Triazines fungicides" include anilazine. "Quinone fungicides" include dithianon.

[0035] Certain fungicides are considered to have an unknown mode of action. These include: "thiazole carboxamide fungicide (b46.1) (Fungicide Resistance Action Committee (FRAC) code U5)", "phenyl-acetamide fungicide (b46.2) (Fungicide Resistance Action Committee (FRAC) code U6)", "quinazolinone fungicide (b46.3) (Fungicide Resistance Action Committee (FRAC) code U7)" and "benzophenone fungicide (b46.4) (Fungicide Resistance Action Committee (FRAC) code U8)". The thiazole carboxamides include ethaboxam. The phenyl-acetamides include cyflufenamid and *N*-[[(cyclopropylmethoxy)amino][6-(difluoromethoxy)-2,3-difluorophenyl]-methylene]benzeneacetamide. The quinazolinones include proquinazid, 6-bromo-3-propyl-2-propyloxy-4(3*H*)-quinazolinone, 6,8-diiodo-3-propyl-2-propyloxy-4-(3*H*)-quinazolinone, 6-chloro-2-propoxy-3-propylthieno[2,3-*d*]pyrimidin-4(3*H*)-one, 2,3-dibutyl-6-chlorothieno[2,3-*d*]pyrimidin-4(3*H*)-one, 6-bromo-2-propoxy-3-propylthieno[2,3-*d*]pyrimidin-4(3*H*)-one, 7-bromo-2-propoxy-3-propylthieno[3,2-*d*]pyrimidin-4(3*H*)-one, 6-bromo-2-propoxy-3-propylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one, 6,7-dibromo-2-propoxy-3-propylthieno[3,2-*d*]pyrimidin-4(3*H*)-one, 3-(cyclopropylmethyl)-6-iodo-2-(propylthio)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one, 2-butoxy-6-iodo-3-propyl-4*H*-1-benzopyran-4-one, 2-ethoxy-6-iodo-3-propyl-4*H*-1-benzopyran-4-one, 6-iodo-2-propoxy-3-propyl-4*H*-1-benzopyran-4-one, 2-(2-butynyloxy)-6-iodo-3-propyl-4*H*-1-benzopyran-4-one, 6-iodo-2-(1-methylbutoxy)-3-propyl-4*H*-1-benzopyran-4-one, 2-(3-butenyloxy)-6-iodo-3-propyl-4*H*-1-benzopyran-4-one, 3-butyl-6-iodo-2-(1-methylethoxy)-4*H*-1-benzopyran-4-one, and 6-iodo-3-propyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dione 2-(*O*-methyloxime). The benzophenones include metrafenone. The (b46) group also includes 5-chloro-6-(2,4,6-trifluorophenyl)-7-(4-methylpiperidin-1-yl)[1,2,4]triazolo[1,5-*a*]pyrimidine (BAS600), 3-[5-(4-chlorophenyl)-2,3-dimethyl-3-isoxazolidinyl]pyridine (SYP-Z048), 4-fluorophenyl *N*-[1-[[[1-(4-cyanophenyl)ethyl]sulfonyl]methyl]propyl]carbamate (XR-539), *N*'-[4-[4-chloro-3-(trifluoromethyl)phenoxy]-2,5-dimethylphenyl]-*N*-ethyl-*N*-methylmethanimidamide, 2-[[2-fluoro-5-(trifluoromethyl)phenyl]thio]-2-[3-(2-methoxyphenyl)-2-thiazolidinylidene]acetonitrile (OK-5203) and *N*-(4-chloro-2-nitrophenyl)-*N*-ethyl-4-methylbenzenesulfonamide (TF-991).

[0036] Accordingly, the present invention comprises compositions of one or more compounds selected from 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone, *N*-oxides and salts thereof, with one or more compounds or salts thereof selected from (b) as described in the

Summary of the Invention.

[0037] Embodiments of this invention can be combined in any manner.

Embodiment A12. The composition wherein component (a) is 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone and its enantiomer (Compound 214).

Embodiment B3. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b3) demethylation inhibitor fungicides epoxiconazole, triadimenol, cyproconazole, difenconazole, flusilazole, metconazole, propiconazole and tebuconazole.

Embodiment B4. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b4) phenylamide fungicides mefenoxam and metalaxyl.

Embodiment B7. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b7) carboxamide fungicides boscalid and penthiopyrad.

Embodiment B11. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b11) quinone outside inhibitor fungicides azoxystrobin, pyraclostrobin, kresoxim-methyl, trifloxystrobin, picoxystrobin, famoxadone and fenamidone.

Embodiment B13. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound that is (b13) quinoline fungicide quinoxyfen.

Embodiment B21. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b21) quinone inside inhibitor fungicides cyazofamid and amisulbrom.

Embodiment B22. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes the (b22) benzamide fungicide zoxamide.

Embodiment B27. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes the (b27) cyanoacetylamideoxime fungicide cymoxanil.

Embodiment B28. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes the (b28) carbamate fungicide propamacarb.

Embodiment B29. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes the (b29) oxidative phosphorylation uncoupling fungicide fluazinam.

Embodiment B33. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b33) phosphonate fungicides phosphorous acid and its various salts, including fosetyl-aluminum.

Embodiment B40. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b40) carboxylic acid amide fungicides dimethomorph, benthiavalicarb, iprovalicarb, valiphenal and mandipropamid.

Embodiment B43. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes the (b43) benzamide fungicide fluopicolide.

Embodiment B45. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b45) multi-site contact fungicides copper oxychloride, copper sulfate, copper hydroxide, mancozeb, metiram, propineb, folpet and chlorothalonil.

Embodiment B46. The composition described in the Summary of the Invention (including the composition of Embodiment A12) wherein component (b) includes at least one compound selected from the (b46) fungicides other than fungicides of component (a) and components (b1) through (b45) ethaboxam and proquinazid.

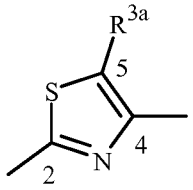
[0038] Of note is the composition of any one of the embodiments described herein, including A12 and B1 through B46.

[0039] Also noteworthy as embodiments are fungicidal compositions of the present invention comprising a fungicidally effective amount of a composition of Embodiments A12, and B1 to B46 and at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents. Embodiments of the invention further include methods for controlling plant diseases caused by fungal plant pathogens comprising applying to the plant or portion thereof, or to the plant seed or seedling, a fungicidally effective amount of a composition of Embodiments A12, and B1 to B46 (e.g., as a composition described herein). The preferred methods of use include those involving the above preferred compositions; and the diseases controlled with particular effectiveness include plant diseases caused by Oomycete fungal plant pathogens. Combinations of fungicides used in accordance with this invention can facilitate disease control and retard resistance development.

[0040] Compositions include those where component (a) and component (b) are present in a fungicidally effective amount and the weight ratio of component (a) to component (b) is from 125:1 to 1:125. These compositions are particularly effective for controlling plant diseases caused by Oomycete fungal plant pathogens. Of note are compositions where the weight ratio of component (a) to component (b) is from 25:1 to 1:25. Of particular note are compositions where the weight ratio of component (a) to component (b) is from 5:1 to 1:5. Compositions also include those where component (a) and component (b) are present in a fungicidally effective amount and the weight ratio of component (a) to component (b) is outside the range of 125:1 to 1:125; see, for example, Table A1 below, which lists specific combinations of a component (a) compound with component (b) illustrative of the mixtures, compositions and methods of the present invention.

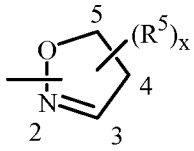
[0041] Compounds of Formula **1** (i.e. the compound 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone) can be prepared by one or more of the following methods and variations as described in the Schemes below. Formulae **1a-1e** are various subsets of Formula **1.**

[0042] In the schemes: A is CHR^{15}; R^{15} is H; G is G-1



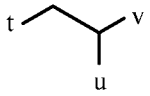
G-1 ;

J is J-29



J-29 ;

W is O; X is X^1

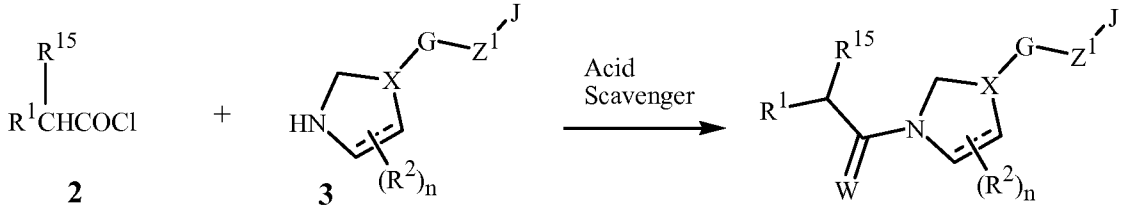


X^1 ;

Z^1 is a bond; n=0 such that R^2 is absent.

[0043] As shown in Scheme 1, compounds of Formula **1a** can be prepared by coupling an acid chloride of Formula **2** with an amine of Formula **3** in the presence of an acid scavenger. Typical acid scavengers include amine bases such as triethylamine, *N*,*N*-diisopropylethylamine and pyridine. Other scavengers include hydroxides such as sodium and potassium hydroxide and carbonates such as sodium carbonate and potassium carbonate. In certain instances it is useful to use polymer-supported acid scavengers such as polymer-bound *N*,*N*-diisopropylethylamine and polymer-bound 4-(dimethylamino)pyridine. Acid salts of the Formula **3** amines can also be used in this reaction, provided that at least 2 equivalents of the acid scavenger is present. Typical acids used to form salts with amines include hydrochloric acid, oxalic acid and trifluoroacetic acid.

Scheme 1

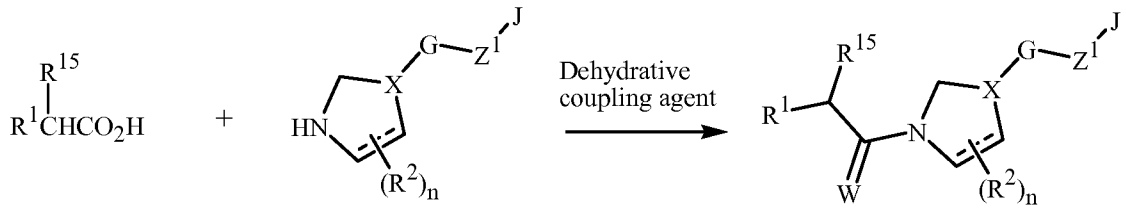


1a wherein W is O

[0044] An alternate procedure for the preparation of compounds of Formula **1a** is depicted in Scheme 2 and involves coupling of an acid of Formula **4** with an amine of Formula **3** (or its acid salt) in the presence of a dehydrative coupling reagent such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU). Polymer-supported reagents are

again useful here, such as polymer-bound cyclohexylcarbodiimide. These reactions are typically run at 0-40 °C in a solvent such as dichloromethane or acetonitrile in the presence of a base such as triethylamine or *N*,*N*-diisopropylethylamine. The acids of Formula **4** are known or can be prepared by methods known to one skilled in the art. For example, R^1CH_2COOH where R^1 is a substituted pyrazole ring linked through nitrogen can be prepared by reacting the corresponding R^1H compound with a haloacetic acid or ester in the presence of base; see, for example, U.S. Patent 4,084,955.

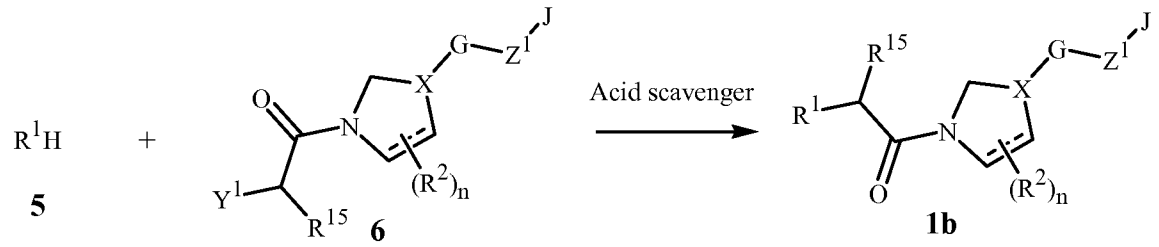
Scheme 2



[0045] As the synthetic literature includes many amide-forming methods, the synthetic procedures of Schemes 1 and 2 are simply representative examples of an wide variety of methods useful for the preparation of Formula **1** compounds. One skilled in the art also realizes that acid chlorides of Formula **2** can be prepared from acids of **Formula 4** by numerous well-known methods.

[0046] Certain compounds of Formula **1b** wherein R^1 is a substituted pyrazole ring linked through the nitrogen atom can be prepared by reaction of the parent heterocycle of Formula **5** and a haloacetamide of Formula **6** as shown in Scheme 3. The reaction is carried out in the presence of a base such as sodium hydride or potassium carbonate in a solvent such as tetrahydrofuran, *N*,*N*-dimethylformamide or acetonitrile at 0 to 80 °C. The haloacetamide of Formula **6** can be prepared by the reaction of an amine of Formula **3** with an α-halo carboxylic acid halide or an α-halo carboxylic acid or its anhydride, analogous to the amide-forming reactions described in Schemes 1 and 2, respectively.

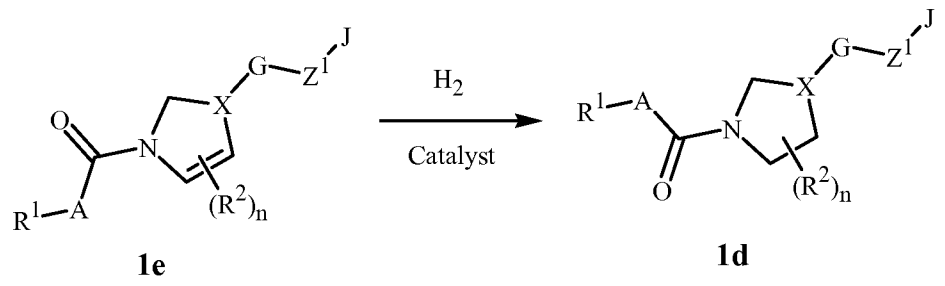
Scheme 3



wherein Y^1 is Cl, Br or I.

[0047] Certain compounds of Formula **1d** can be prepared from compounds of Formula **1e** where the ring containing X is unsaturated by catalytic hydrogenation as shown in Scheme 6. Typical conditions involve exposing a compound of Formula **1e** to hydrogen gas at a pressure of 70 to 700 kPa, preferably 270 to 350 kPa, in the presence of a metal catalyst such as palladium supported on an inert carrier such as activated carbon, in a weight ratio of 5 to 20 % of metal to carrier, suspended in a solvent such as ethanol at ambient temperature. This type of reduction is very well known; see, for example, Catalytic Hydrogenation, L. Cerveny, Ed., Elsevier Science, Amsterdam, 1986. One skilled in the art will recognize that certain other functionalities that may be present in compounds of Formula **1e** can also be reduced under catalytic hydrogenation conditions, thus requiring a suitable choice of catalyst and conditions.

Scheme 6

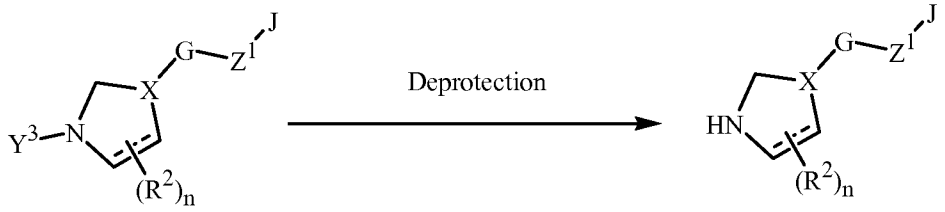


1e **1d**

wherein X is X^1.

[0048] The amine compounds of Formula **3** can be prepared from the protected amine compounds of Formula **14** where Y^3 is an amine-protecting group as shown in Scheme 9. A wide array of amine-protecting groups are available (see, for example, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991), and the use and choice of the appropriate protecting groups will be apparent to one skilled in chemical synthesis. The protecting group can be removed and the amine isolated as its acid salt or the free amine by general methods known in the art. One skilled in the art will also recognize that the protected amines of Formula **14** can be prepared by methods analogous to those described in Scheme 6 above where the group $R^1AC(=W)$ is replaced by Y^3 to give useful intermediates of Formula **14** for the preparation of compounds of Formula **1.**

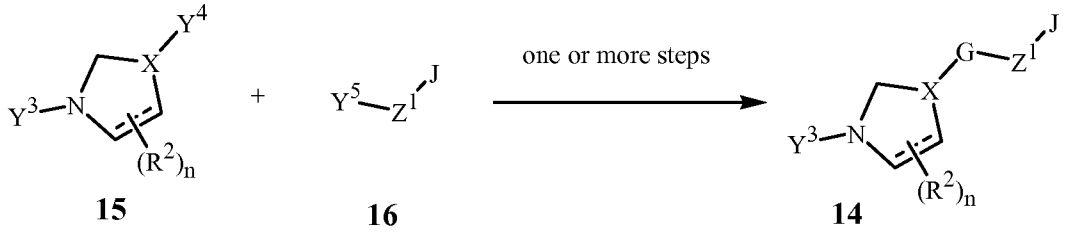
Scheme 9



14 wherein Y^3 is an amine protecting group **3**

[0049] The compounds of Formula **14** can also be prepared by reaction of a suitably functionalized compound of Formula **15** with a suitably functionalized compound of Formula **16** as shown in Scheme 10. The functional groups Y^4 and Y^5 are selected from, but not limited to, moieties such as aldehydes, ketones, esters, acids, amides, thioamides, nitriles, amines, alcohols, thiols, hydrazines, oximes, amidines, amideoximes, olefins, acetylenes, halides, alkyl halides, methanesulfonates, trifluoromethanesulfonates, boronic acids, boronates, and the like, which under the appropriate reaction conditions, will allow the construction of the G-1 ring. As an example, reaction of a compound of Formula **15** where Y^4 is a thioamide group with a compound of Formula **16** where Y^5 is a bromoacetyl group will give a compound of Formula **14** where G is a thiazole ring. The synthetic literature describes many general methods for forming 5-membered heteroaromatic rings and 5-membered partially saturated heterocyclic rings (e.g., G-1 through G-59); see, for example, Comprehensive Heterocyclic Chemistry, Vol. 4-6, A. R. Katritzky and C. W. Rees editors, Pergamon Press, New York, 1984; Comprehensive Heterocyclic Chemistry II, Vol. 2-4, A. R. Katritzky, C. W. Rees, and E. F. Scriven editors, Pergamon Press, New York, 1996; and the series, The Chemistry of Heterocyclic Compounds, E. C. Taylor, editor, Wiley, New York. The use of intermediates of Formula **15** where X is X^1 and Y^4 is Br, I, methanesulfonate or trifluoromethanesulfonate to prepare organozinc reagents for use in cross-coupling reactions with aromatic rings has been described; see, for example, S. Bellotte, Synlett 1998, 379-380, and M. Nakamura et al., Synlett 2005, 1794-1798. One skilled in the art knows how to select the appropriate functional groups to construct the desired heterocyclic rings such as G. Compounds of Formula **15** and **16** are known or can be prepared by one skilled in the art.

Scheme 10

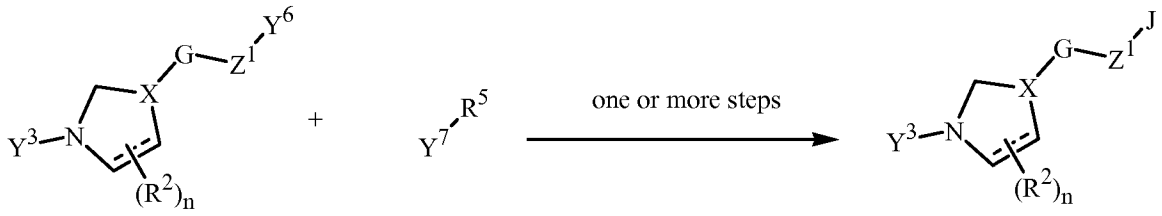


15 16 14

wherein Y^4 and Y^5 are functional groups suitable for construction of the desired heterocycle G-1.

[0050] Compounds of Formula **14** can also be prepared by reaction of a suitably functionalized compound of Formula **21** with a suitably functionalized compound of Formula **22** as shown in Scheme 13. The functional groups Y^6 and Y^7 are selected from, but not limited to, moieties such as aldehydes, ketones, esters, acids, amides, thioamides, nitriles, amines, alcohols, thiols, hydrazines, oximes, amidines, amide oximes, olefins, acetylenes, halides, alkyl halides, methanesulfonates, trifluoromethanesulfonates, boronic acids, boronates, and the like, which, under the appropriate reaction conditions will allow the construction of the heterocyclic ring J-29. As an example, reaction of a compound of Formula **21** where Y^6 is a chloro oxime moiety with a compound of Formula **22** where Y^7 is an acetylene group in the presence of base will give a compound of Formula **14** where J is an isoxazole. The synthetic literature includes many general methods for the formation of carbocyclic and heterocyclic rings and ring systems; see, for example, Comprehensive Heterocyclic Chemistry, Vol. 4-6, A. R. Katritzky and C. W. Rees editors, Pergamon Press, New York, 1984; Comprehensive Heterocyclic Chemistry II, Vol. 2-4, A. R. Katritzky, C. W. Rees, and E. F. Scriven editors, Pergamon Press, New York, 1996; the series, The Chemistry of Heterocyclic Compounds, E. C. Taylor, editor, Wiley, New York, and Rodd's Chemistry of Carbon Compounds, Vol. 2-4, Elsevier, New York. General procedures for cycloaddition of nitrile oxides with olefins are well documented in the chemical literature. For relevant references see Lee, Synthesis 1982, 6, 508-509 and Kanemasa et al., Tetrahedron 2000, 56, 1057-1064 as well as references cited within. One skilled in the art knows how to select the appropriate functional groups to construct the desired heterocyclic ring J. Compounds of Formula **22** are known or can be prepared by general methods known in the art.

Scheme 13

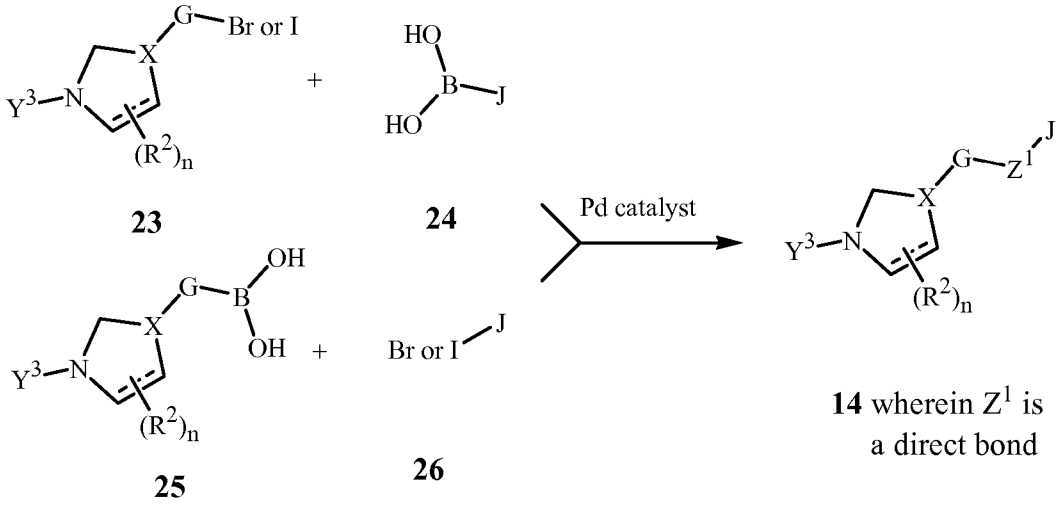


21 22 14

wherein Y^6 and Y^7 are functional groups suitable for construction of the heterocycle J-29.

[0051] An alternate preparation for the compounds of Formula **14** where Z^1 is a bond includes the well known Suzuki reaction involving Pd-catalyzed cross-coupling of an iodide or bromide of Formula **23** or **26** with a boronic acid of Formula **24** or **25**, respectively, as shown in Scheme 14. Many catalysts are useful for this type of transformation; a typical catalyst is tetrakis(triphenylphosphine)palladium. Solvents such as tetrahydrofuran, acetonitrile, diethyl ether and dioxane are suitable. The Suzuki reaction and related coupling procedures offer many alternatives for creation of the G-J bond. For leading references see for example C. A. Zificsak and D. J. Hlasta, Tetrahedron 2004, 60, 8991-9016. For a thorough review of palladium chemistry applicable to the synthesis of G-J bonds see J. J. Li and G. W. Crribble, editors, Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist, Elsevier: Oxford, UK, 2000. Many variations of catalyst type, base and reaction conditions are known in the art for this general method.

Scheme 14



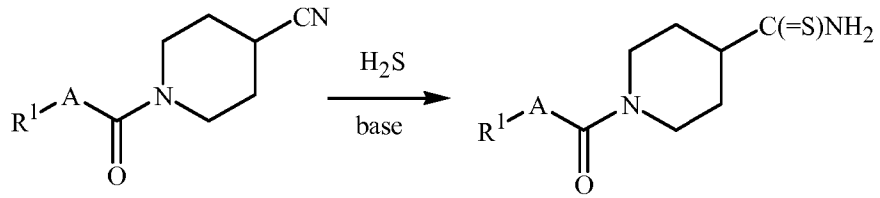
23 24 25 26

14 wherein Z^1 is a direct bond

[0052] One skilled in the art will recognize that many compounds of Formula **1** can be prepared directly by methods analogous to those described in Schemes 10, 13 and 14 above where the group Y^3 is replaced by $R^1AC(=W)$. Thus, compounds corresponding to Formulae **15, 21, 23** and **25** in which Y^3 is replaced by $^1AC(=W)$ are useful intermediates for the preparation of compounds of Formula **1.**

[0053] Thioamides of Formula **1Ab** are particularly useful intermediates for preparing compounds of Formula **1** wherein X is X^1. A thioamide of Formula **1Ab** can be prepared by the addition of hydrogen sulfide to the corresponding nitrile of Formula **1Aa** as shown in Scheme 15.

Scheme 15



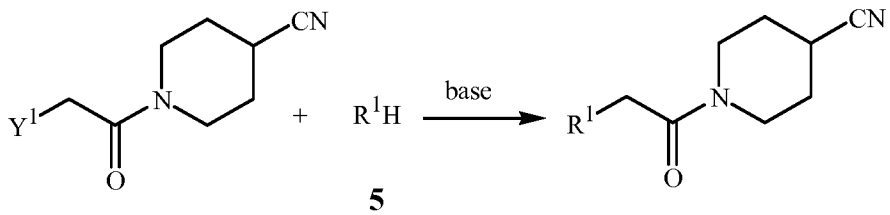
1Aa **1Ab**

wherein R^1 is a substituted pyrazole.

[0054] The method of Scheme 15 can be carried out by contacting a compound of Formula **1Aa** with hydrogen sulfide in the presence of an amine such as pyridine, diethylamine or diethanolamine. Alternatively, hydrogen sulfide can be used in the form of its bisulfide salt with an alkali metal or ammonia. This type of reaction is well documented in the literature (e.g., A. Jackson et al., EP 696,581 (1996)).

[0055] Certain compounds of Formula **1Aa** wherein A is CH_2 and $\mathbf{R^1}$ is a substituted pyrazole ring linked through a nitrogen atom can be prepared by reaction of the parent heterocycle of Formula **5** and a haloacetamide of Formula **27** as shown in Scheme 16. The reaction is carried out in the presence of a base such as sodium hydride or potassium carbonate in a solvent such as tetrahydrofuran, *N,N*-dimethylformamide or acetonitrile at 0 to 80 °C.

Scheme 16

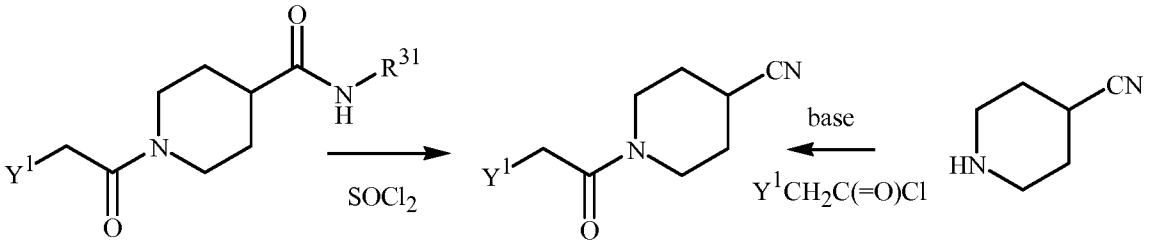


27 **5** **1Aa**

wherein R^1 is a substituted pyrazole ring that is unsubstituted on N (i.e. comprising a ring member of the formula -(NH)-); and Y^1 is Cl, Br or I.

[0056] The haloacetamides of Formula **27** can be prepared by the two methods shown in Scheme 17.

Scheme 17



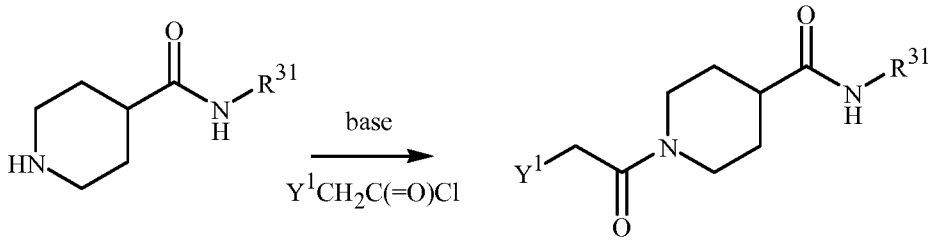
28 **27** **29**

wherein Y^1 is Cl, Br, or I; and R^{31} is a tertiary alkyl group such as $-C(Me)_3$.

[0057] In one method, 4-cyanopiperidine of Formula **29** is haloacetylated by contact with the appropriate haloacetyl chloride typically in the presence of a base according to standard methods. Preferred conditions involve use of an aqueous solution of an inorganic base such as an alkali metal or alkaline-earth carbonate, bicarbonate, or phosphate, and a non-water-miscible organic solvent such as toluene, ethyl acetate or 1,2-dichloroethane. In the second method depicted in Scheme 17, a 1-(haloacetyl)-*N*-substituted isonipecotamide derivative of Formula **28**, wherein R^{31} is tertiary alkyl such as $C(Me)_3$, is dehydrated using a standard amide dehydrating agent such as thionyl chloride or phosphorus oxychloride in a suitable solvent. A particularly preferred solvent for this transformation is an *N*,*N*-dialkylamide such as *N*,*N*-dimethylformamide. The reaction is typically carried out by adding 0.9 to 2 equivalents, preferably 1.1 equivalents, of phosphorus oxychloride or thionyl chloride, to a mixture of a compound of Formula **28** and 0.5 to 10 parts by weight of solvent, at a temperature at which the reaction rapidly proceeds during the addition. The addition time for this reaction is typically around 20 to 90 minutes at typical temperatures of around 35 to 55 °C.

[0058] As shown in Scheme 18, compounds of Formula **28** can be prepared from compounds of Formula **30** by a method analogous to the haloacetylation reaction described for Scheme 17.

Scheme 18



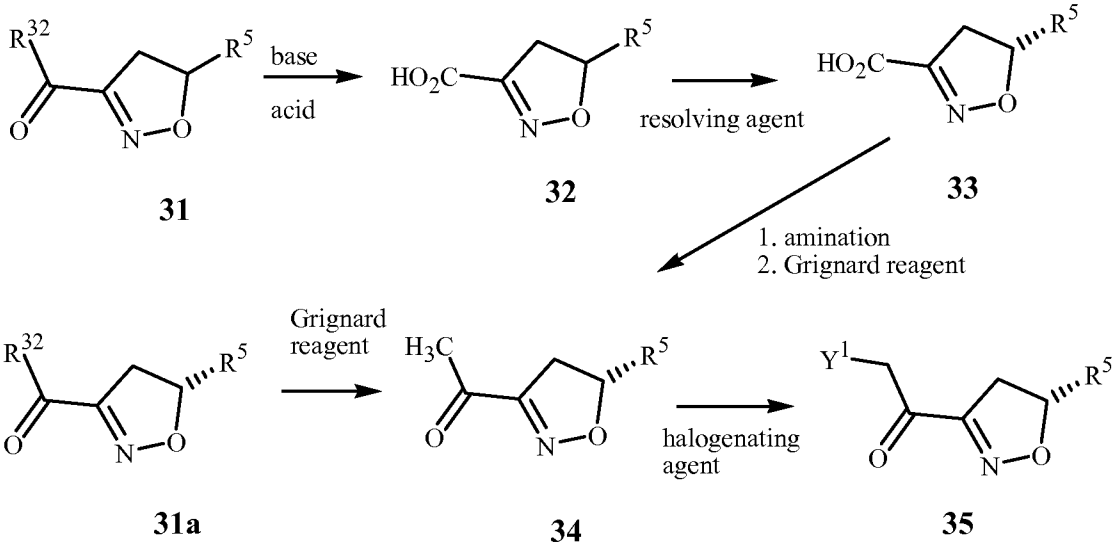
30 **28**

[0059] The compounds of Formula **30** are known or can be prepared from 4-cyanopyridine or isonicotinic acid using methods well-known in the art; see, for example, German patent application DE 3,537,762 (1986) for preparation of *N*-*t*-butyl pyridinecarboxamides from cyanopyridines and *t*-butanol and S. F. Nelsen, et al., J. Org. Chem., 1990, 55, 3825 for hydrogenation of *N*-methylisonicotinamide with a platinum catalyst.

[0060] Halomethyl isoxazoline ketones of Formula **35** are particularly useful intermediates for preparing certain chiral compounds of Formula **1.** Halomethyl isoxazoline ketones of Formula **35** can be prepared by the multi-step reaction sequences shown in Scheme 19.

[0061] One skilled in the art will recognize that Scheme 19 can also be practiced without the use of a resolving agent, so that a compound of Formula **32** is converted directly to a racemic analog of Formula **31a**, which can then be used to prepare racemic analogs of Formulae **34**, **35** and certain racemic compounds of Formula **1.**

Scheme 19

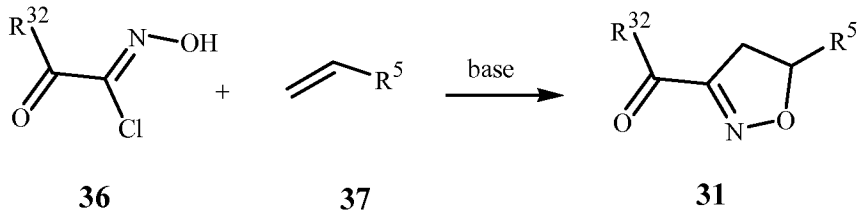


wherein R^{32} is C_2-C_8 dialkylamino, C_2-C_6 haloalkylamino, 1-piperidinyl, 1-pyrrolidinyl or 4-morpholinyl; and R^5 is 2,6-difluorophenyl.

[0062] The preparation of racemic carboxylic acids of Formula **32** can be accomplished according to the well-known methods of basic or acidic hydrolysis of the corresponding compounds of Formula **31**, preferably using a slight excess of sodium hydroxide in a water-miscible co-solvent such as methanol or tetrahydrofuran at 25 to 45 °C. The product can be isolated by adjusting the pH of the reaction mixture to 1 to 3 and then filtration or extraction, optionally after removal of the organic solvent by evaporation. The racemic carboxylic acids of Formula **32** can be resolved by classical fractional crystallization of diastereomeric salts of suitable chiral amine bases such as cinchonine, dihydrocinchonine or a mixture thereof. A cinchonine-dihydrocinchonine mixture in a 85:15 ratio is particularly useful, as it provides, for example, the (R)-configured carboxylic acids of Formula **33**, wherein R^5 is a substituted phenyl group, as the less soluble salt. Furthermore, these chiral amine bases are readily available on a commercial scale. The halomethyl ketones of Formula **35** can be prepared by first reacting the corresponding amides of Formula **31**, either as pure enantiomers (i.e. Formula **31a**) or in enantiomerically enriched or racemic mixtures, with one molar equivalent of a methylmagnesium halide (Grignard reagent) in a suitable solvent or solvent mixture such as tetrahydrofuran and toluene at 0 to 20 °C, and the crude ketone products of Formula **34** can be isolated by quenching with aqueous acid, extraction, and concentration. Then the crude ketones of Formula **34** are halogenated with a reagent such as sulfuryl chloride to afford the chloromethyl ketones of Formula **35** wherein Y^1 is Cl or molecular bromine to afford the corresponding bromomethyl ketones of Formula **35** wherein Y^1 is Br. The halomethyl ketones of Formula **35** can be purified by crystallization from a solvent such as hexanes or methanol, or can be used without further purification in the condensation reaction with thioamides.

[0063] The isoxazoline carboxamides of Formula **31** can be prepared by cycloaddition of the corresponding hydroxamoyl chlorides of Formula **36** with olefin derivatives of Formula **37**, as shown in Scheme 20.

Scheme 20



wherein R^{32} is C_2-C_8 dialkylamino, C_2-C_6 haloalkylamino, 1-piperidinyl, 1-pyrrolidinyl or 4-morpholinyl; and R^5 is 2,6-difluorophenyl.

[0064] In this method, all three reacting components (the compounds of Formulae **36** and **37**, and the base) are contacted so as to minimize hydrolysis or dimerization of the hydroxamoyl chloride of Formula **36.** In one typical procedure, the base, which can either be a tertiary amine base such as triethylamine or an inorganic base such as an alkali metal

or alkaline-earth carbonate, bicarbonate or phosphate, is mixed with the olefin derivative of Formula **37**, and the hydroxamoyl chloride of Formula **36** is added gradually at a temperature at which the cycloaddition proceeds at a relatively rapid rate, typically between 5 and 25 °C. Alternatively, the base can be added gradually to the other two components (the compounds of Formulae **36** and **37**). This alternative procedure is preferable when the hydroxamoyl chloride of Formula **36** is substantially insoluble in the reaction medium. The solvent in the reaction medium can be water or an inert organic solvent such as toluene, hexane or even the olefin derivative used in excess. The product can be separated from the salt co-product by filtration or washing with water, followed by evaporation of the solvent. The crude product can be purified by crystallization, or the crude product can be used directly in the methods of Scheme 19. Compounds of Formula **31** are useful precursors to the corresponding methyl ketones of Formula **34** and halomethyl ketones of Formula **35**, and are also useful for preparing the resolved enantiomers of the compounds of Formulae **34** and **35** by hydrolysis, resolution, methyl ketone synthesis and halogenation, as shown in Scheme 19.

[0065] It is recognized that some reagents and reaction conditions described above for preparing compounds of Formula **1** may not be compatible with certain functionalities present in the intermediates. In these instances, the incorporation of protection/deprotection sequences or functional group interconversions into the synthesis will aid in obtaining the desired products. The use and choice of the protecting groups will be apparent to one skilled in chemical synthesis (see, for example, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991). One skilled in the art will recognize that, in some cases, after the introduction of a given reagent as it is depicted in any individual scheme, it may be necessary to perform additional routine synthetic steps not described in detail to complete the synthesis of compounds of Formula **1.** One skilled in the art will also recognize that it may be necessary to perform a combination of the steps illustrated in the above schemes in an order other than that implied by the particular sequence presented to prepare the compounds of Formula **1.**

[0066] One skilled in the art will also recognize that compounds of Formula **1** and the intermediates described herein can be subjected to various electrophilic, nucleophilic, radical, organometallic, oxidation, and reduction reactions to add substituents or modify existing substituents.

[0067] Without further elaboration, it is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Steps in the following Examples illustrate a procedure for each step in an overall synthetic transformation, and the starting material for each step may not have necessarily been prepared by a particular preparative run whose procedure is described in other Examples or Steps. Percentages are by weight except for chromatographic solvent mixtures or where otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated. ^{1}H NMR spectra are reported in ppm downfield from tetramethylsilane; "s" means singlet, "d" means doublet, "t" means triplet, "m" means multiplet, "q" means quartet, "dd" means doublet of doublet, "br s" means broad singlet, "br d" means broad doublet, "br t" means broad triplet, "br m" means broad multiplet.

REFERENCE EXAMPLE 1

Preparation of 4-[4-[4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (Reference Compound 1)

Step A: Preparation of 1,1-dimethylethyl 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinecarboxylate

[0068] To a suspension of 1,1-dimethylethyl 4-(4-formyl-2-thiazolyl)-1-piperidinecarboxylate (1.0 g, 3.4 mmol) in ethanol (5 mL) was added an aqueous solution of hydroxylamine (50 wt. %, 0.25 mL, 4.0 mmol). The reaction mixture was heated at 60 °C for 1 h, during which time the reaction mixture became homogeneous. The resulting solution was cooled to room temperature and diluted with tetrahydrofuran (10 mL). To the reaction mixture was added styrene (0.57 mL, 5 mmol), followed by portionwise addition of Clorox® aqueous sodium hypochlorite solution (10.5 mL) over 3 h. The reaction mixture was stirred overnight at room temperature, and the resulting solid was filtered, washed with water and diethyl ether, and air dried to give the title compound as a white powder (610 mg). The filtrate was diluted with saturated aqueous sodium bicarbonate solution and extracted with diethyl ether. The extract was dried ($MgSO_4$ and concentrated under reduced pressure to give 850 mg of the title compound as a yellow oil. The oil was diluted with diethyl ether (4 mL) and allowed to stand to give an additional 233 mg of the product as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 1.7 (m, 2H), 2.1 (m, 2H), 2.85 (m, 2H), 3.2 (m, 1H), 3.45 (m, 1H), 3.84 (m, 1H) 4.2 (br s, 2H), 5.75 (m, 1H), 7.25-7.40 (m, 5H), 7.61 (s, 1H).

Step B: Preparation of 4-[4-[4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine

[0069] To a solution of 1,1-dimethylethyl 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinecarboxylate (i.e. the product of Example 1, Step A) (0.815 g, 1.97 mmol) in dichloromethane (50 mL) was added a solution of hydrogen chloride in diethyl ether (2 M, 10 mL, 20 mmol). The reaction mixture was stirred at room temperature for 1 h to give a gummy precipitate. Methanol was added to dissolve the precipitate, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was concentrated under reduced pressure and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution, and the organic layer was dried ($MgSO_4$) and concentrated to give the free amine as a clear oil (0.31 g), which solidified on standing. A mixture of the resulting free amine (0.31 g, 1.0 mmol), 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (0.208 g, 1.0 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.25 g, 1.3 mmol), triethylamine (150 μL, 1.08 mmol) and a catalytic amount of 1-hydroxybenzotriazole hydrate (~1 mg) in dichloromethane (5 mL) was swirled to form a vortex and held at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (10 mL), and washed with 1 N aqueous hydrochloric acid and saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 0.47 g of the title product as a white foam.
^{1}H NMR ($CDCl_3$): δ 1.8 (m, 2H), 2.2 (m, 2H), 2.32 (s, 3H), 2.9 (m, 1H), 3.3 (m, 2H), 3.42 (m, 1H), 3.85 (m, 1H), 4.05 (m, 1H), 4.55 (m, 1H), 4.98 (m, 2H), 5.75 (m, 1H), 6.33 (s, 1H), 7.25-7.42 (m, 5H), 7.63 (s, 1H).

[0070] The following compounds were prepared by procedures analogous to Step B of Example 1:

1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]-2-[3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 128); ^{1}H NMR ($CDCl_3$): δ 1.7-1.9 (m, 2H), 2.16 (m, 1H), 2.24 (m, 1H), 2.29 (s, 3H), 2.84-2.92 (br t, 1H), 3.30 (m, 2H), 3.43 (m, 1H), 3.86 (m, 2H), 4.59 (br d, 1H), 5.04 (s, 2H), 5.75 (m, 1H), 6.47 (s, 1H), 7.29-7.39 (m, 5H), 7.64 (s, 1H).

1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]-2-[5-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 19); m.p. 128-133 °C (crystallized from methyl acetate/petroleum ether); ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H), 1.8 (m, 2H), 2.2 (m, 2H), 2.62 (q, 2H), 2.9 (m, 1H), 3.3 (m, 2H), 3.42 (m, 1H), 3.85 (m, 1H), 4.05 (m, 1H), 4.55 (m, 1H), 4.98 (m, 2H), 5.75 (m, 1H), 6.33 (s, 1H), 7.25-7.42 (m, 5H), 7.63 (s, 1H).

2-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]ethanone (Reference Compound 22); m.p. 130-133 °C (crystallized from methyl acetate/petroleum ether); ^{1}H NMR ($CDCl_3$): δ 1.8 (m, 2H), 2.2 (m, 2H), 2.9 (m, 1H), 3.3 (m, 2H), 3.42 (m, 1H), 3.85 (m, 2H), 4.55 (m, 1H), 5.10 (s, 2H), 5.77 (m, 1H), 6.95 (s, 1H), 7.25-7.42 (m, 5H), 7.64 (s, 1H).

1-[4-[4-(2,3-dihydrospiro[4*H*-1-benzopyran-4,5'(4'*H*)-isoxazol]-3'-yl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 137); ^{1}H NMR ($CDCl_3$): δ 1.83 (m, 2H), 2.18 (m, 3H), 2.33 (s, 3H), 2.42 (m, 1H), 2.90 (m, 1H), 3.31 (m, 2H), 3.47 (d, 1H), 3.83 (d, 1H), 4.05 (m, 1H), 4.27 (m, 1H), 4.40 (m, 1H), 4.58 (d, 1H), 4.97 (m, 2H), 6.33 (s, 1H), 6.87 (d, 1H), 6.95 (dd, 1H), 7.21 (dd, 1H), 7.38 (d, 1H), 7.67 (s, 1H).

1-[4-[4-(2,3-dihydrospiro[4*H*-1-benzothiopyran-4,5'(4'*H*)-isoxazol]-3'-yl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 102); ^{1}H NMR ($CDCl_3$): δ 1.82 (m, 2H), 2.23 (m, 2H), 2.31 (s, 3H), 2.37 (m, 1H), 2.50 (m, 1H), 2.90 (m, 1H), 3.14 (m, 1H), 3.17 (m, 1H), 3.27 (m, 2H), 3.48 (d, 1H), 3.66 (d, 1H), 4.05 (m, 1H), 4.57 (d, 1H), 4.97 (m, 2H), 6.33 (s, 1H), 7.06 (m, 3H), 7.45 (d, 1H), 7.65 (s, 1H).

REFERENCE EXAMPLE 2

Preparation of 1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-[4-(5-phenyl-3-isoxazolyl)-2-thiazolyl]piperidine (Reference Compound 2)

Step A: Preparation of 2-(4-piperidinyl)-4-thiazolecarboxaldehyde monohydrochloride

[0071] To a solution of 1,1-dimethylethyl 4-(4-formyl-2-thiazolyl)-1-piperidinecarboxylate (1.0 g, 3.4 mmol) in dichloromethane (20 mL) was added a solution of hydrogen chloride in diethyl ether (2.0 mL, 15 ml, 30 mmol). The reaction mixture was stirred under nitrogen at room temperature for 2 h and then evaporated under reduced pressure to give 1.2 g of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 2.31-2.38 (m, 2H), 2.44-2.50 (m, 2H), 3.11-3.20 (m, 2H), 3.36-3.44 (m, 1H), 3.57-3.65 (m, 2H), 8.14 (s, 1H), 10.01 (s, 1H).

Step B: Preparation of 4-(4-formyl-2-thiazolyl)-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (also known as 2-[1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidinyl]-4-thiazolecarboxaldehyde)

[0072] To a solution of 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (0.8 g, 3.8 mmol) in dichloromethane (10 mL) was added oxalyl chloride (2.4 g, 19.2 mmol) and two drops of *N,N*-dimethylformamide, resulting in slight exothermicity. The reaction mixture was then heated at reflux for 15 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in tetrahydrofuran (10 mL) and treated with a solution of 2-(4-piperidinyl)-4-thiazolecarboxaldehyde monohydrochloride (i.e. the product of Example 2, Step A) (1.1 g, 5.1 mmol) in tetrahydrofuran (10 mL), followed by dropwise addition of triethylamine (1.2 g, 11.9 mmol). The reaction mixture was stirred overnight at room temperature and then partitioned between 1 N aqueous hydrochloric acid and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate (2 x 30 mL). The combined organic layers were washed with 1 N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, and brine. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give 0.8 g of the title compound as a yellow oil.
^{1}H NMR ($CDCl_3$): δ 1.79-1.90 (m, 2H), 2.18-2.29 (m, 2H), 2.33 (s, 3H), 2.87-2.94 (m, 1H), 3.28-3.40 (m, 2H), 4.05-4.15 (m, 1H), 4.56-4.64 (m, 1H), 4.99-5.02 (m, 2H), 6.35 (s, 1H), 8.12 (s, 1H), 10.01 (s, 1H).

Step C: Preparation of 4-[4-[(hydroxyimino)methyl]-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (also known as 2-[1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazoly-1-yl]-4-piperdinyl]-4-thiazolecarboxaldehyde 4-oxime)

[0073] To a solution of 4-(4-formyl-2-thiazolyl)-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (i.e. the product of Example 2, Step B) (0.8 g, 2.07 mmol) in ethyl alcohol (15 mL) was added hydroxylamine (50% aqueous solution, 0.136 g, 4.1 mmol), and the reaction mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure to give a yellow oil, which was purified by flash column chromatography on silica gel using 50 % ethyl acetate in hexanes as eluant to give 0.7 g of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 1.72-1.85 (m, 2H), 2.17-2.27 (m, 2H), 2.32 (s, 3H), 2.82-2.91 (m, 1H), 3.25-3.37 (m, 2H), 4.02-4.09 (m, 1H), 4.58-4.63 (m, 1H), 4.95-5.03 (m, 2H), 6.35 (s, 1H), 7.43 (s, 1H), 7.71 (s, 1H), 8.19 (s, 1H).

Step D: Preparation of 1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-[4-(5-phenyl-3-isoxazolyl)-2-thiazolyl]piperidine

[0074] 4-[4-[(Hydroxyimino)methyl]-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (i.e. the product of Example 2, Step C) (0.2 g, 0.5 mmol) was suspended in tetrahydrofuran (20 mL), and phenylacetylene (1.1 mL, 1 mmol) was added, followed by a slow dropwise addition of Clorox® bleach solution (6.15 wt. % sodium hypochlorite, 10 mL) over 1 h. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give an oil, which was purified by flash column chromatography on silica gel using 10 % methanol in ethyl acetate as eluant to give to give 70 mg of the title product as a clear yellow oil.
^{1}H NMR ($CDCl_3$): δ 1.80-1.92 (m, 2H), 2.22-2.32 (m, 2H), 2.34 (s, 3H), 2.90-2.98 (m, 1H), 3.31-3.41 (m, 2H), 4.05-4.11 (m, 1H), 4.58-4.65 (m, 1H), 4.97-5.07 (m, 2H), 6.36 (s, 1H), 6.98 (s, 1H), 7.47-7.53 (m, 3H), 7.84 (s, 2H), 7.88 (m, 1H).

REFERENCE EXAMPLE 3

Preparation of 4-[4-(4,5-dihydro-1-methyl-5-phenyl-1*H*-imidazol-2-yl)-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (Reference Compound 7)

[0075] To a solution of 4-(4-formyl-2-thiazolyl)-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (i.e. the product of Example 2, Step B) (0.8 g, 2.07 mmol) in *tert*-butanol (5 mL) was added *N*1-methyl-1-phenyl-1,2-ethanediamine (43.57 mg, 0.29 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 30 minutes, and then potassium carbonate (107.8 mg, 0.78 mmol) and iodine (43.57 mg, 0.33 mmol) were added. The reaction mixture was stirred at 70 °C for 3 h and then quenched by addition of saturated aqueous sodium sulfite solution until the iodine color almost disappeared. The reaction mixture was extracted with chloroform, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel using a mixture of 94 % ethyl acetate, 5 % methanol and 1 % triethylamine as eluant to give 64 mg of the title product as an oil.
^{1}H NMR ($CDCl_3$): δ 1.72-1.87 (m, 2H), 2.15-2.28 (m, 2H), 2.31 (s, 3H), 2.86-2.92 (m, 1H), 2.97 (s, 3H), 3.26-3.37 (m,

2H), 3.62-4.39 (m, 2H), 4.0-4.6 (m, 2H), 4.93-5.05 (m, 2H), 6.31 (s, 1H), 7.30-7.41 (m, 5H), 7.88 (s, 1H).

REFERENCE EXAMPLE 4

Preparation of 4-[4-(4,5-dihydro-3-phenyl-5-isoxazolyl)-2-thiazolyl]-1-[(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetyl]piperidine (Reference Compound 6)

Step A: Preparation of 1,1-dimethylethyl 4-(4-ethenyl-2-thiazolyl)-1- piperidinecarboxylate

[0076] To a cold (-50 °C) suspension of methyltriphenylphosphonium bromide (1.2 g, 3.3 mmol) in tetrahydrofuran (5 mL) was added a solution of sodium bis(trimethyl-silyl)-amide (3.4 mL, 3.4 mmol), and the mixture was stirred for 1 h at room temperature. The resulting cloudy yellow solution was re-cooled to -30 °C, and 1,1-dimethylethyl 4-(4-formyl-2-thiazolyl)-1-piperidinecarboxylate (0.5 g, 1.68 mmol) was added. The resulting slightly yellow solution was stirred at room temperature for 3 h, then diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and purified by column chromatography on silica gel using 15-30 % ethyl acetate in hexanes as eluant to give 471 mg of the title compound as a colorless oil.
^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 1.68 (m, 2H), 2.10 (m, 2H), 2.88 (m, 2H), 3.15 (m, 1H), 4.18 (m, 2H), 5.34 (d, 1H), 6.02 (d, 1H), 6.68 (dd, 1H), 6.99 (s, 1H).

Step B: Preparation of 4-(4-ethenyl-2-thiazolyl)piperidine

[0077] To a solution of 1,1-dimethylethyl 4-(4-ethenyl-2-thiazolyl)-1-piperidinecarboxylate (i.e. the product of Example 4, Step A) (471 mg, 1.6 mmol) in dichloromethane (5 mL) was added a solution of hydrogen chloride in diethyl ether (2.0 M, 7 mL, 14 mmol). The reaction mixture was stirred under nitrogen at room temperature for 4 h, and then 1 N aqueous sodium hydroxide solution was added until pH of the reaction mixture increased to about 10. The resulting mixture was extracted with dichloromethane (2 x). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 302 mg of the title compound as an oil.
^{1}H NMR ($CDCl_3$): δ 1.70 (m, 2H), 1.82 (br s, 1H), 2.12 (br d, 2H), 2.76 (br t, 2H), 3.11 (m, 1H), 3.18 (m, 2H), 5.32 (d, 1H), 6.02 (d, 1H), 6.70 (dd, 1H), 6.99 (s, 1H).

Step C: Preparation of 4-(4-ethenyl-2-thiazolyl)-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine

[0078] To a solution of 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (0.5 g, 2.4 mmol) in dichloromethane (4 mL) was added oxalyl chloride (0.3 mL, 3.6 mmol) and one drop of *N,N*-dimethylformamide, resulting in slight exothermicity. The reaction mixture was then heated at reflux for 15 minutes. The reaction mixture was evaporated, and the resulting residue was suspended in dichloromethane (4 mL) and treated with a solution of 4-(4-ethenyl-2-thiazolyl)piperidine (i.e. the product of Example 4, Step B) (302 mg, 1.5 mmol) in dichloromethane (2 mL), followed by addition of triethylamine (0.32 mL, 2.3 mmol). The reaction mixture was stirred overnight at room temperature, then concentrated, and purified by column chromatography on silica gel using 30-40 % ethyl acetate in hexanes as eluant to give 414 mg of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 1.78 (m, 2H), 2.18 (m, 2H), 2.32 (s, 3H), 2.90 (br t, 1H), 3.30 (m, 2H), 4.03 (d, 1H), 4.55 (d, 1H), 5.00 (m, 2H), 5.35 (d, 1H), 6.02 (d, 1H), 6.33 (s, 1H), 6.68 (dd, 1H), 7.01 (s, 1H).

Step D: Preparation of 4-[4-(4,5-dihydro-3-phenyl-5-isoxazolyl)-2-thiazolyl]-1-[(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetyl]piperidine

[0079] To a solution of benzaldehyde oxime (49 mg, 0.4 mmol) in *N,N*-dimethylformamide (3 mL) was added *N*-chlorosuccinimide (54 mg, 0.4 mmol), followed by addition of 4-(4-ethenyl-2-thiazolyl)-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (i.e. the product of Example 4, Step C) (103 mg, 0.27 mmol) and triethylamine (41 mg, 0.4 mmol). The resulting mixture was stirred at room temperature for 5 h, then diluted with water, and extracted with dichloromethane (2 x). The organic layers were combined and dried ($MgSO_4$), and filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel using 55-70 % ethyl acetate in hexanes as eluant to give 90 mg of the title product as a white solid.
^{1}H NMR ($CDCl_3$): δ 1.76 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.88 (br t, 1H), 3.25 (m, 2H), 3.65 (m, 1H), 3.78 (m, 1H), 4.02 (br d, 1H), 4.56 (br d, 1H), 4.99 (m, 2H), 5.84 (dd, 1H), 6.32 (s, 1H), 7.28 (s, 1H), 7.40-7.42 (m, 3H), 7.69-7.71 (m, 2H).

REFERENCE EXAMPLE 5

Preparation of 1-[4-[4-[5-(2-chlorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 8)

[0080] To a solution of 1-chloro-2-ethenylbenzene (0.035g, 0.25 mmol), triethylamine (2.5 mg, 0.025 mmol) and Clorox® aqueous sodium hypochlorite solution (1 mL, 16.1 mmol) in dichloromethane (5 mL) was added 4-[4-[(hydroxyimino)methyl]-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (i.e. the product of Example 2, Step C) (0.10 g, 0.25 mmol) in dichloromethane (5 mL) dropwise over 1 h at 0 °C. The reaction mixture was allowed to stir for 1 h, then filtered through Celite® diatomaceous filter aid, and concentrated under reduced pressure to give an oil, which was purified by column chromatography on silica gel using 50 % ethyl acetate in hexane as eluant to give 73 mg of the title compound as a white foam, melting at 115-122 °C (crystallized from methyl acetate/petroleum ether).
^{1}H NMR ($CDCl_3$): δ 1.74-1.80 (m, 2H), 2.14-2.22 (m, 2H), 2.32 (s, 3H), 2.85-2.91 (m, 1H), 3.26-3.30 (m, 2H), 3.31-3.32 (m, 1H), 4.05-4.07 (m, 1H), 4.55-4.58 (m, 1H), 4.93-5.03 (q, 2H), 6.01-6.06 (m, 1H), 6.331 (s, 1H), 7.25-7.29 (m, 2H), 7.38-7.40 (m, 1H), 7.56-7.58 (m, 1H), 7.62 (s, 1H).

REFERENCE EXAMPLE 6

Preparation of 1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanethione (Reference Compound 130)

[0081] A solution of 4-[4-[4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-[[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]piperidine (i.e. the product of Example 1, Step B) (235 mg, 0.47 mmol) and phosphorus pentasulfide (104.5 mg, 0.235 mmol) in pyridine (5 ml) was heated at reflux for 2 h. The reaction mixture was then concentrated under reduced pressure, and the residue was partioned between dichloromethane (10 mL) and water (10 mL). The organic layer was washed with 1 N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 240 mg of the title product as a white foam.
^{1}H NMR ($CDCl_3$): δ 1.80-2.00 (m, 2H), 2.20-2.28 (m, 2H), 2.45 (s, 3H), 3.35-3.46 (3H, m), 3.50-3.61 (m, 1H), 3.80-3.88 (m, 1H), 4.70-4.80 (m, 1H), 5.30-5.33 (m, 2H), 5.35-5.40 (m, 1H), 5.74-5.80 (m, 1H), 6.32 (s, 1H), 7.30-7.40 (m, 5H), 7.65 (s, 1H).

REFERENCE EXAMPLE 7

Preparation of 1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperazinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 154)

Step A: Preparation of 1,1-dimethylethyl 4-(aminothioxomethyl)-1-piperazine-carboxylate

[0082] To a solution of thiocarbonyldiimidazole (2.1 g, 11.8 mmol) in tetrahydrofuran (30 mL) at room temperature, was added 1,1-dimethylethyl 1-piperazinecarboxylate (2 g, 10.75 mmol). The reaction mixture was stirred at room temperature for 2 h and then heated to 55 °C for additional 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure until approximately 20 mL of tetrahydrofuran remained. The residue was then treated with a 2 M solution of ammonia in methanol (10 mL) and stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with diethyl ether (25 mL) to give a white precipitate. The precipitate was filtered and dried to give 1.5 g of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 1.39 (s, 9H), 3.32 (m, 4H), 3.73 (m, 4H), 7.49 (br s, 2H).

Step B: Preparation of 3-chloro-*N*-hydroxy-2-oxopropanimidoyl chloride

[0083] To a solution of 1,3-dichloroacetone (100 g, 0.79 mol) in 2 M solution of hydrogen chloride in diethyl ether (400 mL) at 15 °C was added *t*-butyl nitrite (55 g, 0.534 mol) over 10 minutes. The reaction progress was monitored by ^{1}H NMR to obtain ~85 % conversion with no more than 3 % of the bis-nitrosation side product. The reaction mixture was concentrated under reduced pressure to leave a semi-solid, which was then thoroughly rinsed with *n*-BuCl. The resulting solid was collected under filtration to give a 77 g of the title compound as a white solid. The filtrate was further concentrated under reduced pressure to give a semi-solid residue, which was rinsed with additional *n*-BuCl. The resulting solid was collected under filtration to give additional 15 g of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 4.96 (s, 2H), 13.76 (s, 1H).

Step C: Preparation of 2-chloro-1-(4,5-dihydro-5-phenyl-3-isoxazolyl)ethanone

[0084] To a mixture of styrene (6.79 g, 65.3 mmol) and sodium bicarbonate (32.1 g, powder) in acetonitrile (100 mL), 3-chloro-N-hydroxy-2-oxopropanimidoyl chloride (i.e. the product of Example 7, Step B) (10 g, 64.1 mmol) was added in 10 portions over 20 minutes. The reaction mixture was then stirred for an additional 1 h and filtered. The filtered solid was rinsed with acetonitrile, and the combined filtrates were concentrated under reduced pressure to leave an oil, which was triturated first with hexanes and then with 1-chlorobutane to give 13.6 g of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 3.13 (m, 1H), 3.66 (m, 1H), 4.96 (s, 2H), 5.83 (m, 1H), 7.34-7.44 (m, 5H).

Step D: Preparation of 1,1-dimethylethyl 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperazineacetate

[0085] To a solution of 2-chloro-1-(4,5-dihydro-5-phenyl-3-isoxazolyl)ethanone (i.e. the product of Example 7, Step C) (0.450 g, 2.018 mmol) and 1,1-dimethylethyl 4-(amino-thioxomethyl)-1-piperazinecarboxylate (i.e. the product of Example 7, Step A) (0.5 g, 2.04 mmol) in ethanol (10 mL) was added triethylamine (0.204 g, 2.013 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography using 20 % ethyl acetate in petroleum ether as eluant to give 700 mg of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H), 3.30 (m, 1H), 3.54 (m, 8H), 3.74 (m, 1H), 5.71 (m, 1H), 6.91 (s, 1H), 7.40-7.29 (m, 5H).

Step E: Preparation of 1-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-piperazine hydrochloride

[0086] To a solution of 1,1-dimethylethyl 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperazineacetate (i.e. the product of Example 7, Step D) (0.7 g, 1.686 mmol) in diethyl ether (10 mL) was added a 2 M solution of hydrogen chloride in methanol (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 8 h. The resulting white precipitate was filtered and dried to give 500 mg of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 3.21 (m, 4H), 3.27 (m, 1H), 3.68 (m, 4H), 3.79 (m, 1H), 5.68 (m, 1H), 7.41-7.29 (m, 6H), 9.49 (br s, 2H).

Step F: Preparation of 1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperazinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone

[0087] To a solution of 1-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]piperazine hydrochloride (i.e. the product of Example 7, Step E) (200 mg, 0.57 mmol) and 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (0.120 g, 0.57 mmol) in dichloromethane (10 mL) at room temperature was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.110 g, 0.57 mmol), triethylamine (0.086 g, 0.85 mmol) and 1-hydroxybenzotriazole hydrate (0.020 g, 0.14 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography using 3 % methanol in chloroform as eluant to give 180 mg of the title product as a white solid.
^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 3.29 (m, 1H), 3.52 (m, 2H), 3.61 (m, 2H), 3.79-3.72 (m, 5H), 4.98 (m, 2H), 5.69 (m,1H), 6.33 (s, 1H), 6.93 (s, 1H), 7.38-7.28 (m, 5H).
Mass spectrum at 505.5 (M+1).

REFERENCE EXAMPLE 8

Preparation of 1-[4-[4-(3',4'-dihydrospiro[isoxazole-5(4*H*),1',(2'*H*)-naphthalen]-3-yl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 37)

Step A: Preparation of 1-(2-chloroacetyl)-4-piperidinecarbonitrile

[0088] A mixture of 4-piperidinecarbonitrile (200 g, 1.80 mol) and 40 % aqueous potassium carbonate solution (342 g, 0.99 mol) in dichloromethane (1 L) was cooled to -10 °C, and a solution of chloroacetyl chloride (210 g, 1.86 mol) in dichloromethane (300 mL) was added over about 75 minutes while maintaining the reaction mixture at -10 to 0 °C. After the addition was complete, the reaction mixture was separated, the upper aqueous phase was extracted with dichloromethane (2 x 300 mL), and the combined organic phases were concentrated under reduced pressure to give 312 g of the title compound as a liquid which slowly crystallized on standing. This compound was of sufficient purity to use in subsequent reactions.

^{1}H NMR ($CDCl_3$): δ 1.8-2.1 (m, 4H), 2.95 (m, 1H), 3.5-3.8 (m, 4H), 4.08 (q, 2H).

Step A1: Alternative preparation of 1-(2-chloroacetyl)-4-piperidinecarbonitrile

[0089] A solution of *N*-(1,1-dimethylethyl)-4-piperidinecarboxamide (201 g, 1.0 mol) in dichloromethane (1 L) was cooled under nitrogen to -5 °C, and chloroacetyl chloride (124 g, 1.1 mol) in 300 mL of dichloromethane was added dropwise over 30 minutes while maintaining the reaction mixture at 0 to 5 °C. Then 20 % aqueous potassium carbonate solution (450 g, 0.65 mol) was added dropwise over 30 minutes while keeping reaction temperature between 0 and 5 °C. The reaction mixture was stirred for an additional 30 minutes at 0 °C, and then allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with dichloromethane (200 mL). The combined dichloromethane layers were concentrated under reduced pressure to yield a solid, which was triturated with 400 mL of hexanes. The slurry was filtered, and the filter cake was washed with 100 mL of hexanes and dried in a vacuum oven overnight at 50 °C to give 185.5 g of 1-(2-chloroacetyl)-*N*-(1,1-dimethylethyl)-4-piperidinecarboxamide as a solid, melting at 140.5-141.5 °C.

^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.6-2.0 (m, 4H), 2.25 (m, 1H), 2.8 (t, 1H), 3.2 (t, 1H), 3.9 (d, 1H), 4.07 (s, 2H), 4.5 (d, 1H), 5.3 (br s, 1H).

[0090] To a solution of 1-(2-chloroacetyl)-*N*-(1,1-dimethylethyl)-4-piperidinecarboxamide (26.1 g, 0.10 mol) in *N*,*N*-dimethylformamide (35 mL) was added phosphorus oxychloride (18.8 g, 0.123 mol) dropwise over 30 minutes while allowing the temperature of the reaction mixture to rise to 37 °C. The reaction mixture was heated at 55 °C for 1 h and then was slowly added to water (about 150 g) cooled with ice to maintain a temperature of about 10 °C. The pH of the reaction mixture was adjusted to 5.5 with 50 % NaOH aqueous solution. The mixture was extracted with dichloromethane (4 x 100 mL), and the combined extract was concentrated under reduced pressure to give 18.1 g of the title compound as a solid. This compound was of sufficient purity to use in subsequent reactions.

Step B: Preparation of 1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidinecarbonitrile

[0091] A solution of 3-methyl-5-trifluoromethylpyrazole (9.3 g, 62 mmol) and 45 % aqueous potassium hydroxide solution (7.79 g, 62 mmol) in *N*,*N*-dimethylformamide (25 mL) was cooled to 5 °C, and 1-(2-chloroacetyl)-4-piperidinecarbonitrile (i.e. the product of Example 8, Step A or A1) (11.2 g, 60 mmol) was added. The reaction mixture was stirred for 8 h at 5-10 °C, then diluted with water (100 mL), and filtered. The filter cake was washed with water and dried at 50 °C in a vacuum-oven to give 15 g of the title compound as a solid containing 3 % of its regioisomer, i.e. 1-[2-[3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidinecarbonitrile.

^{1}H NMR ($CDCl_3$): δ 1.88 (m, 4H), 2.32 (s, 3H), 2.95 (m, 1H), 3.7 (m, 4H), 5.0 (q, 2H), 6.34 (s, 1H).

Step C: Preparation of 1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidinecarbothioamide

[0092] Hydrogen sulfide gas was passed into a solution of 1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidinecarbonitrile (i.e. the product of Example 8, Step B) (9.0 g, 30 mmol) and diethanolamine (3.15 g, 30 mmol) in *N*,*N*-dimethylformamide (15 mL) at 50 °C in a flask equipped with dry-ice condenser. The hydrogen sulfide feed was stopped when the reaction mixture became saturated with hydrogen sulfide, as indicated by condensation on the cold-finger. The reaction mixture was stirred for an additional 30 minutes at 50 °C. Then excess hydrogen sulfide gas was sparged into the scrubber by a subsurface nitrogen flow, and water (70 mL) was gradually added. The reaction mixture was cooled to 5 °C, filtered, and washed with water (2 x 30 mL). The filter cake was dried at 50 °C in a vacuum-oven to give 8.0 g of the title compound as a solid, melting at 185-186 °C.

^{1}H NMR ($CDCl_3$): δ 1.7 (m, 2H), 2.0 (m, 2H), 2.29 (s, 3H), 2.65 (t, 1H), 3.0 (m, 1H), 3.2 (t, 1H), 4.0 (d, 1H), 4.6 (d, 1H), 4.96 (d, 1H), 5.4 (d, 1H), 6.35 (s, 1H), 7.4 (br s, 1H), 7.5 (br s, 1H).

Step D: Preparation of 1-[4-[4-(3',4'-dihydrospiro[isoxazole-5(4*H*),1',(2'*H*)-naphthalen]-3-yl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone

[0093] A solution of 1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidine-carbothioamide (i.e. the product of Example 8, Step C) (0.5 g, 1.5 mmol), 2-chloro-1-(3',4'-dihydrospiro[isoxazole-5(4*H*),1',(2'*H*)-naphthalen]-3-yl)ethanone (prepared by a method analogous to Example 7, Step C) (0.4 g, 1.5 mmol) and tetrabutylammonium bromide (0.030 g, 0.10 mmol) in tetrahydrofuran (15 mL) was stirred overnight at room temperature and then heated at 55-60 °C for 3 h. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was further purified by medium-pressure liquid chromatography using 50 % ethyl acetate in hexanes as eluant to give 260 mg of the title product as an off-white solid, melting at 81-84 °C.

^{1}H NMR ($CDCl_3$): δ 1.76-1.86 (m, 3H), 2.04-2.08 (m, 2H), 2.16-2.26 (m, 2H), 2.32 (s, 3H), 2.83-2.87 (m, 2H), 2.88-2.93 (m, 1H), 3.27-3.35 (m, 2H), 3.48-3.65 (m, 2H), 4.02-4.06 (m, 1H), 4.55-4.59 (m, 1H), 4.94-5.04 (q, 2H), 6.33 (s, 1H), 7.10-7.12 (m, 1H), 7.19-7.21 (m, 2H), 7.40-7.43 (m, 1H), 7.62 (s, 1H).

[0094] The following compounds were prepared by procedures analogous to Step D of Example 8:

1-[4-[4-(4,5-dihydro-5-methyl-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 15); m.p. 97-100 °C (crystallized from methyl acetate/petroleum ether); ^{1}H NMR ($CDCl_3$): δ 1.74-1.80 (m, 1H), 1.81 (s, 3H), 2.14-2.20 (m, 2H), 2.32 (s, 3H), 2.85-2.91 (m, 1H), 3.26-3.32 (m, 2H), 3.52-3.62 (m, 2H), 4.01-4.05 (m, 1H), 4.54-4.58 (m, 1H), 4.94-5.04 (q, 2H), 6.33 (s, 1H), 7.26-7.29 (m, 1H), 7.35-7.38 (m, 2H), 7.48-7.50 (m, 2H), 7.58 (s, 1H).

2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1-[4-[4-(3*a*,4,5,9*b*-tetrahydro-naphth[2,1-*d*]isoxazol-3-yl)-2-thiazolyl]-1-piperidinyl]ethanone (Reference Compound 16); m.p. 162-165 °C (crystallized from methyl acetate/petroleum ether); ^{1}H NMR ($CDCl_3$): δ 1.79-1.85 (m, 2H), 2.00-2.05 (m, 2H), 2.20-2.26 (m, 2H), 2.33 (s, 3H), 2.68-2.72 (m, 2H), 2.88-2.94 (m, 1H), 3.30-3.35 (m, 2H), 3.92-3.98 (m, 1H), 4.06-4.10 (m, 1H), 4.58-4.60 (m, 1H), 4.94-5.06 (m, 2H), 5.58-5.60 (d, 1H), 6.34 (s, 1H), 7.17-7.20 (m, 1H), 7.28-7.30 (m, 2H), 7.47-7.49 (m, 1H), 7.72 (s, 1H).

1-[4-[4-(2,3-dihydrospiro[1*H*-indene-1,5'(4'*H*)-isoxazol]-3'-yl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 44); ^{1}H NMR ($CDCl_3$): δ 1.77-1.84 (m, 2H), 2.17-2.25 (m, 2H), 2.33 (s, 3H), 2.61-2.68 (m, 1H), 2.90-2.96 (m, 2H), 3.12-3.20 (m, 1H), 3.31-3.35 (m, 2H), 3.54-3.75 (m, 2H), 4.04-4.10 (m, 1H), 4.56-4.60 (m, 1H), 4.94-5.04 (q, 2H), 6.34 (s, 1H), 7.28-7.30 (m, 3H), 7.37-7.38 (m, 1H), 7.64 (s, 1H).

1-[4-[4-[4,5-dihydro-5-(4-methoxyphenyl)-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 18); m.p.t 119-124 °C (crystallized from methyl acetate/petroleum ether); ^{1}H NMR ($CDCl_3$): δ 1.76-1.82 (m, 2H), 2.16-2.24 (m, 2H), 2.32 (s, 3H), 2.86-2.92 (m, 1H), 3.28-3.34 (m, 2H), 3.37-3.43 (m, 1H), 3.76-3.83 (m, 1H), 3.81 (s, 3H), 4.03-4.06 (m, 1H), 4.56-459 (m, 1H), 4.94-5.04 (q, 2H), 5.67-5.72 (m, 1H), 6.33 (s, 1H), 6.89-6.91 (d, 2H), 7.31-7.33 (d, 2H), 7.62 (s, 1H).

REFERENCE EXAMPLE 9

Preparation of 1-[4-[4-(4,5-dihydro-5-(2-pyridinyl)-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 98)

[0095] To a solution of 1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidinecarbothioamide (i.e. the product of Example 8, Step C) (200 mg, 0.6 mmol) in tetrahydrofuran (8 mL) was added 3-chloro-*N*-hydroxy-2-oxopropanimidoyl chloride (i.e. the product of Example 7, Step B) (93 mg, 0.6 mmol), followed by tetrabutylammonium bromide (15 mg, 0.05 mmol). The reaction mixture was heated at 50 °C for 4 h. The reaction mixture was cooled and concentrated under reduced pressure. To the resulting residue, acetonitrile (8 mL) and finely powdered sodium bicarbonate (151 mg, 1.0 mmol) were added followed by 2-ethenylpyridine (63 mg, 0.6 mmol), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on a silica gel (20 g) Varian Bond Elute SI® column using 0 to 75 % ethyl acetate in hexanes as eluant to give 80 mg of the title product as a yellow semi-solid.

^{1}H NMR ($CDCl_3$): δ 1.47-1.62 (m, 1H), 1.70-1.85 (m, 1H), 2.01-2.18 (m, 2H), 2.49 (s. 3H), 2.82 (t, 1H), 3.20-3.42 (m, 2H), 3.73 (dd, 1H), 3.82 (dd, 1H), 3.98 (d, 1H), 4.38 (d, 1H), 5.26 (m, 2H), 5.80 (dd, 1H), 6.50 (s, 1H), 7.38 (dd, 1H), 7.50 (d, 1H), 7.82 (t, 1H), 8.05 (s, 1H), 8.60 (d, 1H).

REFERENCE EXAMPLE 10

Preparation of 2-[5-chloro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]ethanone (Reference Compound 107)

Step A: Preparation of *N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide

[0096] To a solution of 3-trifluoromethylpyrazole (5.0 g, 36 mmol), triethylamine (7.0 mL, 50 mmol) in dichloromethane (40 mL) was added dimethylsulfamoyl chloride (5.5 mL, 51 mmol), and the reaction mixture was heated at reflux for 2 days. The resulting mixture was cooled to ambient temperature and filtered through a pad of silica gel using dichloromethane as eluent. The filtrate was then concentrated under reduced pressure to give an amber residue. The resulting residue was dissolved in diethyl ether. The ether solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give 8.71 g of the title compound.

^{1}H NMR ($CDCl_3$): δ 3.01 (s, 6H), 6.65 (s, 1H), 8.03 (s, 1H).

Step B: Preparation of 5-chloro-*N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide

[0097] A stirred solution of *N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide (i.e. the product of Example 10, Step A) (4.0 g, 16 mmol) in tetrahydrofuran (25 mL) was cooled to -78 °C, and then treated dropwise with 2 M n-butyllithium in cyclohexane (8.6 mL, 17.2 mmol). The reaction mixture was stirred for a further 30 minutes, and then a solution of hexachloroethane (4.2 g, 18 mmol) in tetrahydrofuran (15 mL) was added dropwise. The reaction mixture was stirred for 1 h, warmed to room temperature, and quenched with water (50 mL). The resulting solution was extracted with dichloromethane, dried ($MgSO_4$), and concentrated under reduced pressure to give 4.38 g of title compound. This compound was of sufficient purity to use in subsequent reactions.
^{1}H NMR ($CDCl_3$): δ 3.15 (s, 6 H), 6.58 (s, 1 H).

Step C: Preparation 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole

[0098] A solution of 5-chloro-*N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide (i.e. the product of Example 10, Step B) (4.38 g, 15.8 mmol) and trifluoroacetic acid (2.7 mL, 35 mmol) was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with water (15 mL), and sodium carbonate was added to raise the pH to 12. The solution was extracted with diethyl ether, dried ($MgSO_4$), and concentrated under reduced pressure to give 2.1 g of the title compound. This compound was of sufficient purity to use in subsequent reactions.
^{1}H NMR ($CDCl_3$): δ 6.57 (m, 1 H).

Step D: Preparation of ethyl 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole-1-acetate

[0099] To a suspension of 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole (i.e. the product of Example 10, Step C) (2.1 g, 12.3 mmol) and potassium carbonate (3.6 g, 26.0 mmol) in 20 mL of *N*,*N*-dimethylformamide was added ethyl bromoacetate (2.1 mL, 18.8 mmol), and the resulting mixture was stirred at room temperature for 12 h. The resulting mixture was diluted with ethyl acetate, washed with water, and dried ($MgSO_4$). The reaction mixture was concentrated under reduced pressure and further purified by medium-pressure liquid chromatography using 0-50% of ethyl acetate in hexanes as eluant to give 940 mg of the title compound as an oil.
^{1}H NMR ($CDCl_3$): δ 1.29 (m, 3 H), 4.27 (q, 2 H), 4.96 (m, 2 H), 6.55 (s, 1 H).

Step D1: Alternative preparation of ethyl 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole-1-acetate

[0100] To a solution of aluminum chloride (3.0 g, 22.5 mmol) in dichloromethane (100 mL) was added dropwise a solution of trifluoroacetyl chloride (3 g, 22.6 mmol) in dichloromethane (5 mL) while keeping the temperature of the reaction mixture below -30 °C. The reaction mixture was stirred for 15 minutes at -50 °C. Then a solution of vinylidene chloride (2.2 g, 22.7 mmol) in dichloromethane (10 mL) was added dropwise over 2 h to the reaction mixture. The reaction mixture was stirred an additional 2 h at -50 °C and then warmed gradually to room temperature. The reaction mixture was diluted with water, and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give 4,4-dichloro-1,1,1-trifluoro-3-buten-2-one as an oil which was used for the next step without further purification.
^{1}H NMR ($CDCl_3$): δ 5.30 (s, 1H).
^{19}F NMR ($CDCl_3$): δ -63.6.

[0101] To a mixture of ethyl hydrazinoacetate hydrochloride (2.8 g, 18.1 mmol) and triethylamine (9.2 g, 91 mmol) in a solution of ethanol (20 mL) and *N*,*N*-dimethylformamide (1 mL), a solution of crude 4,4-dichloro-1,1,1-trifluoro-3-buten-2-one in dichloromethane (20 mL) was added dropwise while keeping the temperature of the reaction mixture below 10 °C. After stirring a further 2 h at below 10 °C, the reaction mixture was concentrated under reduced pressure. The residue was diluted with diethyl ether, and the mixture was filtered. The resulting filtrate was concentrated to give 4.34 g of the title compound as a solid. This compound was of sufficient purity to use in subsequent reactions.
^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H), 4.27 (q, 2H), 4.97 (s, 1H), 6.55 (s, 1H).
19F NMR ($CDCl_3$) δ -63.4.

Step E: Preparation of 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid

[0102] A solution of ethyl 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole-1-acetate (i.e. the product of Example 10, Step D or D1) (218 mg, 0.85 mmol) in tetrahydrofuran (1 mL) was treated with a 50 wt. % aqueous solution of sodium hydroxide (0.2 mL) in water (0.6 mL). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was treated with concentrated aqueous hydrochloric acid to lower the pH to 1 and then extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated under pressure to give 140 mg of the title compound. This compound was

of sufficient purity to use in subsequent reactions.
^{1}H NMR (DMSO-d_6): δ 5.41 (s, 2H), 7.09 (s, 1H).

Step F: Preparation of 2-[5-chloro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]ethanone

[0103] To a solution of 1,1-dimethylethyl 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinecarboxylate (i.e. the product of Example 1, Step A) (1.026 g, 2.48 mmol) in ethanol (10 mL) was added a 2 M solution of hydrogen chloride in diethyl ether (4.2 mL, 12.6 mmol). The reaction mixture was stirred at room temperature overnight. Then the reaction mixture was heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to give 0.710 g of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidine hydrochloride as a white solid.

[0104] To 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (i.e. the product of Example 10, Step E) (0.14 g, 0.61 mmol) in dichloromethane (5 mL) was added *N*,*N*-dimethylformamide (1 drop) followed by oxalyl chloride (0.07 mL, 0.80 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. The resulting crude 5-chloro-3-(trifluoromethyl)-1*H*-pyrazole-1-acetyl chloride was taken up in 5 mL of dichloromethane, and the resulting solution was added dropwise to a mixture of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidine hydrochloride (0.20 g, 0.57 mmol) prepared above and triethylamine (0.40 mL, 2.85 mmol) in 10 mL of dichloromethane at 0 °C. The reaction mixture was stirred overnight at room temperature and then diluted with 1 N aqueous hydrochloric acid solution. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure and purified by medium-pressure liquid chromatography using ethyl acetate in hexanes as eluant to give 40 mg of the title product as a solid, melting at 128-131 °C.
^{1}H NMR ($CDCl_3$): δ 1.81 (m, 2H), 2.20 (m, 2H), 2.89 (m, 1H), 3.31 (m, 2H), 3.46 (m, 1H), 3.87 (m, 2H), 4.55 (m, 1H), 5.08 (M, 2H), 5.75 (m, 1H), 6.54 (s, 1H), 7.25-7.42 (m, 5H), 7.63 (s, 1H).

REFERENCE EXAMPLE 11

Preparation of 2-[5-bromo-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]ethanone (Reference Compound 126)

Step A: Preparation of 5-bromo-*N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide

[0105] A stirred solution of *N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide (i.e. the product of Example 10, Step A) (4.25 g, 17.5 mmol) in tetrahydrofuran (50 mL) was cooled to -78 °C, and then 2 M *n*-butyllithium in cyclohexane (10.0 mL, 20.0 mmol) was added dropwise. The reaction mixture was stirred a further 30 minutes, and then bromine (1.0 mL, 3.1 g, 18.7 mmol) was added dropwise. The reaction mixture was stirred for 10 minutes, warmed to room temperature, and quenched with brine (50 mL). The resulting mixture was extracted with diethyl ether, and the extract was dried ($MgSO_4$), and concentrated under reduced pressure to give 6.77 g of title compound as a light yellow oil. This compound was of sufficient purity to use in subsequent reactions.
^{1}H NMR ($CDCl_3$): δ 3.15 (s, 6H), 6.69 (s, 1H).

Step B: Preparation 5-bromo-3-(trifluoromethyl)-1*H*-pyrazole

[0106] A solution of 5-bromo-*N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazole-1-sulfonamide (i.e. the product of Example 11, Step A) (4.50 g, 14.0 mmol) and trifluoroacetic acid (2.0 mL, 26 mmol) was stirred at 25 °C for 4 h. The reaction mixture was diluted with water (20 mL), and sodium hydroxide was added to raise the pH to 12. The solution was extracted with chloroform, dried ($MgSO_4$), and concentrated under reduced pressure to give 2.73 g of the title compound as a yellow light oil. This compound was of sufficient purity to use in subsequent reactions.
^{1}H NMR ($CDCl_3$): δ 6.63 (m, 1H).

Step C: Preparation of ethyl 5-bromo-3-(trifluoromethyl)-1*H*-pyrazole-1-acetate

[0107] A suspension of 5-bromo-3-(trifluoromethyl)-1*H*-pyrazole (i.e. the product of Example 11, Step B) (2.73 g, 12.7 mmol) and potassium carbonate (2.0 g, 14.5 mmol) in *N*,*N*-dimethylformamide (20 mL) was treated with ethyl iodoacetate (3.0 ml, 25.3 mmol), and the resulting mixture was stirred at 95 °C for 3 h. The resulting mixture was diluted with ethyl acetate, washed with water, and dried ($MgSO_4$). The reaction mixture was concentrated under reduced pressure and further purified by medium-pressure liquid chromatography using 0-50 % of ethyl acetate in hexanes as eluant to give 2.84 g of the title compound as a brown oil.

^{1}H NMR ($CDCl_3$): δ 1.29 (m, 3H), 4.26 (q, 2H), 5.00 (m, 2H), 6.64 (s, 1H).

Step D: Preparation of 5-bromo-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid

[0108] A solution of ethyl 5-bromo-3-(trifluoromethyl)-1*H*-pyrazole-1-acetate (i.e. the product of Example 11, Step C) (2.84 g, 9.4 mmol) in tetrahydrofuran (10 mL) was treated with a 50 wt. % aqueous sodium hydroxide solution (1.0 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was treated with concentrated aqueous hydrochloric acid to lower the pH to 1 and then extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated under pressure to give 2.26 g of the title compound as a light brown solid. Recrystallization from 1-chlorobutane (20 mL) gave 0.68 g of the title compound as lustrous light pink plates.
^{1}H NMR ($CDCl_3$): δ 5.08 (s, 2H), 6.65 (s, 1H).

Step E: Preparation of 2-[5-bromo-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-1-[4-[4-(4,5-dihydro-5 -phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidinyl]ethanone

[0109] To a solution of 5-bromo-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (i.e. the product of Example 11, Step D) (0.12 g, 0.61 mmol) in dichloromethane (5 mL) was added *N,N*-dimethylformamide (1 drop) followed by oxalyl chloride (0.25 mL, 2.86 mmol). The reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue containing crude acid chloride was taken up in dichloromethane (5 mL), and the solution was added dropwise to a mixture of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1-piperidine hydrochloride (i.e. the intermediate of Example 10, Step F) (0.15 g, 0.43 mmol) and triethylamine (0.25 mL, 1.8 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred overnight at room temperature. The mixture was then partitioned between 1.0 N aqueous hydrochloric acid solution and dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), concentrated under reduced pressure, and purified by medium-pressure liquid chromatography using ethyl acetate in hexanes as eluant to give 90 mg of the title product as an amorphous solid.
^{1}H NMR ($CDCl_3$): δ 1.84 (m, 2H), 2.20 (m, 2H), 2.89 (m, 1H), 3.31 (m, 2H), 3.46 (m, 1H), 3.89 (m, 2H), 4.58 (m, 1H), 5.11 (m, 2H), 5.75 (m, 1H), 6.63 (s, 1H), 7.25-7.42 (m, 5H), 7.66 (s, 1H).

REFERENCE EXAMPLE 12

Preparation of 1-[4-[4-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 3)

Step A: Preparation of 4,5-dihydro-*N*,*N*-dimethyl-5-phenyl-3-isoxazolecarboxamide

[0110] To a solution of 2-(dimethylamino)-*N*-hydroxy-2-oxoethanimidoyl chloride (prepared according to the procedure of E. Raleigh, U.S. Patent 3,557,089) (6.0 g, 40 mmol) and styrene (6.0 g, 60 mmol) in toluene (15 mL) was added a solution of potassium hydrogen carbonate (5.0 g, 50 mmol) in water (25 mL) over 1 h, while keeping the reaction temperature between 7 and 10 °C. The reaction mixture was diluted with 10 mL of toluene and stirred for an additional 10 minutes. The organic layer was separated and washed with water. The organic layer was concentrated under reduced pressure until no styrene remained to give 8.7 g of the title compound as a light yellow oil. This compound was of sufficient purity to use in subsequent reactions.
^{1}H NMR ($CDCl_3$): δ 3.08 (s, 3H), 3.32 (s, 3H), 3.35 (dd, 1H), 3.71 (dd, 1H), 5.65 (dd, 1H), 7.35 (m, 5H).

Step B: Preparation of 4,5-dihydro-5-phenyl-3-isoxazolecarboxylic acid

[0111] To a solution of 4,5-dihydro-*N*,*N*-dimethyl-5-phenyl-3-isoxazolecarboxamide (i.e. the product of Example 12, Step A) (60.0 g, 275 mmol) in methanol (300 mL) was added an aqueous sodium hydroxide solution (44 g of 50 wt. % aqueous NaOH in 50 mL of water) dropwise over 30 minutes while maintaining the temperature of the reaction mixture at 45 °C. The reaction mixture was allowed to cool to room temperature and stirred overnight. The resulting mixture was concentrated under reduced pressure and treated with 200 mL of water. The pH of the reaction mixture was adjusted using concentrated hydrochloric acid to about 1.0. The crude product was extracted into ethyl acetate (200 mL). The ethyl acetate solution was concentrated under reduced pressure, and the residue was triturated with hexanes. The resulting precipitate was filtered, washed with hexanes (2 x 20 mL), and dried under vacuum to give 46.5 g of the title compound as a solid.
^{1}H NMR ($CDCl_3$): δ 3.25 (dd, 1H), 3.75 (dd, 1H), 5.85 (dd, 1H), 7.35 (m, 5H), 8.1 (br s, 1H).

Step C: Preparation of the cinchonine salt of (5*R*)-4,5-dihydro-5-phenyl-3-isoxazolecarboxylic acid

[0112] A mixture of racemic 4,5-dihydro-5-phenyl-3-isoxazolecarboxylic acid (i.e. the product of Example 12, Step B) (9.5 g, 50 mmol) in methanol (70 mL) was heated to 55 °C, and cinchonine (containing about 15 % dihydrocinchonine, 14.5 g, 50 mmol) was added over 20 minutes while keeping the temperature of the reaction mixture between 53 and 57 °C. The reaction mixture was allowed to cool to room temperature over 60 minutes, and then water (35 mL) was added dropwise over 30 minutes. The resulting slurry was cooled to 10 °C and filtered. The filter cake was washed twice with 10 mL of 25 % methanol in water, and air dried to give 8.52 g of the title compound as a solid. The diastereomeric ratio of the product was determined using chiral high performance liquid chromatography (HPLC) analysis on a Daicel Chiralcel® OD HPLC column to be about 99:1.
^{1}H NMR ($CDCl_3$): δ 3.25 (dd, 1H), 3.75 (dd, 1H), 5.85 (dd, 1H), 7.35 (m, 5H), 8.1 (br s, 1H).

Step D: Preparation of (5*R*)-4,5-dihydro-*N*,*N*-dimethyl-5-phenyl-3-isoxazole-carboxamide

[0113] The cinchonine salt of (5*R*)-4,5-dihydro-5-phenyl-3-isoxazolecarboxylic acid (i.e. the product of Example 12, Step C) (98 % diastereomeric excess, 16.5 g, 34.3 mmol) was slurried in a mixture of 1 N hydrochloric acid (90 mL), cyclohexane (100 mL) and ethyl acetate (40 mL). After all the solids dissolved, the phases were separated, and the organic layer was washed with brine (20 mL) and concentrated under reduced pressure to give 5.6 g of white solid. To a solution of the resulting free acid (5.0 g, 26.2 mmol) in ethyl acetate (100 mL) at room temperature was added *N*,*N*-dimethylformamide (1 drop) followed by thionyl chloride (4.25 g, 35.7 mmol). The reaction mixture was then heated under reflux for 3 h. The resulting mixture was cooled and concentrated under reduced pressure. The residue containing crude acid chloride was dissolved in ethyl acetate (25 mL), and this solution was added in portions to a pre-cooled (5 °C) mixture of dimethylamine in tetrahydrofuran (29 mL of a 2.0 M solution), while maintaining the temperature of the mixture at 5-10 °C. When the addition was complete, the reaction mixture was concentrated under reduced pressure, and diluted with water (50 mL). The resulting precipitate was filtered, washed with water and suction-dried overnight to give 4.1 g of the title compound as a light tan solid, melting at 59-61 °C. This compound was of sufficient purity to use in subsequent reactions.

Step E: Preparation of 2-bromo-1-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazolyl]ethanone

[0114] A solution of (5*R*)-4,5-dihydro-*N*,*N*-dimethyl-5-phenyl-3-isoxazole-carboxamide (i.e. the product of Example 12, Step D) (3.5 g, 16.0 mmol) in a mixture of tetrahydrofuran (5 mL) and toluene (10 mL) was cooled to -15 °C, and methyl magnesium bromide (3.0 M solution in tetrahydrofuran, 8.8 mL, 26.4 mmol) was added over 1 h at -15 °C. Then the reaction mixture was poured over a mixture of 20 g of concentrated hydrochloric acid and 80 g of ice, and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (100 mL), and the combined extract was washed with brine (40 mL) and concentrated under reduced pressure to give 3.2 g of 1-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazoyl]ethanone.
^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 3.17 (dd, 1H), 3.54 (dd, 1H), 5.75 (dd, 1H), 7.35 (m, 5H).
[0115] 1-[(SR)-4,5-dihydro-5-phenyl-3-isoxazoyl]ethanone (3.2 g, 16.7 mmol) was dissolved in 1,2-dichloroethane (15 mL), and a solution of bromine (2.13 g, 13.3 mmol) in dichloroethane (5 mL) was added over 30 minutes while maintaining the temperature of the reaction mixture at about 30 °C. The reaction mixture was diluted with water (10 mL), and the organic layer was concentrated under reduced pressure and purified by medium-pressure liquid chromatography using 35 % of dichloromethane in hexanes as eluant to give 2.6 g of the title compound as a white solid, melting at 31-33 °C.
^{1}H NMR ($CDCl_3$): δ 3.20 (dd, 1H), 3.60 (dd, 1H), 4.49 (s, 2H), 5.80 (dd, 1H), 7.35 (m, 5H).

Step E1: Preparation of 2-bromo-1-(4,5-dihydro-5-phenyl-3-isoxazolyl)ethanone (racemate)

[0116] To a solution of 4,5-dihydro-*N*,*N* dimethyl-5-phenyl-3-isoxazolecarboxamide (i.e. the product of Example 12, Step A) (17 g, 78.0 mmol) in a mixture of tetrahydrofuran (20 mL) and toluene (80 mL) was added methyl magnesium bromide (3.0 M solution in tetrahydrofuran, 28 mL, 84 mmol) over 1 h, while keeping the reaction temperature between -10 and -15 °C. The reaction mixture was poured over a mixture of concentrated hydrochloric acid (20 g) and ice (80 g), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic extracts were washed with brine (40 mL) and concentrated under reduced pressure to give 14.4 g of 1-(4,5-dihydro-5-phenyl-3-isoxazoyl)ethanone as a light yellow oil.
^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 3.17 (dd, 1H), 3.54 (dd, 1H), 5.75 (dd, 1H), 7.35 (m, 5H).
[0117] 1-(4,5-Dihydro-5-phenyl-3-isoxazoyl)ethanone (11.5 g, 60 mmol) was dissolved in ethyl acetate (45 mL), and a solution of bromine (9.6 g, 60.0 mmol) in ethyl acetate (30 mL) was added over 30 minutes while maintaining the temperature of the reaction mixture at about 30 °C. After 1 h, the reaction mixture was diluted with water (10 mL), and

the organic layer was concentrated under reduced pressure to give 16.7 g of reddish oil which contained about 10 % starting methyl ketone and ~10 % dibrominated ketone.
^{1}H NMR ($CDCl_3$) δ 3.20 (dd, 1H), 3.60 (dd, 1H), 4.49 (s, 2H), 5.80 (dd, 1H), 7.35 (m, 5H).

Step F: Preparation of 1-[4-[4-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone

[0118] A mixture of 1-[2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl]-4-piperidine-carbothioamide (i.e. the product of Example 8, Step C) (1.7 g, 5.0 mmol) and 2-bromo-1-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazolyl]ethanone (i.e. the product of Example 12, Step E) (1.35 g, 5 mmol) in ethanol (15 mL) was heated at 50 °C for 30 minutes. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the title product as a pale-yellow gum. High performance liquid chromatography (HPLC) analysis showed that the title product was about 95 % pure and contained the (R)-enantiomer in about 98 % enantiomeric excess.
^{1}H NMR ($CDCl_3$): δ 1.8 (m, 2H), 2.2 (m, 2H), 2.32 (s, 3H), 2.9 (m, 1H), 3.3 (m, 2H), 3.42 (dd, 1H), 3.82 (dd, 1H), 4.05 (m, 1H), 4.6 (m, 1H), 5.0 (q, 2H), 5.78 (dd, 1H), 6.35 (s, 1H), 7.4 (m, 5H), 7.62 (s, 1H).

REFERENCE EXAMPLE 13

Preparation of 1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-3,6-dihydro-1(2*H*)-pyridinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (Reference Compound 217)

Step A: Preparation of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]pyridine

[0119] To a solution of thioisonicotinamide (0.5 g, 3.6 mmol) in 1-methyl-2-pyrrolidinone (25 mL) was added 2-chloro-1-(4,5-dihydro-5-phenyl-3-isoxazolyl)ethanone (0.807 g, 3.6 mmol), at room temperature. The reaction mixture was then heated to 100 °C for 3 h. Then the reaction mixture was cooled to room temperature, quenched with water (100 mL) and extracted with ethyl acetate (50 mL x 2). The reaction mixture was diluted with water (50 mL) and brine (50 mL), and the organic layer was concentrated under reduced pressure and purified by medium-pressure liquid chromatography using 2 % of methanol in chloroform as eluant to give 0.7 g of the title compound as a brown solid.
^{1}H NMR ($CDCl_3$): δ 3.5 (m, 1H), 3.9 (m, 1H), 5.8 (m, 1H), 7.35 (m, 5H), 8.16 (s, 1H), 8.3 (d, 2H), 8.8 (d, 2H).

Step B: Preparation of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1,2,3,6-tetrahydro-1-(phenylmethyl)pyridine

[0120] To a solution of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]pyridine (i.e. the product of Example 13, Step A) (0.60 g, 1.95 mmol) in toluene (10 mL) was added benzyl bromide (0.670 g, 3.90 mmol), and the reaction mixture was heated to 100 °C for 12 h. Then the reaction mixture was cooled to room temperature. The solid that precipitated out was filtered and dried. The solid was dissolved in methanol (10 mL), and sodium borohydride (0.072 g, 1.95 mmol) was added in portions. The reaction mixture was stirred at room temperature for 2 h, diluted with water (50 mL), neutralized with 1.5 N aqueous hydrochloric acid solution, and extracted with ethyl acetate (50 mL). The organic layer was separated, washed with brine (25 mL), and concentrated under reduced pressure. The residue was purified by medium-pressure liquid chromatography using 3 % of methanol in chloroform as eluant to give 0.4 g of the title compound as a white solid.
^{1}H NMR ($CDCl_3$): δ 3.03-3.1 (m, 2H), 3.4-3.6 (m, 4H), 3.8-4.0 (m, 2H), 4.25-4.32 (m, 2H), 5.76-5.79 (m, 1H), 6.47 (s, 1H), 7.34-7.48 (m, 10H), 7.72 (s, 1H).

Step C: Preparation of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1,2,3,6-tetrahydropyridine hydrochloride

[0121] To a solution of 4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1,2,3,6-tetrahydro-1-(phenylmethyl)pyridine (i.e. the product of Example 13, Step B) (0.400 g, 0.99 mmol) in dichloroethane (10 mL) was added 1-chloroethyl chloroformate (0.286 g, 1.99 mmol), and the reaction mixture was heated to 80 °C for 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Methanol (10 mL) was added to the residue, and the resulting mixture was heated to 60 °C for 1 h, cooled to room temperature, and concentrated under reduced pressure. The residue was triturated with 50 % of petroleum ether in ethyl acetate, and the solid formed was filtered and dried to give 0.25 g of the title compound as a white solid.
^{1}H NMR (DMSO-d_6): δ 2.50-2.55 (m, 2H), 3.31-3.39 (m, 3H), 3.86-3.91 (m, 3H), 5.73-5.78 (m, 1H), 6.67 (s, 1H), 7.34-7.39 (m, 5H), 7.68 (s, 1H), 9.47 (s, 2H).

Step D: Preparation of 1-[4-[4-(4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-3,6-dihydro-1(2*H*)-pyridinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone

[0122] To a solution of 4-[4-(-4,5-dihydro-5-phenyl-3-isoxazolyl)-2-thiazolyl]-1,2,3,6 tetrahydropyridine hydrochloride (i.e. the product of Example 13, Step C) (0.250 g, 0.720 mmol) and 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole-1-acetic acid (0.150 g, 0.720 mmol) in dichloromethane (10 mL) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (0.138 g, 0.720 mmol), 1-hydroxybenzotriazole (0.024 g, 0.177 mmol), and triethylamine (0.145 g, 1.44 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure and purified by medium-pressure liquid chromatography using 3 % methanol in chloroform as eluant to give 200 mg of the title product as a white solid.
^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H), 2.71-2.75 (m, 2H), 3.42-3.46 (m, 1H), 3.74-3.88 (m, 3H), 4.24-4.27 (m, 2H), 5.02 (s, 2H), 5.71-5.76 (m, 1H), 6.32 (s, 1H), 6.57 (s, 1H), 7.3-7.38 (m, 5H), 7.64 (s, 1H).

REFERENCE EXAMPLE 14

Preparation of 1-[4-[4-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-*N*-[2,5-dimethylphenyl]carboxamide (Reference Compound 343)

Step A: Preparation of 4-cyano-*N*-(2,5-dimethylphenyl)piperidinecarboxamide

[0123] A solution of 4-cyanopiperidine (11.0 g, 100 mmol) in diethyl ether (350 mL) was cooled to 0 °C with an ice-water bath. A solution of 2,5-dimethylphenyl isocyanate (14.7 g, 100 mmol) in diethyl ether (50 mL) was added into the reaction mixture over 30 minutes to give a thick precipitate. The reaction mixture was warmed to room temperature, and the resulting solids were filtered, washed with diethyl ether and air-dried to give 25.3 g of the title compound as a white powder, melting at 187-190 °C.
^{1}H NMR ($CDCl_3$): δ 1.95 (m, 4H), 2.19 (s, 3H), 2.30 (s, 3H), 2.90 (m, 1H), 3.45 (m, 2H), 3.70 (m, 2H), 6.10 (br s, 1H), 6.85 (m, 1H), 7.04 (m, 1H), 7.37 (m, 1H).

Step B: Preparation of *N*-(2,5-dimethylphenyl)-4-thiocarbamoylpiperidine-carboxamide

[0124] A mixture of 4-cyano-*N*-(2,5-dimethylphenyl) piperidinecarboxamide (i.e. the product of Example 14, Step A) (12.75 g, 49.6 mmol), sodium hydrosulfide hydrate (11.1 g, 150 mmol) and diethylamine hydrochloride (10.9 g, 100 mmol) in *N,N*-dimethylformamide (50 mL) was stirred at room temperature for 3 days. The resulting thick, green suspension was added dropwise into ice water (600 mL). The resulting solid was filtered, washed with water and air-dried to give 12.5 g of the title compound as a tan solid decomposing at 155-156 °C.
^{1}H NMR (DMSO-d_6): δ 1.67 (m, 4H), 2.10 (s, 3H), 2.23 (s, 3H), 2.75 (m, 3H), 4.15 (m, 2H), 6.85 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.95 (br s, 1H), 9.15 (br s, 1H), 9.22 (br s, 1H).

Step C: Preparation of 1-[4-[4-[(5*R*)-4,5-dihydro-5-phenyl-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-*N*-[2,5-dimethylphenyl]carboxamide

[0125] A mixture of *N*-(2,5-dimethylphenyl)-4-thiocarbamoylpiperidine carboxamide (i.e. the product of Example 14, Step B) (291 mg, 1.0 mmol) and 409 (i.e. the product of Example 12, Step E) (268 mg, 1.0 mmol) in acetone (10 mL) was vortexed for 16 h and then heated at 45 °C for 1 h. The reaction mixture was allowed to cool to room temperature, treated with solid sodium bicarbonate (168 mg, 2.0 mmol), and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure, diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the title product as a pale-yellow foam. The sample was dissolved in methyl acetate (2 mL) and allowed to sit at room temperature and then at 0 °C to give 220 mg of colorless crystals melting at 120-125°C. A second preparation was crystallized from methanol to give large prisms melting at 121-124 °C.
^{1}H NMR ($CDCl_3$): δ 1.85 (m, 2H), 1.99 (m, 2H), 2.21 (s, 3H), 2.31 (s, 3H), 3.08 (m, 2H), 3.25 (m, 1H), 3.42 (dd, 1H), 3.82 (dd, 1H), 4.15 (m, 2H), 5.78 (dd, 1H), 6.12 (br s, 1H), 6.82 (m, 1H), 7.02 (m, 1H), 7.2 - 7.4 (m, 5H), 7.46 (m, 1H), 7.62 (s, 1H).

REFERENCE EXAMPLE 15

Preparation of 2-(3,5-dibromo-1*H*-1,2,4-triazol-1-yl)-1-[4-[4-[5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]ethanone (Reference Compound 409)

Step A: Preparation of 3,5-dibromo-1*H*-1,2,4-triazole

[0126] To a solution of 13.8 g (200 mmol) of 1,2,4-triazole in a mixture of water (150 mL) and dichloromethane (20 mL) was added simultaneously sodium hydroxide (48 g of 50 % aqueous solution, 600 mmol) in water (50 mL) and bromine (65.0 g, 406 mmol) in dichloromethane (20 mL) cooled with an ice-bath over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting thick white suspension was acidified with 6 N hydrochloric acid (40 mL, 240 mmol) with cooling in an ice-bath, and stirring was continued for 1 h. The reaction mixture was filtered on a Buchner funnel, and the collected solid was air dried for 5 days to give 41.92 g of the title compound as a pure white solid melting at 213-217 °C.

Step B: Preparation of 3,5-dibromo-1*H*-1,2,4-triazole-1-acetic acid

[0127] A solution of 3,5-dibromo-1*H*-1,2,4-triazole (i.e. the product of Example 15, Step A) (4.54 g, 20.0 mmol) in acetonitrile (20 mL) was treated with potassium carbonate (5.0 g) and ethyl bromoacetate (4.52 g, 27.0 mmol). The reaction mixture was heated at reflux for 4 h and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate (150 mL), filtered, washed with water, 1 N hydrochloric acid and saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). The resulting mixture was filtered and concentrated under reduced pressure to give 6.19 g of ester compound as a pale yellow oil. The ester compound in tetrahydrofuran (40 mL) was treated with 2 N aqueous sodium hydroxide (20 mL) and stirred at room temperature for 3 h. The reaction mixture was cooled in an ice bath and acidified with 6 N hydrochloric acid (10 mL). The resulting mixture was extracted with ether (200 mL), and the separated organic layer was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered and concentrated to give 6.38 g of the title compound as a pale yellow oil. The crude product was triturated with hot n-butyl chloride (100 mL). The mixture was cooled to room temperature and filtered to give 3.77 g of the title compound as a white solid melting at 147-152 °C.
^{1}H NMR ($CDCl_3$): δ 5.00 (s, 2 H).

Step C: Preparation of 2-(3,5-dibromo-1*H*-1,2,4-triazol-1-yl)-1-[4-[4-[5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl] ethanone

[0128] A mixture of 3,5-dibromo-1*H*-1,2,4-triazole-1-acetic acid (i.e. the product of Example 15, Step B) (430 mg, 1.51 mmol) in thionyl chloride (10 mL) was heated at reflux for 1 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting crude acid chloride was dissolved in dichloromethane (5 mL) and added to a solution of 4-[4-[4,5-dihydro-5-(2,6-difluorophenyl)-3-isoxazolyl]-2-thiazolyl]piperidine hydrochloride (prepared by a method analogous to Example 10, Step F) (585 mg, 1.52 mmol) and triethylamine (1 mL) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane, washed with 1 N hydrochloric acid, aqueous sodium chloride, and dried (MgSO4). The reaction mixture was concentrated under reduced pressure and further purified by medium-pressure liquid chromatography to give 338 mg of the title product as a white solid melting at 185-189 °C.
^{1}H NMR ($CDCl_3$): δ 1.90 (m, 2H), 2.27 (m, 2H), 2.97 (m, 1H), 3.33 (m, 2H), 3.64 (m, 1H), 3.81 (m, 2H), 4.57 (m, 1H), 5.03 (s, 2H), 6.09 (m, 1H), 6.92 (m, 2H), 7.31 (m, 1H), 7.68 (s, 1H).

REFERENCE EXAMPLE 16

Preparation of 2-(3,5-dichloro-1*H*-1,2,4-triazol-1-yl)-1-[4-[4-[5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]ethanone (Reference Compound 410)

Step A: Preparation of 3,5-dichloro-1*H*-1,2,4-triazole

[0129] To a solution of concentrated aqueous hydrochloric acid (50 mL) in an ice (50 mL) was added 3,5-diamino-1,2,4-triazole (2.10 g, 21.2 mmol) and sodium nitrite (4.4 g, 63.7 mmol) sequentially over a period of 15 minutes. The reaction mixture was stirred for 1 h and warmed to room temperature. The reaction mixture was extracted with ether (300 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and concentrated to give 2.75 g of the title compound as a light yellow solid suitable for use in subsequent reactions.

Step B: Preparation of 3,5-dichloro-1*H*-1,2,4-triazole-1-acetic acid

[0130] A solution of 3,5-dichloro-1*H*-1,2,4-triazole (i.e. the product of Example 16, Step A), (2.75 g , 19.6 mmol) in ethanol (25 mL) was treated with potassium carbonate (2.0 g) and ethyl bromoacetate (4.52 g, 27.0 mmol). The reaction mixture was heated at reflux for 1 h and then cooled to room temperature. The reaction mixture was diluted with water (100 mL) and extracted with ether (150 mL). The combined organic layers were washed with saturated aqueous sodium chloride and dried ($MgSO_4$). The resulting mixture was filtered and concentrated under reduced pressure to give 3.69 g of ester compound as a pale yellow oil. The ester compound in tetrahydrofuran (75 mL) was treated with 2 N aqueous sodium hydroxide (20 mL) and stirred at room temperature for 2 h. The reaction mixture was cooled in an ice bath and acidified with 1 N hydrochloric acid (35 mL). The resulting mixture was extracted with ether (200 mL), and the separated organic layer was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered and concentrated to give 2.51 g of the title compound a colorless oil.
^{1}H NMR ($CDCl_3$): δ 4.96 (s, 2 H).

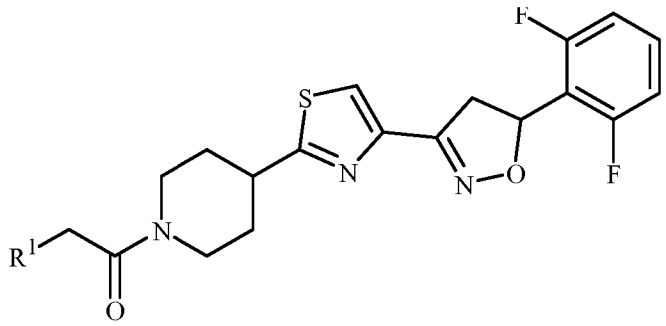
Step C: Preparation of 2-(3,5-dichloro-1*H*-1,2,4-triazol-1-yl)-1-[4-[4-[5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-ethanone

[0131] A mixture of 3,5-dichloro-1*H*-1,2,4-triazole-1-acetic acid (i.e. the product of Example 16, Step B), (114 mg, 0.58 mmol) in thionyl chloride (5 mL) was heated at reflux for 1 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting crude acid chloride was dissolved in dichloromethane (5 mL) and added to a solution of 4-[4-[4,5-dihydro-5-(2,6-difluorophenyl)-3-isoxazolyl]-2-thiazolyl]piperidine hydrochloride (196 mg, 0.51 mmol) and triethylamine (0.5 mL) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 3 h, diluted with dichloromethane, washed with 1 N hydrochloric acid, aqueous sodium chloride, and dried ($MgSO_4$). The reaction mixture was concentrated under reduced pressure and further purified by medium-pressure liquid chromatography to give 80 mg of the title product as a white solid melting at 147-150 °C.
^{1}H NMR ($CDCl_3$): δ 1.89 (m, 2H), 2.26 (m, 2H), 2.95 (m, 1H), 3.34 (m, 2H), 3.62 (m, 1H), 3.80 (m, 2H), 4.57 (m, 1H), 4.98 (s, 2H), 6.08 (m, 1H), 6.92 (m, 2H), 7.32 (m, 1H), 7.67 (s, 1H).

[0132] By the procedures described herein, together with methods known in the art, the following compound can be prepared.

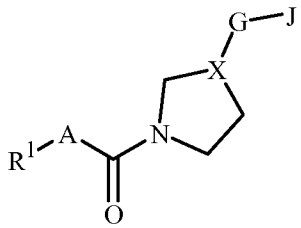
[0133] The invention includes the following component (a) compound.

TABLE 1A



R^1
5-methyl-3-(trifluoromethyl)pyrazol-1-yl

TABLE 5

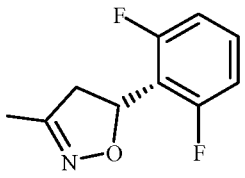


R^1 is 5-methyl-3-(trifluoromethyl)pyrazol-1-yl; A is CH_2; X is X^1; G is G-1**.

(continued)

J
J-29-9

** R^{3a} substituent in G-1 is H. J-29-9 is



Formulation/Utility

[0134] A mixture or compound of this invention will generally be used to provide fungicidal active ingredients in compositions, i.e. formulations, with at least one additional component selected from the group consisting of surfactants, solid diluents and liquid diluents, which serve as a carrier. The formulation or composition ingredients are selected to be consistent with the physical properties of the active ingredients, mode of application and environmental factors such as soil type, moisture and temperature.

[0135] The mixtures of component (a) (1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone, *N*-oxides or salts thereof) with component (b) (e.g., selected from (b1) to (b46) and salts thereof as described above) and/or one or more other biologically active compound or agent (i.e. insecticides, other fungicides, nematocides, acaricides, herbicides and other biological agents) can be formulated in a number of ways, including:

(i) component (a), component (b) and/or one or more other biologically active compound or agent can be formulated separately and applied separately or applied simultaneously in an appropriate weight ratio, e.g., as a tank mix; or
(ii) component (a), component (b) and/or one or more other biologically active compound or agent can be formulated together in the proper weight ratio.

[0136] Useful formulations include both liquid and solid compositions. Liquid compositions include solutions (including emulsifiable concentrates), suspensions, emulsions (including microemulsions and/or suspoemulsions) and the like, which optionally can be thickened into gels. The general types of aqueous liquid compositions are soluble concentrate, suspension concentrate, capsule suspension, concentrated emulsion, microemulsion and suspo-emulsion. The general types of nonaqueous liquid compositions are emulsifiable concentrate, microemulsifiable concentrate, dispersible concentrate and oil dispersion.

[0137] The general types of solid compositions are dusts, powders, granules, pellets, prills, pastilles, tablets, filled films (including seed coatings) and the like, which can be water-dispersible ("wettable") or water-soluble. Films and coatings formed from film-forming solutions or flowable suspensions are particularly useful for seed treatment. Active ingredient can be (micro)encapsulated and further formed into a suspension or solid formulation; alternatively the entire formulation of active ingredient can be encapsulated (or "overcoated"). Encapsulation can control or delay release of the active ingredient. An emulsifiable granule combines the advantages of both an emulsifiable concentrate formulation and a dry granular formulation. High-strength compositions are primarily used as intermediates for further formulation.

[0138] Sprayable formulations are typically extended in a suitable medium before spraying. Such liquid and solid formulations are formulated to be readily diluted in the spray medium, usually water. Spray volumes can range from about from about one to several thousand liters per hectare, but more typically are in the range from about ten to several hundred liters per hectare. Sprayable formulations can be tank mixed with water or another suitable medium for foliar treatment by aerial or ground application, or for application to the growing medium of the plant. Liquid and dry formulations can be metered directly into drip irrigation systems or metered into the furrow during planting. Liquid and solid formulations can be applied onto seeds of crops and other desirable vegetation as seed treatments before planting to protect developing roots and other subterranean plant parts and/or foliage through systemic uptake.

[0139] The formulations will typically contain effective amounts of active ingredient, diluent and surfactant within the following approximate ranges which add up to 100 percent by weight.

	Weight Percent		
	Active Ingredient	Diluent	Surfactant
Water-Dispersible and Water-soluble Granules, Tablets and Powders	0.001-90	0-99.999	0-15
Oil Dispersions, Suspensions, Emulsions, Solutions (including Emulsifiable Concentrates)	1-50	40-99	0-50
Dusts	1-25	70-99	0-5
Granules and Pellets	0.001-99	5-99.999	0-15
High Strength Compositions	90-99	0-10	0-2

[0140] Solid diluents include, for example, clays such as bentonite, montmorillonite, attapulgite and kaolin, gypsum, cellulose, titanium dioxide, zinc oxide, starch, dextrin, sugars (e.g., lactose, sucrose), silica, talc, mica, diatomaceous earth, urea, calcium carbonate, sodium carbonate and bicarbonate, and sodium sulfate. Typical solid diluents are described in Watkins et al., Handbook of Insecticide Dust Diluents and Carriers, 2nd Ed., Dorland Books, Caldwell, New Jersey.

[0141] Liquid diluents include, for example, water, *N,N*-dimethylalkanamides (e.g., *N,N*-dimethylformamide), limonene, dimethyl sulfoxide, *N*-alkylpyrrolidones (e.g., *N*-methylpyrrolidinone), ethylene glycol, triethylene glycol, propylene glycol, dipropylene glycol, polypropylene glycol, propylene carbonate, butylene carbonate, paraffins (e.g., white mineral oils, normal paraffins, isoparaffins), alkylbenzenes, alkylnaphthalenes, glycerine, glycerol triacetate, sorbitol, triacetin, aromatic hydrocarbons, dearomatized aliphatics, alkylbenzenes, alkylnaphthalenes, ketones such as cyclohexanone, 2-heptanone, isophorone and 4-hydroxy-4-methyl-2-pentanone, acetates such as isoamyl acetate, hexyl acetate, heptyl acetate, octyl acetate, nonyl acetate, tridecyl acetate and isobornyl acetate, other esters such as alkylated lactate esters, dibasic esters and γ-butyrolactone, and alcohols, which can be linear, branched, saturated or unsaturated, such as methanol, ethanol, *n*-propanol, isopropyl alcohol, n-butanol, isobutyl alcohol, *n*-hexanol, 2-ethylhexanol, *n*-octanol, decanol, isodecyl alcohol, isooctadecanol, cetyl alcohol, lauryl alcohol, tridecyl alcohol, oleyl alcohol, cyclohexanol, tetrahydrofurfuryl alcohol, diacetone alcohol and benzyl alcohol. Liquid diluents also include glycerol esters of saturated and unsaturated fatty acids (typically C_6-C_{22}), such as plant seed and fruit oils (e.g., oils of olive, castor, linseed, sesame, corn (maize), peanut, sunflower, grapeseed, safflower, cottonseed, soybean, rapeseed, coconut and palm kernel), animal-sourced fats (e.g., beef tallow, pork tallow, lard, cod liver oil, fish oil), and mixtures thereof. Liquid diluents also include alkylated fatty acids (e.g., methylated, ethylated, butylated) wherein the fatty acids may be obtained by hydrolysis of glycerol esters from plant and animal sources, and can be purified by distillation. Typical liquid diluents are described in Marsden, Solvents Guide, 2nd Ed., Interscience, New York, 1950.

[0142] The solid and liquid compositions of the present invention often include one or more surfactants. When added to a liquid, surfactants (also known as "surface-active agents") generally modify, most often reduce, the surface tension of the liquid. Depending on the nature of the hydrophilic and lipophilic groups in a surfactant molecule, surfactants can be useful as wetting agents, dispersants, emulsifiers or defoaming agents.

[0143] Surfactants can be classified as nonionic, anionic or cationic. Nonionic surfactants useful for the present compositions include, but are not limited to: alcohol alkoxylates such as alcohol alkoxylates based on natural and synthetic alcohols (which may be branched or linear) and prepared from the alcohols and ethylene oxide, propylene oxide, butylene oxide or mixtures thereof; amine ethoxylates, alkanolamides and ethoxylated alkanolamides; alkoxylated triglycerides such as ethoxylated soybean, castor and rapeseed oils; alkylphenol alkoxylates such as octylphenol ethoxylates, nonylphenol ethoxylates, dinonyl phenol ethoxylates and dodecyl phenol ethoxylates (prepared from the phenols and ethylene oxide, propylene oxide, butylene oxide or mixtures thereof); block polymers prepared from ethylene oxide or propylene oxide and reverse block polymers where the terminal blocks are prepared from propylene oxide; ethoxylated fatty acids; ethoxylated fatty esters and oils; ethoxylated methyl esters; ethoxylated tristyrylphenol (including those prepared from ethylene oxide, propylene oxide, butylene oxide or mixtures thereof); fatty acid esters, glycerol esters, lanolin-based derivatives, polyethoxylate esters such as polyethoxylated sorbitan fatty acid esters, polyethoxylated sorbitol fatty acid esters and polyethoxylated glycerol fatty acid esters; other sorbitan derivatives such as sorbitan esters; polymeric surfactants such as random copolymers, block copolymers, alkyd peg (polyethylene glycol) resins, graft or comb polymers and star polymers; polyethylene glycols (pegs); polyethylene glycol fatty acid esters; silicone-based surfactants; and sugar-derivatives such as sucrose esters, alkyl polyglycosides and alkyl polysaccharides.

[0144] Useful anionic surfactants include, but are not limited to: alkylaryl sulfonic acids and their salts; carboxylated alcohol or alkylphenol ethoxylates; diphenyl sulfonate derivatives; lignin and lignin derivatives such as lignosulfonates; maleic or succinic acids or their anhydrides; olefin sulfonates; phosphate esters such as phosphate esters of alcohol alkoxylates, phosphate esters of alkylphenol alkoxylates and phosphate esters of styryl phenol ethoxylates; protein-based surfactants; sarcosine derivatives; styryl phenol ether sulfate; sulfates and sulfonates of oils and fatty acids;

sulfates and sulfonates of ethoxylated alkylphenols; sulfates of alcohols; sulfates of ethoxylated alcohols; sulfonates of amines and amides such as *N,N*-alkyltaurates; sulfonates of benzene, cumene, toluene, xylene, and dodecyl and tridecylbenzenes; sulfonates of condensed naphthalenes; sulfonates of naphthalene and alkyl naphthalene; sulfonates of fractionated petroleum; sulfosuccinamates; and sulfosuccinates and their derivatives such as dialkyl sulfosuccinate salts.

[0145] Useful cationic surfactants include, but are not limited to: amides and ethoxylated amides; amines such as *N*-alkyl propanediamines, tripropylenetriamines and dipropylenetetramines, and ethoxylated amines, ethoxylated diamines and propoxylated amines (prepared from the amines and ethylene oxide, propylene oxide, butylene oxide or mixtures thereof); amine salts such as amine acetates and diamine salts; quaternary ammonium salts such as quaternary salts, ethoxylated quaternary salts and diquaternary salts; and amine oxides such as alkyldimethylamine oxides and bis-(2-hydroxyethyl)-alkylamine oxides.

[0146] Also useful for the present compositions are mixtures of nonionic and anionic surfactants or mixtures of nonionic and cationic surfactants. Nonionic, anionic and cationic surfactants and their recommended uses are disclosed in a variety of published references including McCutcheon's Emulsifiers and Detergents, annual American and International Editions published by McCutcheon's Division, The Manufacturing Confectioner Publishing Co.; Sisely and Wood, Encyclopedia of Surface Active Agents, Chemical Publ. Co., Inc., New York, 1964; and A. S. Davidson and B. Milwidsky, Synthetic Detergents, Seventh Edition, John Wiley and Sons, New York, 1987.

[0147] Compositions of this invention may also contain formulation auxiliaries and additives, known to those skilled in the art as formulation aids (some of which may be considered to also function as solid diluents, liquid diluents or surfactants). Such formulation auxiliaries and additives may control: pH (buffers), foaming during processing (antifoams such polyorganosiloxanes), sedimentation of active ingredients (suspending agents), viscosity (thixotropic thickeners), in-container microbial growth (antimicrobials), product freezing (antifreezes), color (dyes/pigment dispersions), wash-off (film formers or stickers), evaporation (evaporation retardants), and other formulation attributes. Film formers include, for example, polyvinyl acetates, polyvinyl acetate copolymers, polyvinylpyrrolidone-vinyl acetate copolymer, polyvinyl alcohols, polyvinyl alcohol copolymers and waxes. Examples of formulation auxiliaries and additives include those listed in McCutcheon's Volume 2: Functional Materials, annual International and North American editions published by McCutcheon's Division, The Manufacturing Confectioner Publishing Co.; and PCT Publication WO 03/024222.

[0148] Compound (a) and any other active ingredients are typically incorporated into the present compositions by dissolving the active ingredient in a solvent or by grinding in a liquid or dry diluent. Solutions, including emulsifiable concentrates, can be prepared by simply mixing the ingredients. If the solvent of a liquid composition intended for use as an emulsifiable concentrate is water-immiscible, an emulsifier is typically added to emulsify the active-containing solvent upon dilution with water. Active ingredient slurries, with particle diameters of up to 2,000 μm can be wet milled using media mills to obtain particles with average diameters below 3 μm. Aqueous slurries can be made into finished suspension concentrates (see, for example, U.S. 3,060,084) or further processed by spray drying to form water-dispersible granules. Dry formulations usually require dry milling processes, which produce average particle diameters in the 2 to 10 μm range. Dusts and powders can be prepared by blending and usually grinding (such as with a hammer mill or fluid-energy mill). Granules and pellets can be prepared by spraying the active material upon preformed granular carriers or by agglomeration techniques. See Browning, "Agglomeration", Chemical Engineering, December 4, 1967, pp 147-48, Perry's Chemical Engineer's Handbook, 4th Ed., McGraw-Hill, New York, 1963, pages 8-57 and following, and WO 91/13546. Pellets can be prepared as described in U.S. 4,172,714. Water-dispersible and water-soluble granules can be prepared as taught in U.S. 4,144,050, U.S. 3,920,442 and DE 3,246,493. Tablets can be prepared as taught in U.S. 5,180,587, U.S. 5,232,701 and U.S. 5,208,030. Films can be prepared as taught in GB 2,095,558 and U.S. 3,299,566.

[0149] For further information regarding the art of formulation, see T. S. Woods, "The Formulator's Toolbox - Product Forms for Modern Agriculture" in Pesticide Chemistry, and Bioscience, The Food-Environment Challenge, T. Brooks and T. R. Roberts, Eds., Proceedings of the 9th International Congress on Pesticide Chemistry, The Royal Society of Chemistry, Cambridge, 1999, pp. 120-133. See also U.S. 3,235,361, Col. 6, line 16 through Col. 7, line 19 and Examples 10-41; U.S. 3,309,192, Col. 5, line 43 through Col. 7, line 62 and Examples 8, 12, 15, 39, 41, 52, 53, 58, 132, 138-140, 162-164, 166, 167 and 169-182; U.S. 2,891,855, Col. 3, line 66 through Col. 5, line 17 and Examples 1-4; Klingman, Weed Control as a Science, John Wiley and Sons, Inc., New York, 1961, pp 81-96; Hance et al., Weed Control Handbook, 8th Ed., Blackwell Scientific Publications, Oxford, 1989; and Developments in formulation technology, PJB Publications, Richmond, UK, 2000.

[0150] In the following Examples, all percentages are by weight and all formulations are prepared in conventional ways. Compound numbers refer to compounds in Index Table A. Without further elaboration, it is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Percentages are by weight except where otherwise indicated.

Reference Example A

[0151]

High Strength Concentrate	
Compound 3	50.0%
folpet	48.5%
silica aerogel	0.5%
synthetic amorphous fine silica	1.0%

Reference Example B

[0152]

Wettable Powder	
Compound 3	50.0%
copper hydroxide	15.0%
dodecylphenol polyethylene glycol ether	2.0%
sodium ligninsulfonate	4.0%
sodium silicoaluminate	6.0%
montmorillonite (calcined)	23.0%

Reference Example C

[0153]

Granule	
Compound 149	8.0%
fluopicolide	2.0%
attapulgite granules (low volatile matter, 0.71/0.30 mm; U.S.S. No. 25-50 sieves)	90.0%

Reference Example D

[0154]

Extruded Pellet	
Compound 2	13.0%
cymoxanil	12.0%
anhydrous sodium sulfate	10.0%
crude calcium ligninsulfonate	5.0%
sodium alkylnaphthalenesulfonate	1.0%
calcium/magnesium bentonite	59.0%

Reference Example E

[0155]

Emulsifiable Concentrate	
Compound 3	5.0%
azoxystrobin	5.0%
polyoxyethylene sorbitol hexoleate	20.0%
C_6-C_{10} fatty acid methyl ester	70.0%

Reference Example F

[0156]

Microemulsion	
Compound 391	4.0%
pyraclostrobin	1.0 %
polyvinylpyrrolidone-vinyl acetate copolymer	30.0%
alkylpolyglycoside	30.0%
glyceryl monooleate	15.0%
water	20.0%

Reference Example G

[0157]

Seed Treatment	
Compound 114	10.00%
fosetyl-aluminum	10. 00%
polyvinylpyrrolidone-vinyl acetate copolymer	5.00%
montan acid wax	5.00%
calcium ligninsulfonate	1.00%
polyoxyethylene/polyoxypropylene block copolymers	1.00%
stearyl alcohol (POE 20)	2.00%
polyorganosilane	0.20%
colorant red dye	0.05%
water	65.75%

[0158] Component (b) fungicides are selected from amisulbrom, azoxystrobin, benthiavalicarb, boscalid, chlorothalonil, copper hydroxide, copper oxychloride, copper sulfate, cyazofamid, cymoxanil, cyproconazole, dithianon, difenoconazole, dimethomorph, ethaboxam, epoxiconazole, famoxadone, fenamidone, fluazinam, fluopicolide, flusilazole, folpet, fosetyl-aluminum, iprovalicarb, kresoxim-methyl, mancozeb, mandipropamid, metalaxyl, metalaxyl-M, metconazole, metiram, penthiopyrad, phosphorous acid and salts, picoxystrobin, propamacarb, propiconazole, propineb, proquinazid, pyraclostrobin, quinoxyfen, tebuconazole, triadimenol, trifloxystrobin, valiphenal, and zoxamide.

[0159] Specifically preferred mixtures (compound numbers refer to compounds in Index Table A) are selected from the group: compound 214 and amisulbrom, compound 214 and azoxystrobin, compound 214 and benthiavalicarb, compound 214 and boscalid, compound 214 and chlorothalonil, compound 214 and copper oxychloride, compound 214 and copper salts such as copper sulfate and copper hydroxide, compound 214 and cyazofamid, compound 214 and cymoxanil, compound 214 and cyproconazole, compound 214 and difenoconazole, compound 214 and dimethomorph, compound 214 and dithianon, compound 214 and epoxiconazole, compound 214 and ethaboxam, compound 214 and famoxadone, compound 214 and fenamidone, compound 214 and fluazinam, compound 214 and fluopicolide, compound 214 and flusilazole, compound 214 and folpet, compound 214 and fosetyl-aluminum, compound 214 and kresoxim-methyl, compound 214 and mancozeb, compound 214 and mandipropamid, compound 214 and metalaxyl, compound 214 and metalaxyl-M, compound 214 and metconazole, compound 214 and metiram, compound 214 and penthiopyrad, compound 214 and phosphorous acid and salts, compound 214 and picoxystrobin, compound 214 and propamocarb, compound 214 and propiconazole, compound 214 and propineb, compound 214 and proquinazid, compound 214 and pyraclostrobin, compound 214 and quinoxyfen, compound 214 and tebuconazole, compound 214 and triadimenol, compound 214 and trifloxystrobin, compound 214 and valiphenal, compound 214 and zoxamide.

[0160] The component (a) compound and combinations thereof with component (b) compounds and/or one or more other biologically active compound or agent can be applied to plants genetically transformed to express proteins toxic to invertebrate pests (such as *Bacillus thuringiensis* delta-endotoxins). The effect of the exogenously applied invertebrate pest control compounds of this invention may be synergistic with the expressed toxin proteins.

[0161] General references for these agricultural protectants (i.e. insecticides, fungicides, nematocides, acaricides, herbicides and biological agents) include The Pesticide Manual, 13h Edition, C. D. S. Tomlin, Ed., British Crop Protection Council, Farnham, Surrey, U.K., 2003 and The BioPesticide Manual, 2nd Edition, L. G. Copping, Ed., British Crop

Protection Council, Farnham, Surrey, U.K., 2001.

[0162] Table A1 lists specific combinations of a component (b) compound with component (a) illustrative of the mixtures, compositions and methods of the present invention. The first column of Table A1 lists the specific component (b) compound (e.g., "amisulbrom" in the first line). The second, third and fourth columns of Table A1 lists ranges of weight ratios for rates at which the component (b) compound is typically applied relative to component (a) (e.g., "60:1 to 1:6" of amisulbrom relative to component (a) by weight). Thus, for example, the first line of Table A1 specifically discloses the combination of amisulbrom with component (a) is typically applied in a weight ratio between 60:1 to 1:6. The remaining lines of Table A1 are to be construed similarly.

Table A1

Component (b)	Typical Weight Ratio	More Typical Weight Ratio	Most Typical Weight Ratio
amisulbrom	60:1 to 1:6	20:1 to 1:2	12:1 to 2:1
azoxystrobin	90:1 to 1:4	30:1 to 1:2	24:1 to 3:1
benthiavalicarb	22:1 to 1:12	7:1 to 1:4	4:1 to 1:2
boscalid	180:1 to 1:2	60:1 to 2:1	36:1 to 4:1
chlorothalonil	900:1 to 1:2	300:1 to 3:1	120:1 to 14:1
copper oxychloride	2250:1 to 4:1	750:1 to 10:1	480:1 to 54:1
copper salts such as copper sulfate and copper hydroxide	1200:1 to 1:2	400:1 to 2:1	60:1 to 7:1
cyazofamid	45:1 to 1:6	15:1 to 1:2	9:1 to 2:1
cymoxanil	60:1 to 1:6	20:1 to 1:2	14:1 to 2:1
cyproconazole	45:1 to 1:6	15:1 to 1:2	9:1 to 2:1
difenoconazole	45:1 to 1:12	15:1 to 1:4	6:1 to 1:2
dimethomorph	90:1 to 1:2	30:1 to 2:1	24:1 to 4:1
dithianon	150:1 to 1:2	50:1 to 3:1	40:1 to 7:1
epoxiconazole	37:1 to 1:12	12:1 to 1:4	10:1 to 2:1
ethaboxam	75:1 to 1:3	25:1 to 1:1	18:1 to 3:1
famoxadone	90:1 to 1:6	30:1 to 1:2	18:1 to 2:1
fenamidone	60:1 to 1:6	20:1 to 1:2	16:1 to 2:1
fluazinam	225:1 to 1:2	75:1 to 2:1	30:1 to 6:1
fluopicolide	37:1 to 1:6	12:1 to 1:2	9:1 to 2:1
flusilazole	150:1 to 1:3	50:1 to 1:1	24:1 to 3:1
folpet	900:1 to 1:2	300:1 to 3:1	120:1 to 14:1
fosetyl-aluminum	2250:1 to 5:1	750:1 to 15:1	240:1 to 40:1
iprovalicarb	90:1 to 1:3	30:1 to 1:1	18:1 to 3:1
kresoxim-methyl	75:1 to 1:6	25:1 to 1:2	18:1 to 2:1
mancozeb	1800:1 to 2:1	600:1 to 4:1	180:1 to 20:1
mandipropamid	60:1 to 1:6	20:1 to 1:2	16:1 to 2:1
metalaxyl	150:1 to 1:15	50:1 to 1:5	12:1 to 2:1
metalaxyl-M	150:1 to 1:15	50:1 to 1:5	12:1 to 2:1
metconazole	30:1 to 1:6	10:1 to 1:2	8:1 to 2:1
metiram	1500:1 to 1:12	500:1 to 1:4	120:1 to 14:1

(continued)

Component (b)	Typical Weight Ratio	More Typical Weight Ratio	Most Typical Weight Ratio
penthiopyrad	120:1 to 1:3	40:1 to 1:1	18:1 to 3:1
phosphorous acid and salts	1500:1 to 1:12	500:1 to 1:4	120:1 to 14:1
picoxystrobin	75:1 to 1:6	25:1 to 1:2	15:1 to 2:1
propiconazole	45:1 to 1:6	15:1 to 1:2	12:1 to 2:1
propineb	450:1 to 2:1	150:1 to 5:1	90:1 to 14:1
proquinazid	30:1 to 1:12	10:1 to 1:4	6:1 to 1:2
pyraclostrobin	90:1 to 1:6	30:1 to 1:2	18:1 to 2:1
quinoxyfen	45:1 to 1:6	15:1 to 1:2	9:1 to 2:1
tebuconazole	75:1 to 1:6	25:1 to 1:2	15:1 to 2:1
triadimenol	150:1 to 1:12	50:1 to 1:4	15:1 to 2:1
trifloxystrobin	60:1 to 1:6	20:1 to 1:2	16:1 to 2:1
valiphenal	60:1 to 1:6	20:1 to 1:2	16:1 to 2:1
zoxamide	60:1 to 1:6	20:1 to 1:2	16:1 to 2:1

[0163] Compositions of component (a) with component (b) can be further mixed with one or more other biologically active compounds or agents including insecticides, nematocides, bactericides, acaricides, herbicides, herbicide safeners, growth regulators such as insect molting inhibitors and rooting stimulants, chemosterilants, semiochemicals, repellents, attractants, pheromones, feeding stimulants, plant nutrients, other biologically active compounds or entomopathogenic bacteria, virus or fungi to form a multi-component pesticide giving an even broader spectrum of agricultural protection. Thus the present invention also pertains to a composition comprising a fungicidally effective amount of a mixture of component (a) with component (b) and a biologically effective amount of at least one additional biologically active compound or agent and can further comprise at least one of a surfactant, a solid diluent or a liquid diluent. The other biologically active compounds or agents can also be separately formulated in compositions comprising at least one of a surfactant, solid or liquid diluent. For compositions of the present invention, one or more other biologically active compounds or agents can be formulated together with one or both of components (a) and (b) to form a premix, or one or more other biologically active compounds or agents can be formulated separately from components (a) and (b) and the formulations combined together before application (e.g., in a spray tank) or, alternatively, applied in succession.

[0164] Examples of such biologically active compounds or agents with which compositions of component (a) with component (b) can be formulated are: insecticides such as abamectin, acephate, acetamiprid, acetoprole, aldicarb, amidoflumet, amitraz, avermectin, azadirachtin, azinphos-methyl, bifenthrin, bifenazate, bistrifluron, buprofezin, carbofuran, cartap, chinomethionat, chlorfenapyr, chlorfluazuron, chlorantraniliprole, 3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[[(1-methylethyl)amino]carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide, 3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide, 3-chloro-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide, 3-chloro-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[[(1-methylethyl)amino]carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide, chlorpyrifos, chlorpyrifos-methyl, chlorobenzilate, chromafenozide, clothianidin, cyflumetofen, cyfluthrin, beta-cyfluthrin, cyhalothrin, gamma-cyhalothrin, lambda-cyhalothrin, cyhexatin, cypermethrin, cyromazine, deltamethrin, diafenthiuron, diazinon, dicofol, dieldrin, dienochlor, diflubenzuron, dimefluthrin, dimethoate, dinotefuran, diofenolan, emamectin, endosulfan, esfenvalerate, ethiprole, etoxazole, fenamiphos, fenazaquin, fenbutatin oxide, fenothiocarb, fenoxycarb, fenpropathrin, fenpyroximate, fenvalerate, fipronil, flonicamid, flubendiamide, flucythrinate, tau-fluvalinate, flufenerim, flufenoxuron, fonophos, halofenozide, hexaflumuron, hexythiazox, hydramethylnon, imicyafos, imidacloprid, indoxacarb, isofenphos, lufenuron, malathion, metaflumizone, metaldehyde, methamidophos, methidathion, methomyl, methoprene, methoxychlor, methoxyfenozide, metofluthrin, monocrotophos, nitenpyram, nithiazine, novaluron, noviflumuron, oxamyl, parathion, parathion-methyl, permethrin, phorate, phosalone, phosmet, phosphamidon, pirimicarb, profenofos, profluthrin, propargite, protrifenbute, pymetrozine, pyrafluprole, pyrethrin, pyridaben, pyridalyl, pyrifluquinazon, pyriprole, pyriproxyfen, rotenone, ryanodine, spinetoram, spinosad, spiridiclofen, spiromesifen, spirotetramat, sulprofos, tebufenozide, tebufenpyrad, teflubenzuron, tefluthrin, terbufos, tetrachlorvinphos, thiacloprid, thiamethoxam, thiodicarb, thiosultap-sodium, tolfenpyrad, tralomethrin, triazamate, trichlorfon, triflumuron; nematocides such as aldicarb, imicyafos, oxamyl

and fenamiphos; bactericides such as streptomycin; acaricides such as amitraz, chinomethionat, chlorobenzilate, cyenopyrafen, cyhexatin, dicofol, dienochlor, etoxazole, fenazaquin, fenbutatin oxide, fenpropathrin, fenpyroximate, hexythiazox, propargite, pyridaben and tebufenpyrad; and biological agents including entomopathogenic bacteria, such as *Bacillus thuringiensis* subsp. *aizawai, Bacillus thuringiensis* subsp. *kurstaki,* and the encapsulated delta-endotoxins of *Bacillus thuringiensis* (e.g., Cellcap, MPV, MPVII); entomopathogenic fungi, such as green muscardine fungus; and entomopathogenic virus including baculovirus, nucleopolyhedro virus (NPV) such as HzNPV, AfNPV; and granulosis virus (GV) such as CpGV.

[0165] Mixtures of this invention and compositions thereof can be applied to plants genetically transformed to express proteins toxic to invertebrate pests (such as *Bacillus thuringiensis* delta-endotoxins). The effect of the exogenously applied fungicidal mixtures of this invention may be synergistic with the expressed toxin proteins.

[0166] General references for agricultural protectants (i.e. insecticides, fungicides, nematocides, acaricides, herbicides and biological agents) include The Pesticide Manual, 13th Edition, C. D. S. Tomlin, Ed., British Crop Protection Council, Farnham, Surrey, U.K., 2003 and The BioPesticide Manual, 2nd Edition, L. G. Copping, Ed., British Crop Protection Council, Farnham, Surrey, U.K., 2001.

[0167] For embodiments where one or more of these various mixing partners are used, the weight ratio of these various mixing partners (in total) to the mixture of component (a) with component (b) is typically between 1:100 and 3000:1. Of note are weight ratios between 1:30 and 300:1 (for example ratios between 1:1 and 30:1). It will be evident that including these additional components may expand the spectrum of diseases controlled beyond the spectrum controlled by a mixture of component (a) with component (b).

[0168] Of note is a composition embodiment wherein granules of a solid composition comprising the compound (a) is mixed with granules of a solid composition comprising component (b). These mixtures can be further mixed with granules comprising additional agricultural protectants. Alternatively, two or more agricultural protectants (e.g., the component (a) compound, a component (b) compound, an agricultural protectant other than component (a) or (b)) can be combined in the solid composition of one set of granules, which is then mixed with one or more sets of granules of solid compositions comprising one or more additional agricultural protectants. These granule mixtures can be in accordance with the general granule mixture disclosure of PCT Patent Publication WO 94/24861 or more preferably the homogeneous granule mixture teaching of U.S. Patent 6,022,552.

[0169] The compositions of this invention are useful as plant disease control agents. The present invention therefore further comprises a method for controlling plant diseases caused by fungal plant pathogens comprising applying to the plant or portion thereof to be protected, or to the plant seed or vegetative propagation unit to be protected, an effective amount of a mixture of the invention or a fungicidal composition comprising said mixture.

[0170] Plant disease control is ordinarily accomplished by applying an effective amount of a mixture of this invention, typically as a formulated composition, either pre- or post-infection, to the portion of the plant to be protected such as the roots, stems, foliage, fruit, seeds, tubers or bulbs, or to the media (soil or sand) in which the plants to be protected are growing. The mixtures can also be applied to seeds to protect the seeds and seedlings developing from the seeds. The mixtures can also be applied through irrigation water to treat plants.

[0171] Rates of application for these mixtures and compositions of this invention can be influenced by many factors of the environment and should be determined under actual use conditions. Foliage can normally be protected when treated at a rate of from less than about 1 g/ha to about 5,000 g/ha of active ingredients. Seed and seedlings can normally be protected when seed is treated at a rate of from about 0.1 to about 10 g per kilogram of seed; and vegetative propagation units (e.g., cuttings and tubers) can normally be protected when propagation unit is treated at a rate of from about 0.1 to about 10g per kilogram of propagation unit.

[0172] The mixtures and/or compositions of this invention provide control of diseases caused by a broad spectrum of fungal plant pathogens in the Basidiomycete, Ascomycete, Oomycete and Deuteromycete classes. They are effective in controlling a broad spectrum of plant diseases, foliar pathogens of crops including: cereal grain crops such as wheat, barley, oats, rye, triticale, rice, maize, sorghum and millet; vine crops such as table and wine grapes; field crops such as oilseed rape (canola), sunflower; sugar beets, sugar cane, soybean, peanuts (groundnut), tobacco, alfafa, clover, lespedeza, trefoil and vetch; pome fruits such as apple, pear, crabapple, loquat, mayhaw and quince; stone fruits such as peaches, cherries, plums, apricots, nectarines and almonds; citrus fruits such as lemons, limes, oranges, grapefruit, mandarin (tangerines) and kumquat; root and tuber vegetables and field crops (and their foliage) such as artichoke, garden and sugar beet, carrot, cassava, ginger, ginseng, horseradish, parsnip, potato, radish, rutabaga, sweet potato, turnip and yam; bulb vegetables such as garlic, leek, onion and shallot; leafy vegetables such as arugula (roquette), celery, celery, cress, endive (escarole), fennel, head and leaf lettuce, parsley, radicchio (red chicory), rhubarb, spinach and Swiss chard; brassica (cole) leafy vegetables such as broccoli, broccoli raab (rapini), Brussels sprouts, cabbage, bok choy, cauliflower, collards, kale, kohlrabi, mustard and greens; legume vegetables (succulent or dried) such as lupin, bean (*Phaseolus* spp.) (including field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean, tepary bean and wax bean), bean (*Vigna* spp.) (including adzuki bean, asparagus bean, blackeyed pea, catjang, Chinese longbean, cowpea, crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean and yardlong bean), broad

bean (fava), chickpea (garbanzo), guar, jackbean, lablab bean, lentil and pea (*Pisum* spp.) (including dwarf pea, edible-podded pea, English pea, field pea, garden pea, green pea, snowpea, sugar snap pea, pigeon pea and soybean); fruiting vegetables such as eggplant, groundcherry (*Physalis* spp.), pepino and pepper (including bell pepper, chili pepper, cooking pepper, pimento, sweet pepper; tomatillo and tomato); cucurbit vegetables such as Chayote (fruit), Chinese waxgourd (Chinese preserving melon), citron melon, cucumber, gherkin, edible gourd (including hyotan, cucuzza, hechima, and Chinese okra), *Momordica* spp. (including balsam apple, balsam pear, bittermelon and Chinese cucumber), muskmelon (including cantaloupe and pumpkin), summer and winter squash (including butternut squash, calabaza, hubbard squash, acorn squash, spaghetti squash) and watermelon; berries such as blackberry (including bingleberry, boysenberry, dewberry, lowberry, marionberry, olallieberry and youngberry), blueberry, cranberry, currant, elderberry, gooseberry, huckleberry, loganberry, raspberry and strawberry; tree nuts such as almond, beech nut, Brazil nut, butternut, cashew, chestnut, chinquapin, filbert (hazelnut), hickory nut, macadamia nut, pecan and walnut; tropical fruits and other crops such as bananas, plantains, mangos, coconuts, papaya, guava, avocado, lichee, agave, coffee, cacao, sugar cane, oil palm, sesame, rubber and spices; fiber crops such as cotton, flax and hemp; turfgrasses (including warm- and cool-season turfgrasses) such as bentgrass, Kentucky bluegrass, St. Augustine grass, tall fescue and Bermuda grass.

[0173] These pathogens include: Oomycetes, including *Phytophthora* diseases such as *Phytophthora infestans, Phytophthora megasperma, Phytophthora parasitica, Phytophthora cinnamomi* and *Phytophthora capsici, Pythium* diseases such as *Pythium aphanidermatum,* and diseases in the Peronosporaceae family such as *Plasmopara viticola, Peronospora* spp. (including *Peronospora tabacina* and *Peronospora parasitica*), *Pseudoperonospora* spp. (including *Pseudoperonospora cubensis)* and *Bremia lactucae*; Ascomycetes, including *Alternaria* diseases such as *Alternaria solani* and *Alternaria brassicae, Guignardia* diseases such as *Guignardia bidwelli, Venturia* diseases such as *Venturia inaequalis, Septoria* diseases such as *Septoria nodorum* and *Septoria tritici,* powdery mildew diseases such as *Erysiphe* spp. (including *Erysiphe graminis* and *Erysiphe polygoni), Uncinula necatur, Sphaerotheca fuligena* and *Podosphaera leucotricha, Pseudocercosporella herpotrichoides, Botrytis* diseases such as *Botrytis cinerea, Monilinia fructicola, Sclerotinia* diseases such as *Sclerotinia sclerotiorum, Magnaporthe grisea, Phomopsis viticola, Helminthosporium* diseases such as *Helminthosporium tritici repentis, Pyrenophora teres,* anthracnose diseases such as *Glomerella* or *Colletotrichum* spp. (such as *Colletotrichum graminicola* and *Colletotrichum orbiculare*), and *Gaeumannomyces graminis*; Basidiomycetes, including rust diseases caused by *Puccinia* spp. (such as *Puccinia recondita, Puccinia striiformis, Puccinia hordei, Puccinia graminis* and *Puccinia arachidis), Hemileia vastatrix* and *Phakopsora pachyrhizi*; other pathogens including *Rhizoctonia* spp. (such as *Rhizoctonia solani and Rhizoctonia oryzae); Fusarium* diseases such as *Fusarium roseum, Fusarium graminearum* and *Fusarium oxysporum*; *Verticillium dahliae*; *Sclerotium rolfsii*; *Rynchosporium secalis; Cercosporidium personatum, Cercospora arachidicola* and *Cercospora beticola; Rutstroemia floccosum* (also known as *Sclerontina homoeocarpa*); and other genera and species closely related to these pathogens. In addition to their fungicidal activity, the compositions or combinations also have activity against bacteria such as *Erwinia amylovora, Xanthomonas campestris, Pseudomonas syringae,* and other related species.

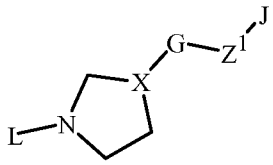
[0174] Mixtures of fungicides may provide significantly better disease control than could be predicted based on the activity of the individual components. This synergism has been described as "the cooperative action of two components of a mixture, such that the total effect is greater or more prolonged than the sum of the effects of the two (or more) taken independently" (see Tames, P. M. L., Neth. J. Plant Pathology, (1964), 70, 73-80).

[0175] Compositions are provided in accordance with this invention that comprise proportions of component (a) and component (b) that are especially useful for controlling particular fungal diseases. These compositions are considered especially useful for controlling Oomycetes (such as *Phytophthora infestans, Phytophthora megasperma, Phytophthora parasitica, Phytophthora cinnamomi, Phytophthora capsici, Pythium aphanidermatum, Plasmopara viticola, Peronospora tabacina, Peronospora parasitica, Pseudoperonospora cubensis* and *Bremia lactucae*).

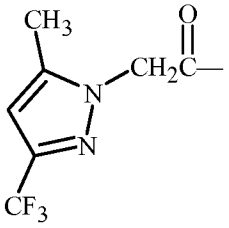
[0176] The following Tests demonstrate the control efficacy of mixtures of this invention on specific pathogens. The disease control afforded by the mixtures is not limited, however, to the pathogenic fungi species exemplified. See Index Table A for compound descriptions of Formula **1.** The stereocenters are labeled as *R* (*rectus*) and *S* (*sinister*) based on Cahn-Ingold-Prelog system. Index Table A lists the molecular weight of the highest isotopic abundance parent ion (M+1) formed by addition of H^+ (molecular weight of 1) to the molecule, observed by mass spectrometry using atmospheric pressure chemical ionization (AP^+).

INDEX TABLE A

[0177]



L groups are defined as illustrated below.



L-1

Cmpd.	L	X	G	Z^1-J	AP^+ (M+1)
214	L-1	X^1	G-1	4,5-dihydro-5-(2,6-difluorophenyl)-3-isoxazolyl [Note 22], [Note 23] and [Note 24]	540

[Note 22]: The m.p. of compound 214 was 125-128 °C when the compound was prepared by the method of Example 12, Step F, with the exception that methanol was used in place of ethanol as the reaction solvent and upon dilution of the reaction mixture with water compound 214 parcipated from the reaction mixture, was collected and allowed to dry.

[Note 23]: The m.p. of compound 214 was 130-135 °C when the compound was prepared prepared according to the procedures disclosed herein and then recystallized from method.

[Note 24]: One skilled in the art recognizes that "4,5-dihydro-5-(2,6-difluorophenyl)-3-isoxazolyl" is equivalent to "5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazoly".

BIOLOGICAL EXAMPLES OF THE INVENTION

[0178] General protocol for preparing test compositions for Tests A-B: 5-chloro-6-(2,4,6-trifluorophenyl)-7-(4-methylpiperidin-1-yl)[1,2,4]triazolo[1,5-a]pyrimidine (BAS600), fenamidone, fluopicolide, penthiopyrad and quinoxyfen were obtained as unformulated, technical-grade materials. Azoxystrobin, benthiovalicarb, boscalid, chlorothalonil, copper hydroxide, cyazofamid, cymoxanil, dimethomorph, ethaboxam, famoxadone, fluazinam, folpet, fosetyl-aluminum, iprovalicarb, kresoxim-methyl, mancozeb, mandipropamid, mefenoxam, propamocarb, proquinazid, pyraclostrobin and trifloxystrobin were obtained as formulated products marketed under the trademarks Amistar®, Benthiovalicard®, Endura®, Bravo®, Weatherstik®, Kocide®, Ranman®, Curzate®, Acrobat®, Guardian®, Famoxate®, Shirlan®, Phaltan®, Aliette®, Melody®, kresoxim-methyl®, Manzate®, Revus®, Ridomil Gold®, Previcur®, Talius®, Headline® and Flint®, respectively. Compound compound 214 was formulated as an oil dispersion containing a mixture of POE (polyoxyethylene) 40 sorbitol hexaoleate, POE 20 sorbitan trioleate, and alkyl-peg resin surfactants in a liquid carrier consisting of a distilled C18 fatty acid methyl ester. Unformulated materials were first dissolved in acetone and then suspended at the desired concentration (inppm) in acetone and purified water (50/50 mix by volume) containing 250 ppm of the surfactant Trem® 014 (polyhydric alcohol esters). Formulated materials were dispersed in sufficient water to give the desired concentration, and neither organic solvent nor surfactant was added to the suspension. The resulting test mixtures were then used in Tests A-B. Spraying a 200 ppm test mixture to the point of run-off on the test plants was the equivalent of a rate of 500 g/ha. The tests were replicated three times and the results reported as the mean average of the three replicates.

[0179] The presence of a synergistic effect between two active ingredients was established with the aid of the Colby equation (see Colby, S. R. "Calculating Synergistic and Antagonistic Responses of Herbicide Combinations", Weeds, (1967), 15, 20-22):

$$p = A + B - \left[\frac{A \times B}{100} \right].$$

[0180] Using the method of Colby, the presence of a synergistic interaction between two active ingredients is established by first calculating the predicted activity, p, of the mixture based on activities of the two components applied alone. If p is lower than the experimentally established effect, synergism has occurred. In the equation above, A is the fungicidal activity in percentage control of one component applied alone at rate x. The B term is the fungicidal activity in percentage control of the second component applied at rate y. The equation estimates p, the expected fungicidal activity of the mixture of A at rate x with B at rate y if their effects are strictly additive and no interaction has occurred.

TEST A

[0181] The test mixture was sprayed to the point of run-off on tomato seedlings. The following day the seedlings were inoculated with a spore suspension of *Phytophthora infestans* (the causal agent of tomato late blight) and incubated in a saturated atmosphere at 20 °C for 24 h, and then moved to a growth chamber at 20 °C for 4 days, after which time disease ratings were made.

TEST B

[0182] The test mixture was sprayed to the point of run-off on cucumber seedlings. The following day the seedlings were inoculated with a spore suspension of *Pseudoperonospora cubensis* (the causal agent of cucumber downy mildew) and incubated in saturated atmosphere at 20 °C for 24 h, and moved to a growth chamber at 20 °C for 6 days, after which time disease ratings were made.

[0183] Results for Tests A to B are given in Tables A-P. Each table corresponds to a set of evaluations performed together at the same time. In each table, a rating of 100 indicates 100 % disease control and a rating of 0 indicates no disease control (relative to the controls). Columns labeled "Obsd" indicate the average of results observed from three replications. Columns labeled "Exp" indicate the expected value for each treatment mixture using the Colby equation.

Table M

Observed and Expected Effects of Compound 214 Alone and Mixtures with Azoxystrobin, Benthiavalicarb, Chlorothalonil, Copper hydroxide, Fosetyl-aluminum, Iprovalicarb and Pyraclostrobin in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	-	0	0	-	0	-
0.00001	-	0	0	-	0	-
0.0001	-	0	7	-	0	-
0.001	-	0	44	-	16	-
0.01	-	0	98	-	83	-
0.1	-	0	100	-	100	-
0	-	0.08	7	-	0	-
0	azoxystrobin	0.4	29	-	0	-
0	azoxystrobin	2	56	-	70	-
0	azoxystrobin	10	90	-	100	-
0	azoxystrobin	40	100	-	100	-
0.001	azoxystrobin	0.08	21	48	8	16
0.001	azoxystrobin	0.4	22	60	17	16

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Azoxystrobin, Benthiavalicarb, Chlorothalonil, Copper hydroxide, Fosetyl-aluminum, Iprovalicarb and Pyraclostrobin in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.001	azoxystrobin	2	53	75	85	74
0.001	azoxystrobin	10	100	94	100	100
0.001	azoxystrobin	40	100	100	100	100
0.01	azoxystrobin	0.08	69	99	75	83
0.01	azoxystrobin	0.4	94	99	64	83
0.01	azoxystrobin	2	100	99	98	95
0.01	azoxystrobin	10	100	100	100	100
0.01	azoxystrobin	40	100	100	100	100
0	benthiavalicarb	0.08	21	-	0	-
0	benthiavalicarb	0.4	82	-	75	-
0	benthiavalicarb	2	100	-	100	-
0	benthiavalicarb	10	100	-	100	-
0	benthiavalicarb	40	100	-	100	-
0.001	benthiavalicarb	0.08	29	56	0	16
0.001	benthiavalicarb	0.4	100	90	81	79
0.001	benthiavalicarb	2	100	100	100	100
0.001	benthiavalicarb	10	100	100	100	100
0.001	benthiavalicarb	40	100	100	100	100
0.01	benthiavalicarb	0.08	95	99	73	83
0.01	benthiavalicarb	0.4	100	100	99	96
0.01	benthiavalicarb	2	100	100	100	100
0.01	benthiavalicarb	10	100	100	100	100
0.01	benthiavalicarb	40	100	100	100	100
0	chlorothalonil	0.08	14	-	0	-
0	chlorothalonil	0.4	14	-	0	-
0	chlorothalonil	2	21	-	0	-
0	chlorothalonil	10	100	-	70	-
0	chlorothalonil	40	100	-	71	-
0.001	chlorothalonil	0.08	36	52	0	16
0.001	chlorothalonil	0.4	28	52	0	16
0.001	chlorothalonil	2	36	56	0	16
0.001	chlorothalonil	10	92	100	62	74
0.001	chlorothalonil	40	100	100	95	75
0.01	chlorothalonil	0.08	82	99	75	83

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Azoxystrobin, Benthiavalicarb, Chlorothalonil, Copper hydroxide, Fosetyl-aluminum, Iprovalicarb and Pyraclostrobin in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.01	chlorothalonil	0.4	70	99	79	83
0.01	chlorothalonil	2	86	99	72	83
0.01	chlorothalonil	10	100	100	75	95
0.01	chlorothalonil	40	100	100	99	95
0	copper hydroxide	2	22	-	0	-
0	copper hydroxide	10	36	-	0	-
0	copper hydroxide	40	50	-	0	-
0	copper hydroxide	200	71	-	29	-
0	copper hydroxide	500	77	-	37	-
0.001	copper hydroxide	2	56	56	0	16
0.001	copper hydroxide	10	61	64	0	16
0.001	copper hydroxide	40	84	72	26	16
0.001	copper hydroxide	200	71	83	52	40
0.001	copper hydroxide	500	82	87	64	47
0.01	copper hydroxide	2	88	99	47	83
0.01	copper hydroxide	10	80	99	47	83
0.01	copper hydroxide	40	74	99	47	83
0.01	copper hydroxide	200	71	100	47	88
0.01	copper hydroxide	500	85	100	47	89
0	fosetyl-aluminum	10	0	-	0	-
0	fosetyl-aluminum	40	0	-	0	-

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Azoxystrobin, Benthiavalicarb, Chlorothalonil, Copper hydroxide, Fosetyl-aluminum, Iprovalicarb and Pyraclostrobin in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	fosetyl-aluminum	200	50	-	0	-
0	fosetyl-aluminum	1000	99	-	68	-
0	fosetyl-aluminum	2000	100	-	73	-
0.001	fosetyl-aluminum	10	29	44	47	16
0.001	fosetyl-aluminum	40	58	44	0	16
0.001	fosetyl-aluminum	200	90	72	33	16
0.001	fosetyl-aluminum	1000	99	100		
0.001	fosetyl-aluminum	2000	100	100	67	78
0.01	fosetyl-aluminum	10	92	98	52	83
0.01	fosetyl-aluminum	40	99	98	75	83
0.01	fosetyl-aluminum	200	100	99	90	83
0.01	fosetyl-aluminum	1000	100	100	100	94
0.01	fosetyl-aluminum	2000	100	100	100	95
0	iprovalicarb	0.08	0	-	0	-
0	iprovalicarb	0.4	21	-	0	-
0	iprovalicarb	2	74	-	0	-
0	iprovalicarb	10	98	-	99	-
0	iprovalicarb	40	100	-	100	-
0.001	iprovalicarb	0.08	36	44	0	16
0.001	iprovalicarb	0.4	54	56	0	16
0.001	iprovalicarb	2	79	85	0	16
0.001	iprovalicarb	10	100	99	100	99
0.001	iprovalicarb	40	100	100	100	100
0.01	iprovalicarb	0.08	82	98	71	83
0.01	iprovalicarb	0.4	79	99	64	83

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Azoxystrobin, Benthiavalicarb, Chlorothalonil, Copper hydroxide, Fosetyl-aluminum, Iprovalicarb and Pyraclostrobin in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.01	iprovalicarb	2	99	100	58	83
0.01	iprovalicarb	10	100	100	100	100
0.01	iprovalicarb	40	100	100	100	100
0	pyraclostrobin	0.08	15	-	0	-
0	pyraclostrobin	0.4	35	-	0	-
0	pyraclostrobin	2	63	-	68	-
0	pyraclostrobin	10	90	-	100	-
0	pyraclostrobin	40	94	-	100	-
0.001	pyraclostrobin	0.08	42	52	0	16
0.001	pyraclostrobin	0.4	79	63	40	16
0.001	pyraclostrobin	2	65	79	62	73
0.001	pyraclostrobin	10	82	94	100	100
0.001	pyraclostrobin	40	95	96	100	100
0.01	pyraclostrobin	0.08	94	99	60	83
0.01	pyraclostrobin	0.4	94	99	60	83
0.01	pyraclostrobin	2	95	99	95	95
0.01	pyraclostrobin	10	99	100	100	100
0.01	pyraclostrobin	40	92	100	100	100

Table N

Observed and Expected Effects of Compound 214 Alone and Mixtures with Cymoxanil, Dimethomorph, Fluazinam, Folpet, Mancozeb, Mandipropamid and Propamocarb in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	-	0	30	-	15	-
0.00001	-	0	8	-	23	-
0.0001	-	0	38	-	31	-
0.001	-	0	56	-	21	-
0.01	-	0	99	-	73	-
0.1	-	0	100	-	100	-
0	cymoxanil	0.04	44	-	15	-
0	cymoxanil	2	46	-	0	-
0	cymoxanil	10	100	-	0	-

(continued)

Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	cymoxanil	40	100	-	0	-
0	cymoxanil	200	100	-	21	-
0.001	cymoxanil	0.04	67	75	0	33
0.001	cymoxanil	2	72	76	15	21
0.001	cymoxanil	10	100	100	0	21
0.001	cymoxanil	40	100	100	15	21
0.001	cymoxanil	200	100	100	0	38
0.01	cymoxanil	0.04	96	99	89	77
0.01	cymoxanil	2	96	99	83	73
0.01	cymoxanil	10	100	100	65	73
0.01	cymoxanil	40	100	100	85	73
0.01	cymoxanil	200	100	100	79	78
0	dimethomorph	0.08	31	-	52	-
0	dimethomorph	0.4	62	-	54	-
0	dimethomorph	2	95	-	88	-
0	dimethomorph	10	88	-	100	-
0	dimethomorph	40	100	-	100	-
0.001	dimethomorph	0.08	62	70	16	62
0.001	dimethomorph	0.4	62	83	0	64
0.001	dimethomorph	2	88	98	80	91
0.001	dimethomorph	10	78	95	100	100
0.001	dimethomorph	40	97	100	100	100
0.01	dimethomorph	0.08	94	99	39	87
0.01	dimethomorph	0.4	89	99	70	87
0.01	dimethomorph	2	94	100	94	97
0.01	dimethomorph	10	88	100	100	100
0.01	dimethomorph	40	99	100	100	100
0	fluazinam	0.04	23	-	56	-
0	fluazinam	2	71	-	89	-
0	fluazinam	10	99	-	98	-
0	fluazinam	40	99	-	100	-
0	fluazinam	200	100	-	100	-
0.001	fluazinam	0.04	75	66	8	65
0.001	fluazinam	2	90	87	75	92
0.001	fluazinam	10	97	100	100	98
0.001	fluazinam	40	100	99	100	100

(continued)

Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.001	fluazinam	200	100	100	99	100
0.01	fluazinam	0.04	95	99	75	88
0.01	fluazinam	2	97	100	90	97
0.01	fluazinam	10	100	100	100	99
0.01	fluazinam	40	100	100	100	100
0.01	fluazinam	200	100	100	100	100
0	folpet	0.04	0	-	0	-
0	folpet	2	8	-	0	-
0	folpet	10	31	-	44	-
0	folpet	40	46	-	74	-
0	folpet	200	93	-	87	-
0.001	folpet	0.04	16	56	0	21
0.001	folpet	2	23	59	0	21
0.001	folpet	10	44	70	65	56
0.001	folpet	40	51	76	87	79
0.001	folpet	200	87	97	86	90
0.01	folpet	0.04	85	99	31	73
0.01	folpet	2	86	99	75	73
0.01	folpet	10	75	99	86	85
0.01	folpet	40	65	99	89	93
0.01	folpet	200	95	100	99	97
0	mancozeb	0.04	23	-	0	-
0	mancozeb	2	24	-	0	-
0	mancozeb	10	66	-	36	-
0	mancozeb	40	100	-	92	-
0	mancozeb	200	100	-	100	-
0.001	mancozeb	0.04	31	66	69	21
0.001	mancozeb	2	60	66	49	21
0.001	mancozeb	10	77	85	49	50
0.001	mancozeb	40	100	100	95	93
0.001	mancozeb	200	100	100	100	100
0.01	mancozeb	0.04	92	99	93	73
0.01	mancozeb	2	100	99	86	73
0.01	mancozeb	10	98	99	88	82
0.01	mancozeb	40	99	100	99	98
0.01	mancozeb	200	100	100	95	100

(continued)

Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	mandipropamid	0.08	80	-	86	-
0	mandipropamid	0.4	97	-	100	-
0	mandipropamid	2	99	-	100	-
0	mandipropamid	10	100	-	100	-
0	mandipropamid	40	100	-	100	-
0.001	mandipropamid	0.08	96	91	79	89
0.001	mandipropamid	0.4	93	99	100	100
0.001	mandipropamid	2	95	99	100	100
0.001	mandipropamid	10	98	100	100	100
0.001	mandipropamid	40	100	100	100	100
0.01	mandipropamid	0.08	98	100	97	96
0.01	mandipropamid	0.4	95	100	100	100
0.01	mandipropamid	2	100	100	100	100
0.01	mandipropamid	10	100	100	100	100
0.01	mandipropamid	40	100	100	100	100
0	propamocarb	10	0	-	46	-
0	propamocarb	40	0	-	31	-
0	propamocarb	200	0	-	86	-
0	propamocarb	1000	38	-	99	-
0	propamocarb	5000	92	-	100	-
0.001	propamocarb	10	38	56	72	57
0.001	propamocarb	40	51	56	76	45
0.001	propamocarb	200	56	56	88	89
0.001	propamocarb	1000	92	73	100	99
0.001	propamocarb	5000	98	96	100	100
0.01	propamocarb	10	97	99	93	85
0.01	propamocarb	40	95	99	93	81
0.01	propamocarb	200	97	99	100	96
0.01	propamocarb	1000	99	99	99	100
0.01	propamocarb	5000	100	100	100	100

Table O

Observed and Expected Effects of Compound 214 Alone and Mixtures with Ethanboxam, Fluopicolide, Fenamidone, Penthiopyrad and Quinoxyfen in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	-	0	0	-	0	-
0.00001	-	0	22	-	0	-
0.0001	-	0	7	-	0	-
0.001	-	0	22	-	24	-
0.01	-	0	98	-	88	-
0.1	-	0	100	-	100	-
0	ethaboxam	0.016	22	-	0	-
0	ethaboxam	0.08	15	-	0	-
0	ethaboxam	0.4	95	-	41	-
0	ethaboxam	2	87	-	100	-
0	ethaboxam	10	100	-	100	-
0.001	ethaboxam	0.016	22	40	0	24
0.001	ethaboxam	0.08	33	34	0	24
0.001	ethaboxam	0.4	67	96	0	56
0.001	ethaboxam	2	91	90	100	100
0.001	ethaboxam	10	96	100	100	100
0.01	ethaboxam	0.016	84	99	58	88
0.01	ethaboxam	0.08	99	99	53	88
0.01	ethaboxam	0.4	100	100	66	93
0.01	ethaboxam	2	100	100	100	100
0.01	ethaboxam	10	100	100	100	100
0	fluopicolide	0.08	7	-	0	-
0	fluopicolide	0.4	0	-	0	-
0	fluopicolide	2	90	-	83	-
0	fluopicolide	10	100	-	100	-
0	fluopicolide	40	100	-	100	-
0.001	fluopicolide	0.08	22	28	9	24
0.001	fluopicolide	0.4	69	22	33	24
0.001	fluopicolide	2	85	92	87	87
0.001	fluopicolide	10	100	100	100	100
0.001	fluopicolide	40	100	100	100	100
0.01	fluopicolide	0.08	99	99	79	88
0.01	fluopicolide	0.4	100	98	71	88
0.01	fluopicolide	2	100	100	95	98
0.01	fluopicolide	10	100	100	100	100

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Ethanboxam, Fluopicolide, Fenamidone, Penthiopyrad and Quinoxyfen in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.01	fluopicolide	40	100	100	100	100
0	fenamidone	0.08	22	-	0	-
0	fenamidone	0.4	30	-	0	-
0	fenamidone	2	99	-	85	-
0	fenamidone	10	100	-	100	-
0	fenamidone	40	100	-	100	-
0.001	fenamidone	0.08	30	40	0	24
0.001	fenamidone	0.4	74	45	0	24
0.001	fenamidone	2	92	99	91	89
0.001	fenamidone	10	100	100	100	100
0.001	fenamidone	40	100	100	100	100
0.01	fenamidone	0.08	99	99	80	88
0.01	fenamidone	0.4	94	99	76	88
0.01	fenamidone	2	100	100	97	98
0.01	fenamidone	10	100	100	100	100
0.01	fenamidone	40	100	100	100	100
0	penthiopyrad	0.4	0	-	0	-
0	penthiopyrad	2	22	-	0	-
0	penthiopyrad	10	7	-	0	-
0	penthiopyrad	40	15	-	0	-
0	penthiopyrad	200	7	-	16	-
0.001	penthiopyrad	0.4	65	22	16	24
0.001	penthiopyrad	2	22	40	0	24
0.001	penthiopyrad	10	61	28	0	24
0.001	penthiopyrad	40	70	34	0	24
0.001	penthiopyrad	200	48	28	40	36
0.01	penthiopyrad	0.4	100	98	66	88
0.01	penthiopyrad	2	100	99	63	88
0.01	penthiopyrad	10	99	99	68	88
0.01	penthiopyrad	40	100	99	63	88
0.01	penthiopyrad	200	98	99	94	90
0	quinoxyfen	0.4	0	-	0	-
0	quinoxyfen	2	7	-	0	-
0	quinoxyfen	10	7	-	0	-
0	quinoxyfen	40	0	-	0	-

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Ethanboxam, Fluopicolide, Fenamidone, Penthiopyrad and Quinoxyfen in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	quinoxyfen	200	0	-	0	-
0.001	quinoxyfen	0.4	7	22	0	24
0.001	quinoxyfen	2	49	28	0	24
0.001	quinoxyfen	10	68	28	0	24
0.001	quinoxyfen	40	76	22	0	24
0.001	quinoxyfen	200	53	22	0	24
0.01	quinoxyfen	0.4	99	98	47	88
0.01	quinoxyfen	2	100	99	47	88
0.01	quinoxyfen	10	93	99	17	88
0.01	quinoxyfen	40	100	98	16	88
0.01	quinoxyfen	200	100	98	0	88

Table P

Observed and Expected Effects of Compound 214 Alone and Mixtures with Cyazofamid, Valiphenal, Boscalid, Famoxadone, Kresoxim-methyl, Trifloxystrobin and proquinazid in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	-	0	24	-	37	-
0.00001	-	0	8	-	31	-
0.0001	-	0	17	-	16	-
0.001	-	0	39	-	63	-
0.01	-	0	94	-	68	-
0.1	-	0	100	-	100	-
0	cyazofamid	0.016	25	-	43	-
0	cyazofamid	0.08	52	-	57	-
0	cyazofamid	0.4	58	-	100	-
0	cyazofamid	2	100	-	100	-
0	cyazofamid	10	100	-	100	-
0.001	cyazofamid	0.016	8	54	72	78
0.001	cyazofamid	0.08	38	71	82	84
0.001	cyazofamid	0.4	84	74	100	100
0.001	cyazofamid	2	95	100	100	100
0.001	cyazofamid	10	100	100	100	100
0.01	cyazofamid	0.016	94	95	90	82

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Cyazofamid, Valiphenal, Boscalid, Famoxadone, Kresoxim-methyl, Trifloxystrobin and proquinazid in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.01	cyazofamid	0.08	95	100	98	100
0.01	cyazofamid	0.4	96	100	99	100
0.01	cyazofamid	2	100	100	100	100
0.01	cyazofamid	10	100	100	100	100
0	valiphenal	0.016	8	-	31	-
0	valiphenal	0.08	8	-	16	-
0	valiphenal	0.4	8	-	16	-
0	valiphenal	2	32	-	53	-
0	valiphenal	10	99	-	100	-
0.001	valiphenal	0.016	17	44	67	74
0.001	valiphenal	0.08	24	44	64	68
0.001	valiphenal	0.4	32	44	68	68
0.001	valiphenal	2	72	59	78	82
0.001	valiphenal	10	99	99	95	100
0.01	valiphenal	0.016	81	94	92	78
0.01	valiphenal	0.08	72	100	95	100
0.01	valiphenal	0.4	75	100	94	100
0.01	valiphenal	2	93	100	90	100
0.01	valiphenal	10	99	100	99	100
0	boscalid	0.04	25	-	68	-
0	boscalid	2	0	-	0	-
0	boscalid	10	0	-	0	-
0	boscalid	40	17	-	0	-
0	boscalid	200	32	-	0	-
0.001	boscalid	0.04	8	54	31	88
0.001	boscalid	2	21	39	16	63
0.001	boscalid	10	25	39	21	63
0.001	boscalid	40	17	49	0	63
0.001	boscalid	200	25	59	0	63
0.01	boscalid	0.04	63	95	93	90
0.01	boscalid	2	62	100	91	100
0.01	boscalid	10	68	100	76	100
0.01	boscalid	40	70	100	73	100
0.01	boscalid	200	71	100	0	100

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Cyazofamid, Valiphenal, Boscalid, Famoxadone, Kresoxim-methyl, Trifloxystrobin and proquinazid in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0	famoxadone	0.04	100	-	100	-
0	famoxadone	2	32	-	21	-
0	famoxadone	10	93	-	72	-
0	famoxadone	40	98	-	100	-
0	famoxadone	200	100	-	100	-
0.001	famoxadone	0.04	65	100	0	100
0.001	famoxadone	2	90	59	47	71
0.001	famoxadone	10	84	96	60	90
0.001	famoxadone	40	100	99	100	100
0.001	famoxadone	200	100	100	100	100
0.01	famoxadone	0.04	83	100	95	100
0.01	famoxadone	2	81	100	95	100
0.01	famoxadone	10	95	100	96	100
0.01	famoxadone	40	100	100	100	100
0.01	famoxadone	200	100	100	100	100
0	kresoxim-methyl	0.04	8	-	9	-
0	kresoxim-methyl	2	32	-	9	-
0	kresoxim-methyl	10	86	-	30	-
0	kresoxim-methyl	40	96	-	37	-
0	kresoxim-methyl	200	100	-	100	-
0.001	kresoxim-methyl	0.04	17	44	31	66
0.001	kresoxim-methyl	2	39	59	16	66
0.001	kresoxim-methyl	10	85	92	75	74
0.001	kresoxim-methyl	40	99	98	93	76
0.001	kresoxim-methyl	200	100	100	100	100
0.01	kresoxim-methyl	0.04	90	94	90	71

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Cyazofamid, Valiphenal, Boscalid, Famoxadone, Kresoxim-methyl, Trifloxystrobin and proquinazid in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.01	kresoxim-methyl	2	87	100	92	100
0.01	kresoxim-methyl	10	94	100	95	100
0.01	kresoxim-methyl	40	99	100	100	100
0.01	kresoxim-methyl	200	100	100	100	100
0	trifloxystrobin	0.04	0	-	0	-
0	trifloxystrobin	2	0	-	0	-
0	trifloxystrobin	10	72	-	16	-
0	trifloxystrobin	40	38	-	89	-
0	trifloxystrobin	200	25	-	100	-
0.001	trifloxystrobin	0.04	38	39	63	63
0.001	trifloxystrobin	2	38	39	39	63
0.001	trifloxystrobin	10	39	83	68	68
0.001	trifloxystrobin	40	25	62	83	96
0.001	trifloxystrobin	200	52	54	100	100
0.01	trifloxystrobin	0.04	62	94	89	68
0.01	trifloxystrobin	2	87	100	85	100
0.01	trifloxystrobin	10	62	100	83	100
0.01	trifloxystrobin	40	82	100	93	100
0.01	trifloxystrobin	200	87	100	98	100
0	proquinazid	0.04	17	-	0	-
0	proquinazid	2	0	-	0	-
0	proquinazid	10	8	-	0	-
0	proquinazid	40	8	-	0	-
0	proquinazid	200	17	-	0	-
0.001	proquinazid	0.04	55	49	0	63
0.001	proquinazid	2	17	39	0	63
0.001	proquinazid	10	8	44	0	63
0.001	proquinazid	40	25	44	31	63
0.001	proquinazid	200	25	49	9	63
0.01	proquinazid	0.04	77	95	24	68
0.01	proquinazid	2	81	100	37	100

(continued)

Observed and Expected Effects of Compound 214 Alone and Mixtures with Cyazofamid, Valiphenal, Boscalid, Famoxadone, Kresoxim-methyl, Trifloxystrobin and proquinazid in Controlling Tomato Late Blight and Cucumber Downy Mildew						
Application Rate (ppm) of Compound 214	Component (b)	Application Rate (ppm) of Component (b)	TLB		CDM	
			Obsd	Exp	Obsd	Exp
0.01	proquinazid	10	96	100	47	100
0.01	proquinazid	40	82	100	58	100
0.01	proquinazid	200	96	100	72	100

[0184] Tables M-P show compositions of the present invention comprising mixtures of the (a) compound with a variety of component (b) compounds demonstrating synergistic control of tomato late blight and cucumber downy mildew. As control cannot exceed 100 %, the increase above expected fungicidal activity can be greatest when the separate active ingredient components alone are at application rates providing considerably less than 100 % control. Synergy may not be evident at low application rates where the individual active ingredient components alone have little activity. However, in some instances high activity was observed for combinations wherein individual active ingredients alone at the same application rates had essentially no activity. As demonstrated above, this invention provides advantageous method of combating tomato late blight (*Phytophthora infestans*) and cucumber downy mildew (*Pseudoperonospora cubensis*) diseases.

Claims

1. A fungicidal composition comprising:

(a) at least one compound selected from 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone, its enantiomer or a mixture thereof, *N*-oxides, and salts thereof; and
(b) at least one additional fungicidal compound selected from amisulbrom, azoxystrobin, benthiavalicarb, boscalid, chlorothalonil, copper hydroxide, copper oxychloride, copper sulfate, cyazofamid, cymoxanil, cyproconazole, dithianon, difenoconazole, dimethomorph, ethaboxam, epoxiconazole, famoxadone, fenamidone, fluazinam, fluopicolide, flusilazole, folpet, fosetyl-aluminum, iprovalicarb, kresoxim-methyl, mancozeb, mandipropamid, metalaxyl, metalaxyl-M, metconazole, metiram, penthiopyrad, phosphorous acid and salts, picoxystrobin, propamacarb, propiconazole, propineb, proquinazid, pyraclostrobin, quinoxyfen, tebuconazole, triadimenol, trifloxystrobin, valiphenal, and zoxamide.

2. A fungicidal composition of Claim 1, wherein component (b) is selected from azoxystrobin, benthiovalicarb, chlorothalonil, dimethomorph, dithianon, difenoconazole, famoxadone, folpet, fluazinam, fosetyl-aluminum, mancozeb, mandipropamid, metalaxyl, metalaxyl-M, phosphorous acid and salts, and zoxamide.

3. A fungicidal composition of Claim 1 or Claim 2, wherein component (a) is 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone.

4. A fungicidal composition of Claim 1 or Claim 2, wherein component (a) is a racemic mixture of 1-[4-[4-[(5*R*)-5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone and its enantiomer.

5. The composition of any of Claims 1-4 further comprising at least one additional component selected from the group consisting of a surfactant, a solid diluent and a liquid diluent.

6. The composition of any of Claims 1-5 wherein weight ratio of component (a) to component (b) is from 125:1 to 1:125.

7. A method for controlling a plant disease caused by a fungal plant pathogen comprising applying to the plant or portion thereof, or to the plant seed, a fungicidally effective amount of the composition of any of Claims 1 to 6.

Patentansprüche

1. Fungizide Zusammensetzung, umfassend:

   (a) mindestens eine Verbindung ausgewählt unter 1-[4-[4-[(5R)-5-(2,6-Difluorphenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluormethyl)-1H-pyrazol-1-yl]ethanon, ihrem Enantiomer oder einer Mischung davon, N-oxiden und Salzen davon; und
   (b) mindestens eine zusätzliche fungizide Verbindung ausgewählt unter Amisulbrom, Azoxystrobin, Benthiavalicarb, Boscalid, Chlorthalonil, Kupferhydroxid, Kupferoxychlorid, Kupfersulfat, Cyazofamid, Cymoxanil, Cyproconazol, Dithianon, Difenoconazol, Dimethomorph, Ethaboxam, Epoxiconazol, Famoxadon, Fenamidon, Fluazinam, Fluopicolid, Flusilazol, Folpet, Fosetyl-Aluminium, Iprovalicarb, Kresoxim-Methyl, Mancozeb, Mandipropamid, Metalaxyl, Metalaxyl-M, Metconazol, Metiram, Penthiopyrad, Phosphorsäure und -salzen, Picoxystrobin, Propamacarb, Propiconazol, Propineb, Proquinazid, Pyraclostrobin, Quinoxyfen, Tebuconazol, Triadimenol, Trifloxystrobin,Valiphenal und Zoxamid.

2. Fungizide Zusammensetzung nach Anspruch 1, wobei die Komponente (b) ausgewählt wird unter Azoxystrobin, Benthiovalicarb, Chlorthalonil, Dimethomorph, Dithianon, Difenoconazol, Famoxadon, Folpet, Fluazinam, Fosetyl-Aluminium, Mancozeb, Mandipropamid, Metalaxyl, Metalaxyl-M, Phosphorsäure und -salzen und Zoxamid.

3. Fungizide Zusammensetzung nach Anspruch 1 oder Anspruch 2, wobei die Komponente (a) 1-[4-[4-[(SR)-5-(2,6-Difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanon ist.

4. Fungizide Zusammensetzung nach Anspruch 1 oder Anspruch 2, wobei die Komponente (a) eine racemische Mischung ist von 1-[4-[4-[(5R)-5-(2,6-Difluorphenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluormethyl)-1H-pyrazol-1-yl]ethanon und seinem Enantiomer.

5. Zusammensetzung nach einem der Ansprüche 1 - 4, ferner mindestens eine zusätzliche Komponente umfassend ausgewählt aus der Gruppe bestehend aus einem Tensid, einem festen Verdünnungsmittel und einem flüssigen Verdünnungsmittel.

6. Zusammensetzung nach einem der Ansprüche 1 - 5, wobei das Gewichtsverhältnis der Komponente (a) zur Komponente (b) 125:1 bis 1:125 beträgt.

7. Verfahren zum Bekämpfen einer Pflanzenkrankheit, die durch einen pflanzenschädigenden Pilzerreger verursacht wird, umfassend das Aufbringen auf die Pflanze oder einen Teil davon oder auf den Pflanzensamen einer fungizid wirksamen Menge der Zusammensetzung nach einem der Ansprüche 1 bis 6.

Revendications

1. Composition fongicide comprenant:

   (a) au moins un composé sélectionné parmi la 1-[4-[4-[(*5R*)-5-(2,6-difluorophényl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-pipéridinyl]-2-[5-méthyl-3-(trifluorométhyl)-1*H*-pyrazol-1-yl]éthanone, son énantiomère ou un mélange de ceux-ci, les *N*-oxydes, et les sels de ceux-ci; et
   (b) au moins un composé fongicide additionnel sélectionné parmi l'amisulbrom, l'azoxystrobine, le benthiavalicarbe, le boscalid, le chlorothalonil, l'hydroxyde de cuivre, l'oxychlorure de cuivre, le sulfate de cuivre, le cyazofamide, le cymoxanil, le cyproconazole, le dithianon, le difénoconazole, le diméthomorphe, l'éthaboxam, l'époxiconazole, la famoxadone, la fénamidone, le fluazinam, le fluopicolide, le flusilazole, le folpet, le fosétyl-aluminium, l'iprovalicarb, le krésoxim-méthyle, le mancozeb, le mandipropamide, le métalaxyle, le métalaxyl-M, le metconazole, le métirame, le penthiopyrad, l'acide et les sels phosphoreux, la picoxystrobine, le propamacarb, le propiconazole, le propineb, le proquinazid, la pyraclostrobine, le quinoxyfène, le tébuconazole, le triadiménol, la trifloxystrobine, le valiphénal, et le zoxamide.

2. Composition fongicide selon la revendication 1, dans laquelle le composant (b) est sélectionné parmi l'azoxystrobine, le benthiovalicarb, le chlorothalonil, le diméthomorphe, le dithianon, le difénoconazole, la famoxadone, le folpet, le fluazinam, le fosétyl-aluminium, le mancozeb, le mandipropamide, le métalaxyle, le métalaxyl-M, l'acide et les sels

phosphoreux, et le zoxamide.

3. Composition fongicide selon la revendication 1 ou 2, dans laquelle le composant (a) est la 1-[4-[4-[(5*R*)-5-(2,6-difluorophényl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-pipéridinyl]-2-[5-méthyl-3-(trifluorométhyl)-1*H*-pyrazol-1-yl]éthanone.

4. Composition fongicide selon la revendication 1 ou 2, dans laquelle le composant (a) est un mélange racémique de 1-[4-[4-[(5*R*)-5-(2,6-difluorophényl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-pipéridinyl]-2-[5-méthyl-3-(trifluorométhyl)-1*H*-pyrazol-1-yl]éthanone et son énantiomère.

5. Composition selon l'une quelconque des revendications 1 à 4 comprenant en outre au moins un composant additionnel sélectionné dans le groupe constitué d'un tensioactif, d'un diluant solide et d'un diluant liquide.

6. Composition selon l'une quelconque des revendications 1 à 5, dans laquelle le rapport en poids du composant (a) au composant (b) est de 125:1 à 1:125.

7. Procédé de régulation d'une phytopathologie causée par un pathogène fongique des végétaux comprenant l'application à la plante ou à une partie de celle-ci, ou à la semence de la plante, d'une quantité fongicidement efficace de la composition selon l'une quelconque des revendications 1 à 6.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2007014290 A **[0002]**
- WO 0134150 A **[0002]**
- WO 2008091580 A **[0002]**
- WO 2008013622 A **[0002]**
- WO 2008013925 A **[0002]**
- WO 2008091594 A **[0002]**
- WO 2009094407 A **[0002]**
- WO 2003010149 A **[0023]**
- US 4084955 A **[0044]**
- EP 6965811996 A, A. Jackson **[0054]**
- DE 35377621986 **[0059]**
- US 3557089 A, E. Raleigh **[0110]**
- WO 03024222 A **[0147]**
- US 3060084 A **[0148]**
- WO 9113546 A **[0148]**
- US 4172714 A **[0148]**
- US 4144050 A **[0148]**
- US 3920442 A **[0148]**
- DE 3246493 **[0148]**
- US 5180587 A **[0148]**
- US 5232701 A **[0148]**
- US 5208030 A **[0148]**
- GB 2095558 A **[0148]**
- US 3299566 A **[0148]**
- US 3235361 A **[0149]**
- US 3309192 A **[0149]**
- US 2891855 A **[0149]**
- WO 9424861 A **[0168]**
- US 6022552 A **[0168]**

Non-patent literature cited in the description

- **T. L. GILCHRIST.** Comprehensive Organic Synthesis. Pergamon Press, vol. 7, 748-750 **[0017]**
- **M. TISLER ; B. STANOVNIK.** Comprehensive Heterocyclic Chemistry. Pergamon Press, vol. 3, 18-20 **[0017]**
- **M. R. GRIMMETT ; B. R. T. KEENE.** Advances in Heterocyclic Chemistry. Academic Press, vol. 43, 149-161 **[0017]**
- **M. TISLER ; B. STANOVNIK.** Advances in Heterocyclic Chemistry. Academic Press, vol. 9, 285-291 **[0017]**
- **G. W. H. CHEESEMAN ; E. S. G. WERSTIUK.** Advances in Heterocyclic Chemistry. Academic Press, vol. 22, 390-392 **[0017]**
- **K. H. KUCK et al.** Modern Selective Fungicides - Properties, Applications and Mechanisms of Action. Gustav Fischer Verlag, 1995, 205-258 **[0021]**
- Catalytic Hydrogenation. Elsevier Science, 1986 **[0047]**
- **T. W. GREENE ; P. G. M. WUTS.** Protective Groups in Organic Synthesis. Wiley, 1991 **[0048] [0065]**
- Comprehensive Heterocyclic Chemistry. Pergamon Press, 1984, vol. 4-6 **[0049] [0050]**
- Comprehensive Heterocyclic Chemistry II. Pergamon Press, 1996, vol. 2-4 **[0049] [0050]**
- The Chemistry of Heterocyclic Compounds. Wiley **[0049] [0050]**
- **S. BELLOTTE.** *Synlett,* 1998, 379-380 **[0049]**
- **M. NAKAMURA et al.** *Synlett,* 2005, 1794-1798 **[0049]**
- Rodd's Chemistry of Carbon Compounds. Elsevier, vol. 2-4 **[0050]**
- *Synthesis,* 1982, vol. 6, 508-509 **[0050]**
- **KANEMASA et al.** *Tetrahedron,* 2000, vol. 56, 1057-1064 **[0050]**
- **C. A. ZIFICSAK ; D. J. HLASTA.** *Tetrahedron,* 2004, vol. 60, 8991-9016 **[0051]**
- Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist. Elsevier, 2000 **[0051]**
- **S. F. NELSEN et al.** *J. Org. Chem,* 1990, vol. 55, 3825 **[0059]**
- **WATKINS et al.** Handbook of Insecticide Dust Diluents and Carriers,. Dorland Books **[0140]**
- **MARSDEN.** Solvents Guide. Interscience, 1950 **[0141]**
- McCutcheon's Emulsifiers and Detergents. annual American and International Editions. McCutcheon's Division, The Manufacturing Confectioner Publishing Co, **[0146]**
- **SISELY ; WOOD.** Encyclopedia of Surface Active Agents. Chemical Publ. Co., Inc, 1964 **[0146]**
- **A. S. DAVIDSON ; B. MILWIDSKY.** Synthetic Detergents. John Wiley and Sons, 1987 **[0146]**
- Functional Materials. **MCCUTCHEON.** annual International and North American editions. McCutcheon's Division, The Manufacturing Confectioner Publishing Co, vol. 2 **[0147]**
- Agglomeration. **BROWNING.** Chemical Engineering. 04 December 1967, 147-48 **[0148]**

- Perry's Chemical Engineer's Handbook. McGraw-Hill, 1963, 8-57 **[0148]**
- The Formulator's Toolbox - Product Forms for Modern Agriculture. **T. S. WOODS.** Pesticide Chemistry, and Bioscience, The Food-Environment Challenge. The Royal Society of Chemistry, 1999, 120-133 **[0149]**
- **KLINGMAN.** Weed Control as a Science. John Wiley and Sons, Inc, 1961, 81-96 **[0149]**
- **HANCE et al.** Weed Control Handbook. Blackwell Scientific Publications, 1989 **[0149]**
- Developments in formulation technology. PJB Publications, 2000 **[0149]**
- The Pesticide Manual. British Crop Protection Council, 2003 **[0161] [0166]**
- The BioPesticide Manual. British Crop Protection Council, 2001 **[0161] [0166]**
- **TAMES, P. M. L.** *Neth. J. Plant Pathology,* 1964, vol. 70, 73-80 **[0174]**
- **COLBY, S. R.** Calculating Synergistic and Antagonistic Responses of Herbicide Combinations. *Weeds,* 1967, vol. 15, 20-22 **[0179]**

SZABADALMI IGÉNYPONTOK

1. Fungicid kompozíció, amely tartalmaz:

(a) legalább egy vegyületet, amely ki van választva a következők közül:: 1-[4-[4-[(5*R*)-5-(2,6-difluorfenil)-4,5-dihidro-3-izoxazolil]-2-thiazolil]-1-piperidinil]-2-[5-metil-3-(trifluormetil)-1*H*-pirazol-1-il]etanon, enantiomere vagy annak keveréke, annak *N*-oxidjai, és sói; és

(b) legalább egy további fungicid vegyület, amely ki van választva a következők közül: amisulbrom, azoxistrobin, benthiavalicarb, boscalid, klórthalonil, rézhidroxid, rézoxiklorid, rézszulfát, cyazofamid, cymoxanil, cyproconazol, dithianon, difenoconazol, dimethomorph, ethaboxam, epoxiconazol, famoxadon, fenamidon, fluazinam, fluopicolide, flusilazol, folpet, fosetil-aluminum, iprovalicarb, kresoxim-metil, mancozeb, mandipropamid, metalaxil, metalaxil-M, metconazol, metiram, pentiopirad, foszforsav és sók, picoxistrobin, propamacarb, propiconazol, propineb, proquinazid, piraclostrobin, kinoxifen, tebuconazol, triadimenol, trifloxistrobin, valiphenal, és zoxamid.

2. Az 1. igénypont szerinti fungicid kompozíció, ahol komponens (b) ki van választva a következők közül: azoxistrobin, benthiovalicarb, klórthalonil, dimethomorf, dithianon, difenoconazol, famoxadon, folpet, fluazinam, fosetil-aluminum, mancozeb, mandipropamid, metalaxil, metalaxil-M, foszforossav és sók , és zoxamid.

3. Az 1. vagy 2. igénypont szerinti fungicid kompozíció , ahol komponens (a) 1-[4-[4-[(5*R*)-5-(2,6-difluorfenil)-4,5-dihidro-3-izoxazolil]-2-thiazolil]-1-piperidinil]-2-[5-metil-3-(trifluormetil)-1*H*-pirazol-1-il]etanon.

4. Az 1. vagy 2. igénypont szerinti fungicid kompozíció, ahol komponens (a) 1-[4-[4-[(5*R*)-5-(2,6-difluorfenil)-4,5-dihidro-3-izoxazolil]-2-thiazolil]-1-piperidinil]-2-[5-metil-3-(trifluormetil)-1*H*-pirazol-1-il]etanon és enantiomerének racém keveréke.

5. Az 1-4. igénypontok bármelyike szerinti kompozíció, amely továbbá tartalmaz legalább egy további komponenst, amely ki van választva a következőkből álló csoportból: szurfaktáns, szilárd oldószer és folyékony oldószer.

6. Az 1-5. igénypontok bármelyike szerinti kompozíció, ahol komponens (a)-nak komponens (b)-hez viszonyított súlyaránya 125:1 - 1:125.

7. Eljárás növénybetegség leküzdésére, amelyet gomba növény patogén okoz, amely tartalmazza az 1-6. igénypontok bármelyike szerinti kompozíció fungicidesen hatásos mennyiségének növényre vagy annak részére alkalmazását, vagy növény magjára alkamazását.