US 20190256501A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2019/0256501 A1**

Tosatti et al. (43) **Pub. Date: Aug. 22, 2019**

(54) **HETEROARYL-1,2,4-TRIAZOLE AND HETEROARYL-TETRAZOLE COMPOUNDS FOR CONTROLLING ECTOPARASITES**

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(21) Appl. No.: **16/399,330**

(22) Filed: **Apr. 30, 2019**

Related U.S. Application Data

(63) Continuation of application No. 15/556,722, filed on Sep. 8, 2017, now Pat. No. 10,287,276, filed as application No. PCT/US2017/030082 on Apr. 28, 2017.

(60) Provisional application No. 62/332,004, filed on May 5, 2016.

Publication Classification

(51) **Int. Cl.**

C07D 405/14	(2006.01)
C07D 401/04	(2006.01)
A61P 33/14	(2006.01)
C07D 403/04	(2006.01)
C07D 401/14	(2006.01)

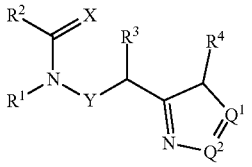
(52) **U.S. Cl.**

CPC ***C07D 405/14*** (2013.01); ***C07D 401/04*** (2013.01); ***C07D 401/14*** (2013.01); ***C07D 403/04*** (2013.01); ***A61P 33/14*** (2018.01)

(57) **ABSTRACT**

The present invention provides compounds of the formula: (I) wherein: X is O or S; Q^1 and Q^2 are independently CR^5 or N, provided at least one of Q^1 and Q^2 is N; Y is a direct bond or CH_2; R^1 is H, optionally substituted alkyl, alkenyl, alkynyl, cycloalkylalkyl, benzyl or oxetan-3-yl-CH_2—; R^2 is optionally substituted phenyl, pyridine, pyrimidine, pyrazine or pyridazine; R^3 is alkyl or haloalkyl; R^4 is optionally substituted pyridine, pyrimidine, pyrazine or pyridazine; R^5 is H, alkyl, haloalkyl, cycloalkyl, alkoxy, alkoxyC(O)— or (alkoxy)$_2$CH—; or a salt thereof. The compounds are useful for controlling ectoparasites on animals.

(I)



HETEROARYL-1,2,4-TRIAZOLE AND HETEROARYL-TETRAZOLE COMPOUNDS FOR CONTROLLING ECTOPARASITES

[0001] The present invention relates to novel heteroaryl-1,2,4-triazole and heteroaryl-tetrazole compounds, to formulations comprising the compounds and to their use in the control of ectoparasites on animals.

[0002] The present invention is in the field of pest control, in particular the control of ectoparasites on animals. Parasitic infections result in significant suffering to the animal, both as a consequence of the infection itself and the diseases transmitted by the parasites. In addition, parasitic infection in livestock animals can result in significant economic loss. This is observed, for example, in the cattle industry where tick infestation, in particular, causes major losses. When ticks feed in large numbers they consume large quantities of blood which can result in anaemia and loss of nutrients. In addition, the irritation caused by the ticks leads to a reduction in food intake by the cattle. All these factors negatively impact weight gain and milk production (Rajput et al., J. Zhejiang Univ. SCIENCE B, 2006, 7(11):912-921). Furthermore, ticks cause damage to the hide (Rajput et al.) and predispose the cattle to bacterial and fungal infections. A number of diseases are known to be transmitted via tick-borne pathogens, among them are the cattle diseases bovine babesiosis, also known as pyroplasmosis or red water fever, and bovine anaplasmosis, also known as gall sickness (Rajput et al.). These diseases lead to lower weight gain, decreased milk production and increased mortality.

[0003] There are many commercially available compounds in common usage for the control of ectoparasites. For livestock animals these include amitraz; fluazuron; synthetic pyrethroids, for example permethrin; macrocyclic lactones, for example ivermectin; and organophosphates. For companion animals these include fipronil; synthetic pyrethroids; and GABA-gated chloride channel inhibitors, for example fluralaner. Despite the wide range of products on the market, there remains a need for alternative compounds which are effective in the control of ectoparasites.

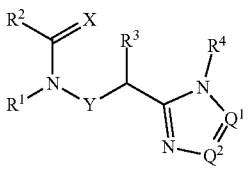
[0004] WO 2006/004924 discloses a series of heteroaryl-imidazole compounds which are modulators of the CXCR3 receptor. Modulators of the CXCR3 receptor are useful in the treatment and prevention of certain inflammatory and immunoregulatory disorders and diseases.

[0005] The present invention provides novel heteroaryl-1,2,4-triazole and heteroaryl-tetrazole compounds which are useful in the control of pests, especially the control of ectoparasites on animals.

[0006] The present invention provides compounds of Formula 1:

[0007] wherein:

(I)



[0008] X is O or S;

[0009] Q^1 and Q^2 are independently CR^5 or N, provided at least one of Q^1 and Q^2 is N;

[0010] Y is a direct bond or CH_2;

[0011] R^1 is H; C_1-C_6alkyl optionally substituted with one substituent selected from: CN, $CONH_2$, COOH, NO_2 and —$Si(CH_3)_3$; C_1-C_6haloalkyl; C_2-C_6alkenyl; C_2-C_6haloalkenyl; C_2-C_6alkynyl; C_2-C_6haloalkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted with halo or C_1-C_3haloalkyl;

[0012] R^2 is phenyl, pyridine, pyrimidine, pyrazine or pyridazine, wherein the phenyl, pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one to three substituents, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group, each independently selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3thiohaloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halo, NO_2, SF_5, CN, $CONH_2$, COOH and $C(S)NH_2$;

[0013] R^3 is C_1-C_3alkyl or C_1-C_3haloalkyl;

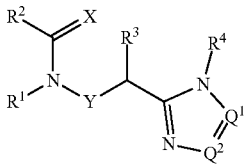
[0014] R^4 is pyridine, pyrimidine, pyrazine or pyridazine, wherein the pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one substituent selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_3-C_4cycloalkyl, halo or hydroxy;

[0015] R^5 is H, C_1-C_3alkyl, C_1-C_3haloalkyl, C_3-C_4cycloalkyl, C_1-C_3alkoxy, C_1-C_3alkoxyC(O)— or (C_1-C_3alkoxy)$_2$CH—;

[0016] or a salt thereof.

[0017] In an alternative embodiment the present invention provides compounds of Formula 1:

(I)



[0018] wherein:

[0019] X is O or S;

[0020] Q^1 and Q^2 are independently CR^5 or N, provided at least one of Q^1 and Q^2 is N;

[0021] Y is a direct bond or CH_2;

[0022] R^1 is H; C_1-C_6alkyl optionally substituted with one substituent selected from: CN, $CONH_2$, COOH and NO_2; C_1-C_6haloalkyl; C_2-C_6alkenyl; C_2-C_6haloalkenyl; C_2-C_6alkynyl; C_2-C_6haloalkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted with halo or C_3-C_3haloalkyl;

[0023] R^2 is phenyl, pyridine, pyrimidine, pyrazine or pyridazine, wherein the phenyl, pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one to three

substituents, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group, each independently selected from: C_1-C_3alkyl, C_1-C_3haloakyl, C_1-C_3thiohaloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halo, NO_2, SF_5, CN, $CONH_2$ and COOH;

[0024] R^3 is C_1-C_3alkyl or C_1-C_3haloalkyl;

[0025] R^4 is pyridine, pyrimidine, pyrazine or pyridazine, wherein the pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one substituent selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_3-C_4cycloalkyl, halo or hydroxy;

[0026] R^5 is H, C_1-C_3alkyl, C_1-C_3haloalkyl, C_3-C_4cycloalkyl or C_1-C_3alkoxy;

[0027] or a salt thereof.

[0028] The present invention also provides a formulation comprising a compound of the invention, or a salt thereof, and at least one acceptable carrier.

[0029] The present invention provides a compound of the invention, or a salt thereof, for use in therapy. The present invention provides a compound of the invention, or a salt thereof, for use in controlling parasites in or on an animal. The present invention further provides a compound of the invention, or a salt thereof, for use in controlling ectoparasites on an animal. The present invention further provides a compound of the invention, or a salt thereof, for use in preventing and/or treating diseases transmitted by ectoparasites.

[0030] The present invention provides the use of a compound of the invention, or a salt thereof, for the manufacture of a medicament for controlling parasites in or on an animal. The present invention further provides the use of a compound of the invention, or a salt thereof, for the manufacture of a medicament for controlling ectoparasites on an animal. The present invention further provides the use of a compound of the invention, or a salt thereof, for the manufacture of a medicament for preventing and/or treating diseases transmitted by ectoparasites.

[0031] The present invention provides the use of a compound of the invention, or a salt thereof, in controlling parasites in or on an animal. The present invention further provides the use of a compound of the invention, or a salt thereof, in controlling ectoparasites on an animal.

[0032] The present invention provides a method of controlling parasites in or on an animal in need thereof comprising administering an effective amount of a compound of the invention, or a salt thereof. The present invention further provides a method of controlling ectoparasites on an animal in need thereof comprising administering an effective amount of a compound of the invention, or a salt thereof. The present invention further provides a method for preventing and/or treating diseases transmitted by ectoparasites comprising administering an effective amount of a compound of the invention, or a salt thereof, to an animal in need thereof.

[0033] The present invention additionally provides a method for controlling pests comprising contacting the pests or their environment with an effective amount of a compound of the invention, or a salt thereof.

[0034] As used herein, the term "C_1-C_6alkyl" refers to a straight or branched, monovalent saturated aliphatic chain of one to six carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like.

[0035] Likewise, the term "C_1-C_3alkyl" includes methyl, ethyl, isopropyl, and the like.

[0036] As used herein, the term "C_1-C_6haloalkyl" refers to a C_1-C_6alkyl moiety substituted with one or more halogen atoms which may be the same or different. Examples include trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, 4-chlorobutyl, and the like.

[0037] Likewise, the term "C_1-C_3haloalkyl" includes trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, and the like.

[0038] As used herein the term "C_1-C_3thiohaloalkyl" refers to a C_1-C_3haloalkyl moiety linked through a sulfur atom.

[0039] As used herein, the term "C_3-C_4cycloalkyl" refers to cyclopropyl or cyclobutyl.

[0040] As used herein, the term "C_3-C_4cycloalkyl-C_1-C_2alkyl-" refers to a C_3-C_4cycloalkyl linked through a C_1-C_2alkyl chain.

[0041] As used herein, the term "C_2-C_6alkenyl" refers to a straight or branched alkenyl chain having form two to six carbon atoms and one double bond, for example, ethenyl, prop-1-enyl, but-2-enyl, and the like.

[0042] As used herein, the term "C_2-C_6haloalkenyl" refers to a C_2-C_6alkenyl moiety substituted with one or more halo atoms which may be the same or different.

[0043] As used herein, the term "C_2-C_6alkynyl" refers to a straight or branched alkynyl chain having from two to six carbon atoms and one triple bond, for example, ethynyl, prop-2-ynyl, but-3-ynyl, and the like.

[0044] As used herein, the term "C_2-C_6haloaknyl" refers to a C_2-C_6alkynyl moiety substituted with one or more halo atoms which may be the same or different.

[0045] As used herein, the term "halo" refers to a chlorine, bromine, iodine or fluorine atom.

[0046] As used herein, the term "C_1-C_3alkoxy" refers to a straight or branched alkyl chain having from 1 to 3 carbon atoms attached to an oxygen atom, for example, ethoxy, propoxy, tert-butoxy, and the like.

[0047] As used herein, the term "C_1-C_3haloalkoxy" refers to a C_1-C_3alkoxy moiety substituted with one or more halogen atoms which may be the same or different. Examples include trifluoromethoxy, 2-fluoroethoxy, 3-fluoropropoxy, 3,3,3-trifluoropropoxy, 4-chlorobutoxy, and the like.

[0048] As used herein, the term "controlling" refers to reducing the number of pests or parasites, eliminating pests or parasites and/or preventing further pest or parasite infestation.

[0049] As used herein, the term "treating" refers to restraining, slowing, stopping or reversing the progression or severity of an existing symptom or disease.

[0050] As used herein, the term "preventing" refers to the avoidance of a symptom or disease developing in the animal.

[0051] As used herein, the term "animal" may refer to a mammal and a non-mammal, such as a bird or fish. In the case of a mammal, it may be a human or non-human mammal. Non-human mammals include, but are not limited to, livestock animals and companion animals. Livestock animals include, but are not limited to, cattle, camellids,

pigs, sheep, goats and horses. Companion animals include, but are not limited to, dogs, cats and rabbits.

[0052] As used herein, the term "pest" includes, but is not limited to, animal and plant pests. The term encompasses all stages in the life cycle of the pest.

[0053] A "parasite" is a pest which lives in or on the host animal and benefits by deriving nutrients at the host animal's expense. An "endoparasite" is a parasite which lives in the host animal. An "ectoparasite" is a parasite which lives on the host animal. Ectoparasites include, but are not limited to, acari, insects and crustaceans (e.g. sea lice). The Acari (or Acarina) sub-class comprises ticks and mites. Ticks include, but are not limited to, members of the following genera: *Rhipicephalus*, for example, *Rhipicaphahts* (*Boophilus*) *microplus* and *Rhipicephalus sanguineus; Amblyomma; Dermacentor; Haemaphysalis; Hyalomma; Ixodes; Rhipicentor; Margaropus; Argas; Otobius*; and *Ornithodoros*. Mites include, but are not limited to, members of the following genera: *Chorioptes*, for example *Chorioptes Bovis; Psoroptes*, for example *Psoroptes avis; Cheyletiella; Dermanyssus*; for example *Dermanyssus gallinae; Ortnithonyssus; Demodex*, for example *Demodex canis; Sarcoptes*, for example *Sarcoptes scabiei*; and *Psorergates*. Insects include, but are not limited to, members of the orders: Siphonaptera, Diptera, Phthiraptera, Lepidoptera, Coleoptera and Homoptera. Members of the Siphonaptera order include, but are not limited to, *Ctenocephalides felis* and *Ctenocephalides canis*. Members of the Diptera order include, but are not limited to, *Musca* spp; bot fly, for example *Gasterophilus intestinalis* and *Oestrus ovis*; biting flies; horse flies, for example *Haematopota* spp. and *Tabunus* app.; *haematobia*, for example *haematobia irritans; Stomoxys; Lucilia*; midges; and mosquitoes. Members of the Phthiraptera class include, but are not limited to, blood sucking lice and chewing lice, for example *Bovicola Ovis* and *Bovicola Bovis.*

[0054] As used herein, the term "effective amount" refers to the amount or dose of the compound of the invention, or a salt thereof, which, upon single or multiple dose administration to the animal, provides the desired effect in or on the animal.

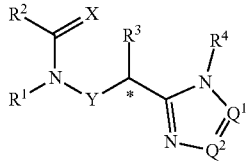
[0055] An effective amount can he readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the parasite to be controlled and the degree of infestation; the specific disease or disorder involved: the degree of or involvement or the severity of the disease or disorder; the response of the individual; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

[0056] The compounds of the invention may be administered to the animal by any route which has the desired effect including, but not limited to topically, orally, parenterally and subcutaneously. Topical administration is preferred. Formulations suitable for topical administration include, for example, solutions, emulsions and suspensions and may take the form of a pour-on, spot-on, spray-on, spray race or dip. In the alternative, the compounds of the invention may be administered by means of an ear tag or collar.

[0057] Salt forms of the compounds of the invention include both pharmaceutically acceptable salts and veterinary acceptable salts. Pharmaceutically and veterinary acceptable salts and common methodology for preparing them are well known in the art. See, for example, Gould, P. L., "Salt selection for basic drugs,"*International Journal of Pharmaceutics,* 33: 201-217 (1986); Bastin, R. J., et al. "Salt Selection and Optimization Procedures for Pharmaceutical New Chemical Entities," *Organic Process Research and Development,* 4: 427-435 (2000); and Berge, S. M., et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences,* 66: 1-19, (1977). One skilled in the art of synthesis will appreciate that the compounds of the invention are readily converted to and may be isolated as a salt, such as a hydrochloride salt, using techniques and conditions well known to one of ordinary skill in the art. In addition, one skilled in the art of synthesis will appreciate that the compounds of the invention are readily converted to and may be isolated as the corresponding free base from the corresponding salt.

[0058] As one of ordinary skill in the art will appreciate, compounds of Formula I contain a stereogenic centre which is indicated with an asterisk in the structure below:

(I)



[0059] The present invention contemplates both racemates and individual enantiomers. Compounds having preferred stereochemistry are set out below.

[0060] Preferred compounds of Formula I, or salts thereof, include compounds having one or more of the following features:

[0061] a) Y is a direct bond;

[0062] b) X is O;

[0063] c) X is S;

[0064] d) R^3 is methyl;

[0065] e) Q^1 is N;

[0066] f) Q^2 is CR^5 and R^5 is H, C_1-C_3alkyl, C_1-C_3alkoxyC(O)—, or $(C_1$-C_3alkoxy$)_2$CH—;

[0067] g) Q^2 is CR^5 and R^5 is H, C_1-C_3alkyl, or $(C_1$-C_3alkoxy$)_2$CH—;

[0068] h) Q^2 is CR^5 and R^5 is H or C_1-C_3alkyl;

[0069] i) Q^2 is CR^5 and R^5 is H, methyl or $(CH_3CH_2O)_2CH$—;

[0070] j) Q^2 is CR^5 and R^5 is H or methyl;

[0071] k) Q^2 is CR^5 and R^5 is H;

[0072] l) Q^1 is N, Q^2 is CR^5 and R^5 is H, methyl or $(CH_3CH_2O)_2CH$—;

[0073] m) Q^1 is N, Q^2 is CR^5 and R^5 is H or methyl;

[0074] n) R^4 is a 2-pyridine; or 2-pyrimidine optionally substituted with C_1-C_3alkoxy or halo;

[0075] o) R^4 is a 2-pyridine; or 2-pyrimidine optionally substituted with C_1-C_3alkoxy;

[0076] p) R^4 is 2-pyridine or 2-pyrimidine;

[0077] q) R^4 is 2-pyrimidine;

[0078] r) R^1 is H; C_1-C_6haloalkyl; C_1-C_6alkyl optionally substituted with CN or $Si(CH_3)_3$; C_3-C_6alkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted with halo;

[0079] s) R^1 is H; C_1-C_6haloalkyl; C_1-C_6alkyl optionally substituted with CN or $Si(CH_3)_3$; C_3-C_6alkynyl; or C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms;

[0080] t) R^1 is C_1-C_6haloalkyl; C_1-C_6alkyl; C_3-C_6alkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms;

[0081] u) R^1 is cyclopropyl-CH_2—; n-propyl, $CF_3{\equiv}CH_2$—CH_2—, FCH_2CH_2—, $FCH_2CH_2CH_2$—, 2,2-difluorocyclopropyl-CH_2, 2,2-dichlorocyclopropyl-CH_2—, H, CH_3—, $(CH_3)_3SiCH_2$—, CH_3CH_2— or CN—CH_2—;

[0082] v) R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH_2—, $CF_3CH_2CH_2$—, FCH_2CH_2—, $FCH_2CH_2CH_2$—, 2,2-difluorocyclopropyl-CH_2— or 2,2-dichlorocyclopropyl-CH_2—;

[0083] w) R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH2—, $CF_3CH_2CH_2$—, FCH_2CH_2—, $FCH_2CH_2CH_2$—, 2,2-difluorocyclopropyl-CH_2—, H, CH_3, $(CH_3)_3SiCH_2$— or CH_3CH_2—;

[0084] x) R^1 is cyclopropyl-CH_2—; n-propyl, CH≡C—CH_2—, $CF_3CH_2CH_2$—, FCH_2CH_2—, $FCH_2CH_2CH_2$—, or 2,2-difluorocyclopropyl-CH_2—;

[0085] x) R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH_2—, $CF_3CH_2CH_2$—, FCH_2CH_2—, or $FCH_2CH_2CH_2$—;

[0086] y) R^1 is CH≡C—CH_2—, cyclopropyl-CH_2—, H or CH_3;

[0087] z) R^1 is CH≡C—CH_2— or cyclopropyl-CH_2—;

[0088] aa) R^1 is cyclopropyl-CH_2—;

[0089] bb) R^2 is phenyl, 3-pyridine or 4-pyridine substituted with one or two substituents selected from: C_1-C_3haloalkyl, C_1-C_3haloalkoxy, halo, CN or C(S)NH_2, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group;

[0090] cc) R^2 is phenyl, 3-pyridine or 4-pyridine substituted with one or two substituents selected from: C_1-C_3haloalkyl, C_1-C_3haloalkoxy, halo or CN, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group;

[0091] dd) R^2 is phenyl or 3-pyridine substituted with one or two substituents selected from: C_1-C_3haloalkyl, C_1-C_3haloalkoxy, halo or CN, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group;

[0092] ee) R^2 is 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-trifluoromethoxyphenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, 5-trifluoromethylpyridin-3-yl, 3-bromo-5-trifluoromethylphenyl, 3-cyano-5-trifluoromethyl-phenyl or 2,6-bis(trifluoromethyl)pyridin-4-yl;

[0093] ff) R^2 is 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-trifluoromethoxyphenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, 5-trifluoromethylpyridin-3-yl, 3-bromo-5-trifluoromethylphenyl or 3-cyano-5-trifluoromethyl-phenyl;

[0094] gg) R^2 is 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-trifluoromethoxyphenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, or 5-trifluoromethylpyridin-3-yl;

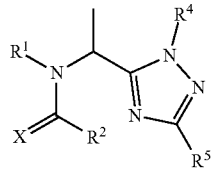
[0095] hh) R^2 is 3,5-bis(trifluoromethyl)phenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, 5-trifluoromethyl-pyridin-3-yl or 3-cyano-5-trifluoromethylphenyl;

[0096] ii) R^2 is 3,5-bis(trifluoromethyl)phenyl, 3-chloro-5-trifluoromethylphenyl, 3-chloro-5-trifluoromethoxyphenyl or 5-trifluoromethylpyridin-3-yl;

[0097] jj) R^2 is 3,5-bis(trifluoromethyl)phenyl.

[0098] Preferred compounds of the present invention are compounds of Formula II':

(II')



[0099] X is O or S;

[0100] $R^1$is H; C_1-C_6haloalkyl; C_1-C_6alkyl optionally substituted with CN or —$Si(CH_3)_3$; C_3-C_6alkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted by halo;

[0101] R^2 is phenyl, 3-pyridine or 4-pyridine substituted with one or two substituents selected from: C_1-C_3haloalkyl, C_1-C_3haloalkoxy, halo, CN or C(S)NH_2, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

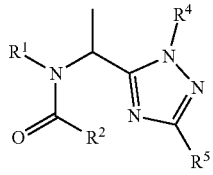
group;

[0102] R^4 is 2-pyridine; or 2-pyrimidine optionally substituted with C_1-C_3alkoxy or halo;

[0103] R^5 is H, C_1-C_3alkyl, C_1-C_3alkoxyC(O)— or (C_1-C_3alkoxy)$_2$CH—, or a salt thereof.

[0104] Preferred compounds of the present invention are compounds of Formula II:

(II)



[0105] wherein:

[0106] R^1 is C_1-C_6haloalkyl; C_1-C_6alkyl; C_3-C_6alkynyl; or C_3-C_4cycloalkyl-C_1-C_2alkyl wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms;

[0107] R^2 is phenyl or 3-pyridine substituted with one or two substituents selected from C_1-C_3haloalkyl, C_1-C_3haloalkoxy, halo or CN, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

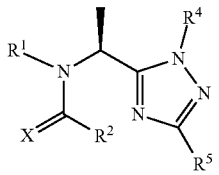
group;

[0108] R^4 is 2-pyridine; or 2-pyrimidine optionally substituted with C_1-C_3alkoxy;

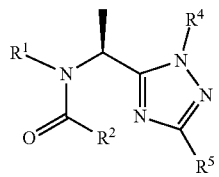
[0109] R^5 is H or C_1-C_3alkyl, or a salt thereof.

[0110] Particularly preferred compounds of the present invention are compounds of Formula II' or IIa:

(II'a)



(IIa)



wherein X, R^1, R^2, R^4 and R^5 are as defined for Formula II' or Formula II respectively; or a salt thereof.

[0111] Preferred compounds of Formula I, II' and II'a, or salts thereof, include those in which R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH_2—, $CF_3C_2CH_2$—, FCH_2CH_2—, $FCH_2CH_2CH_2$—, 2,2-difluorocyclopropyl-CH_2—, 2,2-dichlorocyclopropyl-CH_2—, H, CH_3, $(CH_3)_3SiCH_2$—, CH_3CH_2—, or CN—CH_2—; R^2 is 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-trifluoromethoxyphenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, 5-trifluoromethylpyridin-3-yl, 3-bromo-5-trifluoromethylphenyl, 3-cyano-5-trifluoromethylphenyl or 2,6-bis(trifluoromethyl)pyridin-4-yl; R^4 is 2-pyridine, or 2-pyrimidine optionally substituted with C_1-C_3alkoxy; and R^5 is H, methyl or $(CH_3CH_2O)_2CH$—.

[0112] Preferred compounds of Formula I, II', II, II'a and IIa, or salts thereof, include those in which R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH_2—, $CF_3CH_2CH_2$—, FCH_2CH_2—, $FCH_2CH_2CH_2$—, 2,2-difluorocyclopropyl-CH_2— or 2,2-dichlorocyclopropyl-CH_2—; R^2 is 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-trifluoromethoxyphenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, or 5-trifluoromethylpyridin-3-yl; R^4 is 2-pyridine, or 2-pyrimidine optionally substituted by C_1-C_3 alkoxy and R^5 is H or methyl.

[0113] Further preferred compounds of Formula I, II', II, II'a and IIa, or salts thereof, include those in which R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH_2—, $CF_3CH_2CH_2$—, FCH_2CH_2—, $FCH_2CH_2CH_2$— or 2,2-difluorocyclopropyl-CH_2—; R^2 is 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-trifluoromethoxyphenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanomethyl, 3-chloro-5-trifluoromethoxyphenyl, or 5-trifluoromethylpyridin-3-yl; R^4 is 2-pyridine, or 2-pyrimidine optionally substituted with C_1-C_3alkoxy; and R^5 is H or methyl.

[0114] Further preferred compounds of Formula I, II', II, II'a and IIa, or salts thereof, include those in which R^1 is cyclopropyl-CH_2—, n-propyl, CH≡C—CH_2—, $CF_3CH_2CH_2$—, FCH_2CH_2— or $FCH_2CH_2CH_2$—; R^2 is 3,5-bis(trifluoromethyl)phenyl, 3-chloro-5-trifluoromethylphenyl, 3-chloro-5-trifluoromethoxyphenyl or 5-trifluoromethylpyridin-3-yl; R^4 is 2-pyridine or 2-pyrimidine; and R^5 is H or methyl.

[0115] Further preferred compounds of Formula I, II', and II'a, or salts thereof, include those in which R^1 is CH≡C—CH_2—, cyclopropyl-CH_2—, H or CH_3; R^2 is 3,5-bis(trifluoromethyl)phenyl, 3-chloro-5-trifluoromethylphenyl, 3-cyanophenyl, 3-chloro-5-trifluoromethoxyphenyl, 5-trifluoromethylpyridin-3-yl or 3-cyano-5-trifluoromethylphenyl; R^4 is 2-pyridine, or 2-pyrimidine; and R^5 is H, methyl or $(CH_3CH_2O)_2CH$—.

[0116] A preferred compound of the present invention is N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide, or a salt thereof. An especially preferred compound is N-(cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide, or a salt thereof. Another preferred compound of the present invention is N-prop-2-ynyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide, or a salt thereof. An especially preferred compound is N-prop-2-ynyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide, or a salt thereof. Another preferred compound of the present invention is N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide, or a salt thereof. An especially preferred compound is N-methyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide, or a salt thereof.

[0117] The compounds of the present invention may be used for controlling parasites. In particular, they are useful for controlling ectoparasites on an animal. In one embodiment, the compounds of the present invention may be used for controlling ticks on cattle. In an alternative embodiment, the compounds of the present invention may be used for controlling ticks on sheep. In another alternative embodiment, the compounds of the present invention may be used for controlling lice on sheep. In another alternative embodiment, the compounds of the present invention may be used for controlling ticks on a dog or a cat. In another alternative embodiment, the compounds of the present invention may be used for controlling fleas on a dog or a cat. In another alternative embodiment, the compounds of the present invention may be used for controlling lice on a dog or a cat.

[0118] The compounds of the present invention may also be used for preventing and/or treating diseases, for example protozoan, bacterial and viral diseases, transmitted by ectoparasites. In particular, they may be used for the prevention and/or treatment of babesiosis, anaplasmosis and lyme disease.

[0119] The compounds of the present invention may be used alone or combination with one or more other compounds with are active against parasites or pests, including afoxolaner, fluralaner, lotilaner, surolaner, albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, parabendazole, tiabendazole, triclabendazole, arnitraz, demiditraz, clorsulon, closantel, oxyclonazide, rafoxanide, cyphenothrin, flumethrin, permethrin, cyromazine, derquantel, diamphenetide, dicyclanil, dinotefuran, imidacloprid, nitenpyram, thiamethoxam, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin oxime, emodepside, epsiprantel, fipronil, fluazuron, fluhexafon, indoxacarb, levamisol, lufenuron, metaflumizone, methoprene, monepantel, morantel, niclosamide, nitroscanate, nitroxynil, novaluron, oxantel, praziquantel, pyrantel, pyriprole, pyriproxyfen, sisapronil, spinosad, spinetoram and triflumezopyrim.

[0120] The compounds of Formula I, II', II, II'a and IIa can be prepared by one of ordinary skill in the art following art recognized techniques and procedures. More specifically, compounds of Formula I, II', II, II'a and IIa can be prepared as set forth in the schemes, methods, and examples set forth below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I, II', II, II'a and IIa. The reagents and starting materials are readily available to one of ordinary skill in the art. All substituents, unless otherwise specified, are as previously defined.

[0121] Certain stereogenic centers have been left unspecified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. Furthermore, individual enantiomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention or pharmaceutically acceptable salts there by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E. L. Eliel and S. H. Wilen, "*Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994).

ABBREVIATIONS AND SYMBOLS

[0122] AcOH: acetic acid

[0123] aq.: aqueous

[0124] br: broad

[0125] d: doublet

[0126] DCC: N,N'-dicyclohexylcarbodiimide

[0127] DIPEA: diisopropylethylamine

[0128] DMF: N,N-Dimethylformamide

[0129] DMSO: dimethylsulfoxide

[0130] ee: enantiomeric excess

[0131] eq.: equivalent

[0132] ES: electrospray ionization

[0133] EtOAc: ethyl acetate

[0134] HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid

[0135] hexafluorophosphate

[0136] HOBt: 1-Hydroxybenzotriazole hydrate

[0137] HPLC: high performance liquid chromatography

[0138] iPrOH: isopropanol

[0139] J: coupling constant

[0140] LCMS: liquid chromatography—mass spectrometry

[0141] m/z: mass-to-charge ratio

[0142] M: molarity

[0143] m: multiplet

[0144] MeOH: methanol

[0145] NMR: nuclear magnetic resonance

[0146] q: quartet

[0147] r.t.: room temperature

[0148] R_t: retention time

[0149] s: singlet

[0150] sat.: saturated

[0151] T: temperature

[0152] t: triplet

[0153] T3P: Propylphosphonic anhydride

[0154] THF: tetrahydrofuran

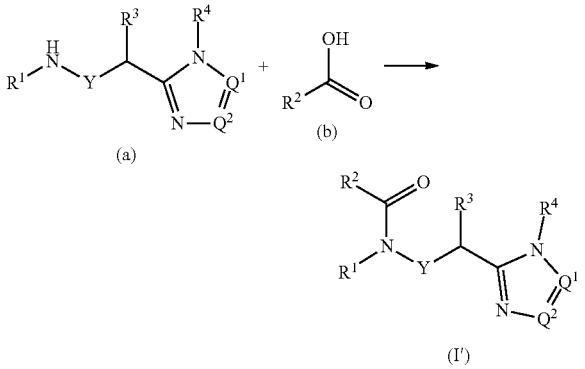
[0155] wt.: weight

[0156] δ: chemical shift

[0157] λ: wavelength

[0158] Compounds of formula I' may be prepared as illustrated in the following scheme where R^1, R^2, R^3, R^4 Q^1, Q^2 and Y are as previously defined.

SCHEME 1

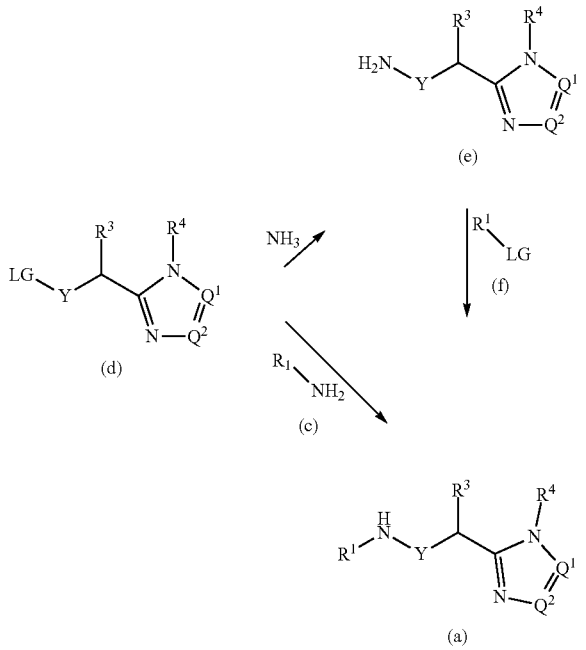


[0159] Au azole compound of formula (a) is reacted with a carboxylic acid of formula (b) to form compounds of formula I. For example, a mixture of an azole of formula (a), a carboxylic acid of formula (b), a suitable coupling reagent, such as T3P®, HATU, DCC or HOBt, a suitable base such as triethylamine or DIPEA, in a suitable solvent, such as ethyl acetate or DMF are mixed at temperatures ranging from around 0 to 100° C. to provide compounds of formula I which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

[0160] Carboxylic acids of formula (b) are commercially available or may be synthesized by methods known to the skilled artisan.

[0161] The requisite azole compounds of formula (a) may be prepared as illustrated in the following scheme, where R^1, R^3, R^4 Q^1, Q^2 and Y are as previously described and LG is a suitable leaving group.

SCHEME 2



[0162] An amine of formula (c) is reacted with a substituted azole of formula (d) to form compounds of formula (a). For example, a mixture of an azole of formula (d), an amine of formula (c), a suitable base, such as K_2CO_3, NaH or DIPEA in a suitable solvent, such as acetonitrile or DMF are mixed at temperatures ranging from around 20 to 120° C. to provide compounds of formula (a) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

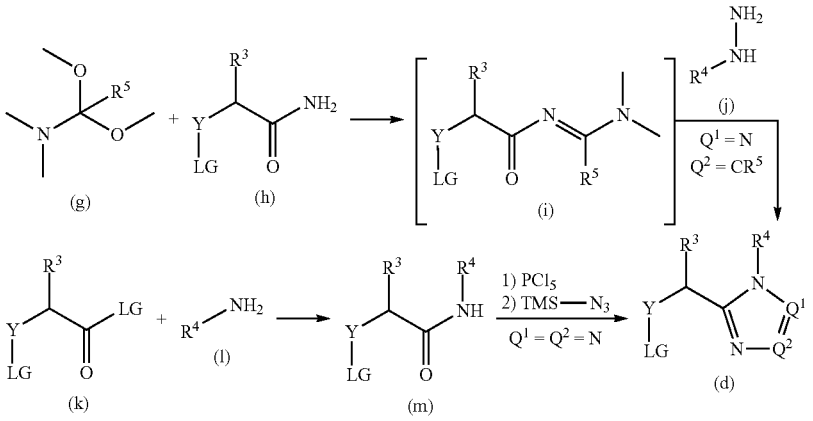
[0163] Alternatively, a substituted azole of formula (d) is reacted with ammonia to form compounds of formula (e). For example, a solution of ammonia in a suitable solvent, such as methanol, and a substituted azole of formula (d) are mixed in a sealed tube at temperatures ranging from around 0 to 25° C. to provide compounds of formula (e) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as trituration.

[0164] A substituted azole of formula (e), a compound of formula (F), a suitable base, such as K_2CO_3 or DIPEA in a suitable solvent, such as acetonitrile or DMF are mixed at temperatures ranging from around 20 to 120° C. to provide compounds of formula (a) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

[0165] Amines of formula (c) and compounds of formula (f) are commercially available or may be synthesized by methods known to the skilled artisan.

[0166] The requisite azole compounds of formula (d) may be prepared as illustrated in the following scheme, where R^3, R^4, R^5, Q^1, Q^2 and Y are as previously described, LG is a suitable leaving group.

SCHEME 3



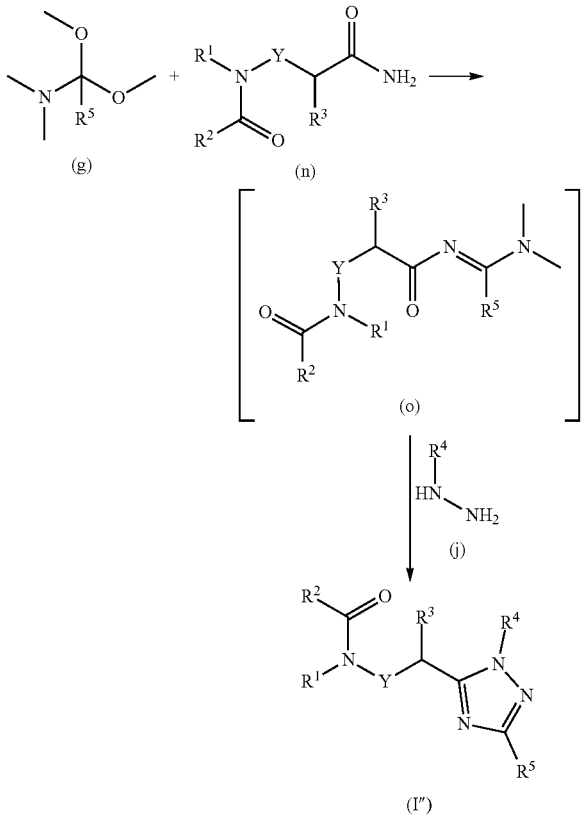
[0167] An amide of formula (h) is reacted with an N,N-dimethylamide dimethyl acetal (g) to form compounds of formula (i) which are subsequently reacted with hydrazines (j) under acidic conditions to form compounds of formula (d). For example, a compound of formula (h) and an N,N-dimethylamide dimethyl acetal of formula (g) are reacted in a suitable solvent, such as CH_2Cl_2 at reflux to provide compounds of formula (i). Upon removal of the solvent, compounds of formula (i) are reacted with a substituted hydrazine (j) in a suitable solvent such as 1,4-dioxane, acetic acid or a mixture of such solvents at temperatures ranging from around 20 to 100° C. to provide compounds of formula (d) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

[0168] Alternatively, a carboxylic acid derivative of formula (k) is reacted with an amine of formula (l) and a suitable base, such as triethylamine or DIPEA, in a suitable solvent, such as toluene, at temperatures ranging from around 0 to 120° C. The resulting compounds (m) may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography. The resulting amides of formula (m) and phosphorus pentachloride are reacted in a suitable solvent, such as CH_2Cl_2, at r.t. and then trimethylsilyl azide is added to the mixture at 0° C. and the mixture is stirred at r.t. to provide compounds of formula (d) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

[0169] N,N-dimethylamide acetals of formula (g), amides of formula (h), carboxylic acid derivatives of formula (k) and hydrazines of formula (j) are commercially available or may be synthesized by methods known to the skilled artisan.

[0170] Compounds of formula I" may be prepared as illustrated in the following scheme where R^1, R^2, R^3, R^4, R^5 and Y are as previously defined.

SCHEME 4

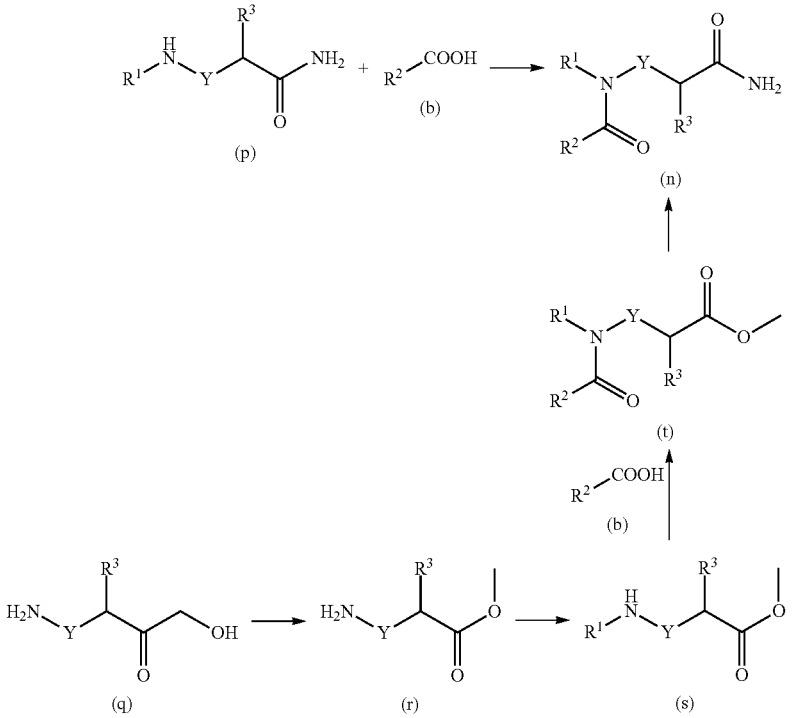


[0171] An amide of formula (n) is reacted with an N,N-dimethyamide dimethyl acetal of formula (g) to form compounds of formula (o) which are subsequently reacted with substituted hydrazines of formula (j) under acidic conditions to form compounds of formula I". For example, a compound of formula (n) and an N,N-dimethyl amide dimethyl acetal of formula (g) are reacted in a suitable solvent, such as CH_2Cl_2 at reflux to provide compounds of formula (o). Upon removal of the solvent, compounds of formula (o) are

reacted with a substituted hydrazine of formula (j) in a suitable solvent such as 1,4-dioxane, acetic acid or a mixture of such solvents at temperatures ranging from around 20 to 100° C. The resulting compounds of formula I" may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

[0172] The requisite amides of formula (n) may be prepared as illustrated in the following scheme, where R^1, R^2, R^3, and Y are as previously described.

SCHEME 5



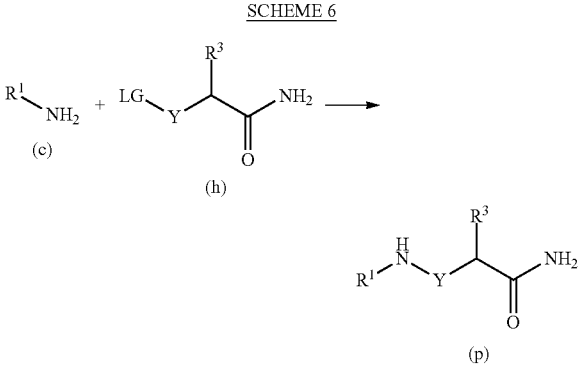
[0173] An amino amide of formula (p) is reacted with a carboxylic acid of formula (b) to form compounds of formula (n). For example, a mixture of an amino amide of formula (p), a carboxylic acid (b), a suitable coupling reagent, such as T3P®. HATU, DCC or HOBt, a suitable base such as triethylamine or DIPEA, in a suitable solvent, such as ethyl acetate or DMF are mixed at temperatures ranging from around 0 to 100° C. to provide compounds of formula (n) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

[0174] Alternatively, an amino acid of formula (q) is reacted with thionyl chloride in a suitable solvent, such as MeOH, at r.t. to provide amino esters of formula (r). The resulting amino esters (r) are reacted with an aldehyde or a ketone, a suitable reducing agent, such as sodium triacetoxyborohydride, a dehydrating agent, such as Na_2SO_4, in a suitable solvent, such as acetic acid, at r.t. to provide compounds of formula(s). The resulting amino esters of formula (s) are then reacted with a carboxylic acid of formula (b), a suitable coupling reagent, such as T3P®, a suitable base such as DIPEA, in a suitable solvent, such as ethyl acetate at about 90° C. to provide amido esters of formula (t) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography. The resulting amido esters of formula (t) are reacted with magnesium nitride in a suitable solvent, such as MeOH at about 80° C. in a sealed tube to provide compounds of formula (n) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography or extraction.

[0175] Compounds of formula (b) and (q) are commercially available. The requisite amino amide compounds of formula (p) are commercially available or may be prepared as illustrated in the following scheme, where R^1, R^3 and Y are as previously described and LG is a suitable leaving group.

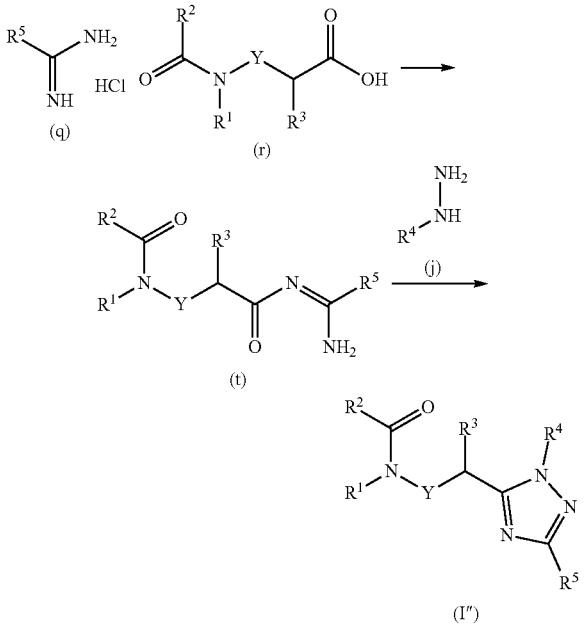
[0176] Compounds of formula (c) and (h) are commercially available.

SCHEME 6



[0177] An amine of formula (c) is reacted with an amide of formula (h) to form compounds of formula (p). For example, a mixture of an amine of formula (c), an amide of formula (h), a suitable base, such as K_2CO_3 or DIPEA in a suitable solvent, such as acetonitrile or DMF are mixed at 25-80° C. to provide compounds of formula (p) which may then be isolated and, if necessary and desired, purified using techniques well known in the art, such as chromatography.

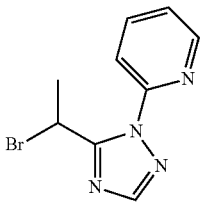
SCHEME 7



[0178] An amidine hydrochloride of formula (q) is reacted with an acid of formula (r) to form compounds of formula (t) which are subsequently reacted with substituted hydrazines of formula (j) under acidic conditions to form compounds of formula I".

Preparation 1

[0179]

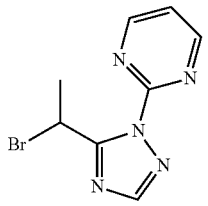


2-[5-(1-Bromoethyl)-1,2,4-triazol-1-yl]pyridine

[0180] Add N,N-dimethylamide dimethylacetal (3.00 mL) to a solution of 2-brompropanamide (2.28 g) in CH_2Cl_2 (50 mL) and stir at reflux for 1 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (15 ml /15 mL), add 2-hydrazinopyridine (1.80 g) and stir at 90° C. for 2 h. Cool to r.t., concentrate under reduced pressure, partition the residue between $NaHCO_3$ (aq. sat.) and CH_2Cl_2. Separate the layers, extract the aqueous phase three times with CH_2Cl_2, dry the combined organic extracts over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 2-[5-(1-bromoethyl)-1,2,4-triazol-1-yl]pyridine (2.82 g, 74%). LCMS (method 2): R_t 1.31 min, m/z. (ES+)=253 [M(^{79}Br)+H]$^+$ and 255 [M(^{81}Br)+H]$^+$.

Preparation 2

[0181]

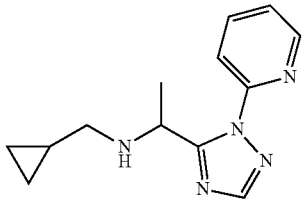


2-[5-(1-Bromoethyl)-1,2,4-triazol-1-yl]pyrimidine

[0182] Add N,N-dimethylamide dimethylacetal (3.3 mL) to a solution of 2-brompropanamide (2.5 g) in CH_2Cl_2 (30 mL) and stir at reflux for 1,5 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (15 mL/15 mL), add 2-hydrazinopyrimidine (2.2 g) and stir at 50° C. overnight. Cool to r.t., concentrate under reduced pressure and partition the residue between water and EtOAc. Separate the layers, wash the organic phase with $NaHCO_3$ (aq. sat.), dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 2-[5-(1-bromoethyl)- 1,2,4-triazol-1-yl]pyrimidine (2.0 g, 48%). LCMS (method 4): R_t 0.55 min, m/z (ES+)=254 [M(^{79}Br)+H]$^+$ and 256 [M(^{81}Br)+H]^4.

Preparation 3

[0183]



N-(Cyclopropylmethyl)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine

[0184] Add cyclopropanemethylamine (8.29 mL) to a suspension of 2-[5-(1-bromoethyl)-1,2,4-triazol-1-yl]pyridine (12.2 g) and K_2CO_3 (20.1 g) in DMF (100 mL) and stir the mixture at 80° C. for 2 h. Cool the mixture to r.t. and filter through Celite® washing with EtOAc. Concentrate the filtrate under reduced pressure and partition the residue between water and EtOAc. Separate the layers and extract the aqueous layer twice with EtOAc. Dry the combined

organic extracts over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-(cyclopropylmethyl)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine (11.4 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm −0.09-0.11 (2H, m), 0.36-0.47 (2H, m), 0.83-1.03 (1H, m), 1.59 (3H, d, J 6.6 Hz), 2.29 (1H, dd, J 11.9, 7.5 Hz), 2.50 (1H, dd, J 11.7, 6.6 Hz), 4.96 (1H, q, J 6.8 Hz), 7.31-7.38 (1H, m), 7.90-7.93 (2H, m), 7.97 (1H, s), 8.52 (1H, dt, J 4.7, 1.3 Hz).

[0185] The compounds of Preparations 4-19 set forth in table 1 may be prepared essentially as described in Preparation 3.

TABLE 1

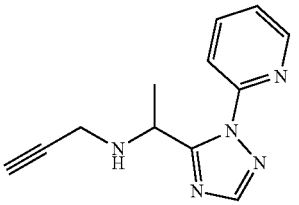
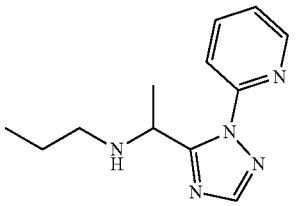
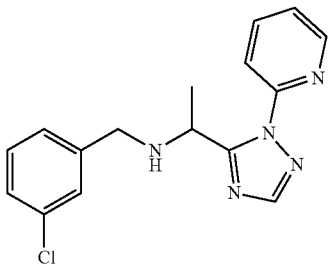
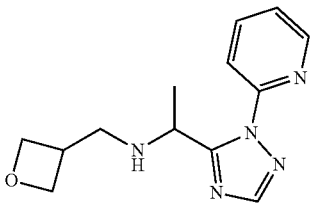
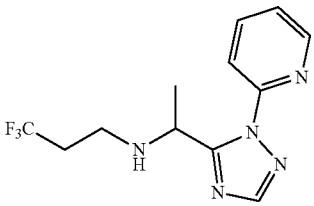
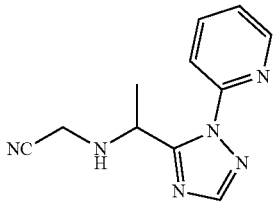
Prep	Structure	Compound	Analytical data	Remarks
4		N-[1-[2-(2-Pyridyl)-1,2,4-triazol-3-yl]ethyl]prop-2-yn-1-amine	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.60 (3H, d, J 6.8 Hz), 2.07 (1H, d, J 4.9 Hz), 3.07 (1H, s), 3.38 (1H, dd, J 16.7, 2.5 Hz), 3.49 (1H, dd, J 16.8, 2.5 Hz), 5.03 (1H, q, J 6.8 Hz), 7.29-7.40 (1H, m), 7.93 (2H, dd, J 3.7, 1.2 Hz), 7.99 (1H, s), 8.54 (1H, dt, J 4.9, 1.4 Hz)	—
5		N-[1-[2-(2-Pyridyl)-1,2,4-triazol-3-yl]ethyl]propan-1-amine	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (3H, t, J 7.4 Hz), 1.42-1.54 (2H, m),1.56 (3H, d, J 6.9 Hz), 2.42 (1H, ddd, J 11.0, 8.1, 6.3 Hz), 2.50 (1H, ddd, J 11.0, 8.1, 6.8 Hz), 2.68 (1H, s), 4.84-4.98 (1H, m), 7.34 (1H, td, J 4.9, 3.6 Hz), 7.87-7.95 (2H, m), 7.99 (1H,d, J 0.5 Hz), 8.48-8.55 (1H, m)	—
6		N-[(3-Chlorophenyl)methyl]-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine	LCMS: (method 1) R_t 1.70 min, m/z (ES+) 314 $[M + H]^+$	Reaction time: 20 h
7		N-(Oxetan-3-ylmethyl)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine	LCMS: (method 7) R_t 1.40 min, m/z (ES+) 260 $[M + H]^+$	Reaction time: 16 h: T = r.t.
8		3,3,3-Trifluoro-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]propan-1-amine	LCMS: (method 7) R_t 1.59 min, m/z (ES+) 286 $[M + H]^+$	Additional 1.0 eq. of DIPEA; Reaction time: 18 h; T = 50° C.
9		2-[1-[2-(2-Pyridyl)-1,2,4-triazol-3-yl]ethylamino]acetonitrile	LCMS: (method 7) R_t 1.65 min, m/z (ES+) 229 $[M + H]^+$	DIPEA used in same amount as solvent in place of K_2CO_3; Reaction time: 18 h; T = r.t.

TABLE 1-continued

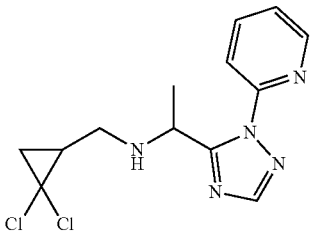
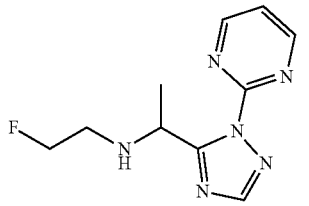
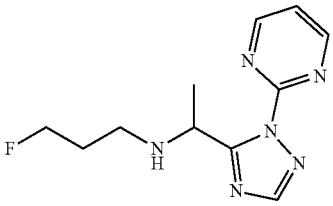
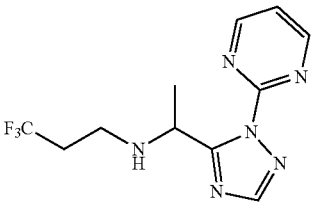
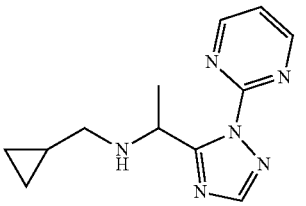
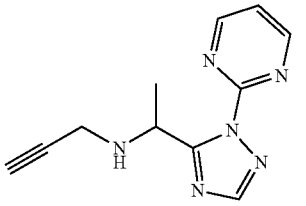
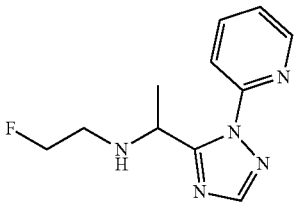
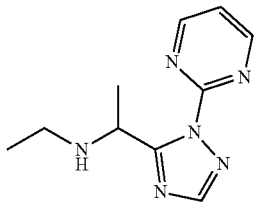
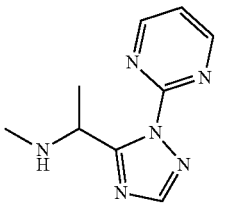
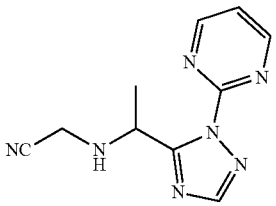
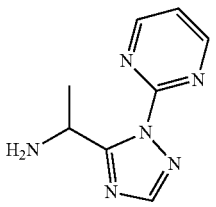
Prep	Structure	Compound	Analytical data	Remarks
10		N-[(2,2-Dichlorocyclopropyl)methyl]-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine	LCMS: (method 7) R_t 1.69 min, m/z (ES+) 312 $[M + H]^+$	Amine used as limiting reagent; Reaction time: 16 h; T = r.t.
11		N-(2-Fluoroethyl)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethanamine	LCMS: (method 4) R_t 0.31 min, m/z (ES+) 237 $[M + H]^+$	Solvent: MeCN; T = reflux; Reaction time: 16 h
12		3-Fluoro-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]propan-1-amine	LCMS: (method 5) R_t 0.44 min, m/z (ES+) 251 $[M + H]^+$	Solvent: MeCN; T = reflux; Reaction time: 1 h
13		3,3,3-Trifluoro-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]propan-1-amine	LCMS: (method 5) R_t 0.33 min, m/z (ES+) 287 $[M + H]^+$	Solvent: MeCN; T = reflux
14		N-(Cyclopropylmethyl)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethanamine	LCMS: (method 5) R_t 0.34 min, m/z (ES+) 245 $[M + H]^+$	Solvent: MeCN; T = reflux
15		N-[1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]prop-2-yn-1-amine	LCMS: (method 4) R_t 0.31 min, m/z (ES+) 229 $[M + H]^+$	Solvent: MeCN; Reaction time: 16 h; T = reflux

TABLE 1-continued

Prep	Structure	Compound	Analytical data	Remarks
16		N-(2-fluoroethyl)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine	LCMS: (method 8) R_t 2.88 min, m/z (ES+) 236 $[M + H]^+$	DIPEA (1.0 eq.) and NaH (2.0 eq.) used in place of K_2CO_3: Reaction time: 18 h; T = r.t.
17		N-Ethyl-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethanamine	LCMS: (method 4) R_t 0.39 min, m/z (ES+) 219 $[M + H]^+$	Solvent: MeCN; Reaction time: 1 h 45 min; T = reflux
18		N-Methyl-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethanamine	LCMS: (method 4) R_t 0.29 min, m/z (ES+) 205 $[M + H]^+$	Solvent: MeCN; Reaction time: 1 h; T = reflux
19		2-[1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethylamino]acetonitrile	LCMS: (method 4) R_t 0.37 min, m/z (ES+) 230 $[M + H]^+$	Solvent: MeCN; Reaction time: 1 h; T = reflux

Preparation 20

[0186]

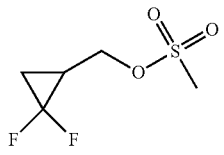


1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethanamine

[0187] Add ammonia (7 M in MeOH, 15 mL) to 2-[5(1-bromoethyl)-1,2,4-triazol-1-yl]pyrimidine (1.14 g) and stir at r.t. for 24 h. Concentrate under reduced pressure to provide 1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethanamine (1.27 g, 61% purity, 90%). LCMS (method 5): R_t 0.35 min, m/z (ES+)=191 $[M+H]^+$.

Preparation 21

[0188]

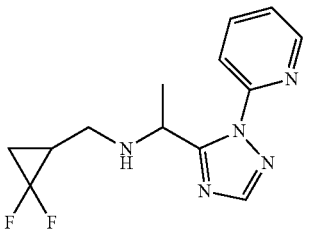


(2,2-Difluorocyclopropyl)methyl methanesulfonate

[0189] Add methanesulfonyl chloride (600 μL) to a mixture of triethylamine (1.4 mL) and (2,2-difluorocyclopropyl) methanol (677 mg) in CH_2Cl_2 (10 mL) at 0° C. and stir for 2 h. Warm to r.t. and stir overnight. Partition between water and CH_2Cl_2, separate the layers, extract the aqueous phase twice with CH_2Cl_2, dry the combined organic extracts over Na_2SO_4, filter and concentrate under reduced pressure to provide (2,2-difluorocyclopropyl)methyl methanesulfonate (1.17 g, 86%). ^1H NMR (400 MHz, $CDCl_3$) δppm 1.27-1.35 (1 H, m), 1.63 (1 H, tdd, J 11.4, 8.2, 4.9 Hz), 1.97-2.14 (1 H, m), 3.04 (3 H, s), 4.18-4.38 (2 H, m).

Preparation 22

[0190]



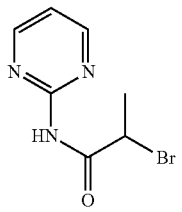
N-[(2,2-Difluorocyclopropyl)methyl]-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine

[0191] Add ammonia (sat. in MeOH, 1.8 mL) to 2[5-(1-bromoethyl)-1,2,4-triazol-1-yl]pyridine (1.80 g) in a sealed tube at 0° C. and stir for 1 h. Allow to warm to r.t. and stir overnight. Concentrate under reduced pressure and triturate the residue in pentane to provide 1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine (1.10 g, 82%). LCMS (method 8): R_t 2.51 min, m/z (ES+)=190 $[M+H]^+$.

[0192] Add (2,2-difluorocyclopropyl)methyl methanesulfonate (500 mg) to a mixture of 1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine (660 mg) and K_2CO_3 (1.11 g) in DMF (5.0 mL) and stir at r.t. overnight. Dilute with water and extract three times with EtOAc. Wash the organic extracts with NaCl (aq. sat.), dry over Na_2SO_4, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-[(2,2-difluorocyclopropyl)methyl]-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine (250 mg, 32%). LCMS (method 7): R_t 1.66 min, (ES+)=280 $[M+H]^+$.

Preparation 23

[0193]

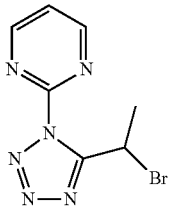


2-Bromo-N-pyrimidin-2-yl-propanamide

[0194] Add 2-aminopyrimidine (1.72 g) and triethylamine (1.85 mL) to 2-bromopropanoyl chloride (900 μL) in toluene (30 mL) and stir at reflux for 2 h. Cool to r.t. and partition between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers, dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 2-bromo-N-pyrimidin-2-yl-propanamide (750 mg, 40%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.64 (3 H, d, J 6.7 Hz), 5.03 (1 H, q, J 6.7 Hz), 7.20 (1 H, t, J 4.8 Hz), 8.67 (2 H, d, J 4.9 Hz), 10.42 (1 H, s).

Preparation 24

[0195]

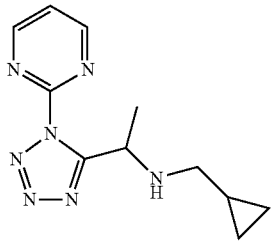


2-[5-(1-Bromoethyl)tetrazol-1-yl]pyrimidine

[0196] Add phosphorus pentachloride (360 mg) to a solution of 2-bromo-N-pyrimidin-2-yl-propanamide (304 mg) in CH_2Cl_2 (6.5 mL) and stir at r.t. for 5 h. Cool to 0° C., add trimethylsilyl azide (280 μl), warm to r.t. and stir overnight. Partition between $NaHCO_3$ (aq. sat.) and CH_2Cl_2, separate the layers and wash the organic phase with water. Dry the organic phase over $MgSO_4$, filter, concentrate wider reduced pressure and purify the residue by chromatography to provide 2-[5-(1-bromoethyl)tetrazol-1-yl]pyrimidine (333 mg, 38%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.20 (3 H, d, J 6.9 Hz), 6.16-6.22 (1 H, m), 7.57 (1 H, t, J 4.9 Hz), 9.00 (2 H, dd, J 4.9, 1.1 Hz).

Preparation 25

[0197]

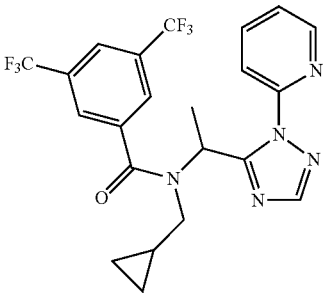


N-(Cyclopropylmethyl)-1-(1-pyrimidin-2-yltetrazol-5-yl)ethanamine

[0198] Add K_2CO_3 (213 mg) and cyclopropylmethanamine (90 μL) to a solution of 2-[5-(1-bromoethyl)tetrazol-1-yl]pyrimidine (120 mg) in acetonitrile (2.0 mL) and stir at reflux for 3.5 h and at r.t. for 5 days. Concentrate under reduced pressure, partition the residue between water and EtOAc, separate the layers and extract the aqueous phase with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-(cyclopropylmethyl)-1-(1-pyrimidin-2-yltetrazol-5-yl)ethanamine (34 mg, 29%). LCMS (method 5): R_t 0.56 min, m/z (ES+) =246 $[M+H]^+$.

EXAMPLE 1

[0199]



N-(Cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide

[0200] Add 3,5-bis(trifluoromethyl)benzoic acid (12.1 g) to a solution of N-(cyclopropylmethyl)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine (10.4 g) and DIPEA (24.6 mL) in EtOAc (415 mL) and stir the mixture at r.t. for 10 min. Add T3P® (≥50 wt. % in EtOAc, 45.7 mL) and stir at r.t. overnight. Partition the mixture between water and EtOAc, separate the layers and wash the organic phase sequentially with water, $NaHCO_3$ (aq. sat.) and NH_4Cl (aq. sat.). Dry over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide (17.2 g, 83%). LCMS (method 2): R_t 1.86 min, m/z (ES+)=484 $[M+H]^+$.

[0201] The compounds of Examples 2-32 and 50-60 set forth in table 2 may be prepared essentially as described in Example 1.

TABLE 2

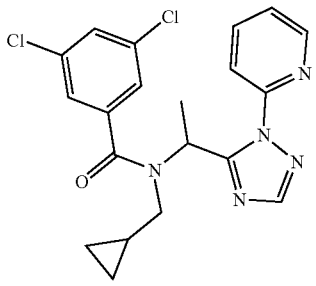
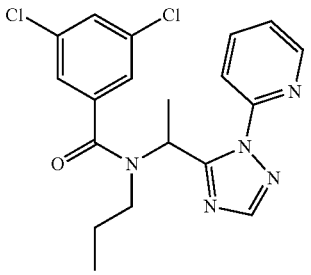
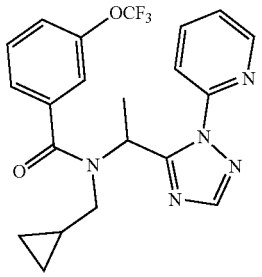
Example	Structure	Compound	LCMS method	Remarks
2		3,5-Dichloro-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide	LCMS (method 2): R_t 1.79 min, m/z (ES+) = 416 $[M + H]^+$	—
3		3,5-Dichloro-N-propyl-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide	LCMS (method 2): R_t 1.78 min, m/z (ES+) = 404 $[M + H]^+$	Reaction time: 48 h
4		N-(Cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3-(trifluoromethoxy)benzamide	LCMS (method 1): R_t 2.59 min, m/z (ES+) = 432 $[M + H]^+$	—

TABLE 2-continued

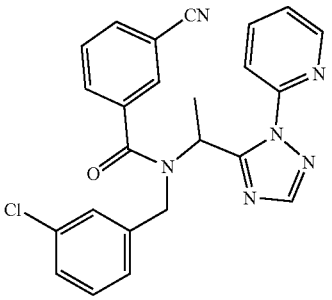
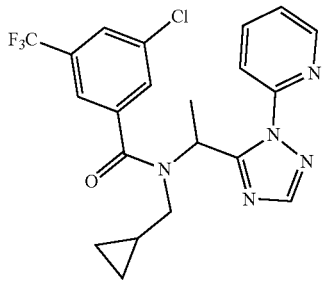
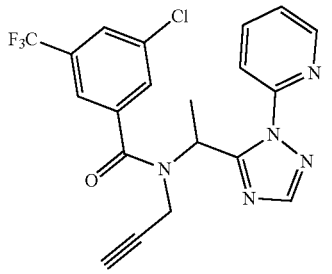
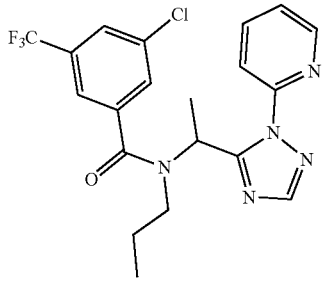
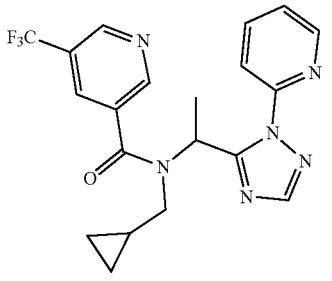
Example	Structure	Compound	LCMS method	Remarks
5		N-[(3-Chlorophenyl)methyl]-3-cyano-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide	LCMS (method 1): R_t 2.52 min, m/z (ES+) = 443 $[M + H]^+$	—
6		3-Chloro-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.68 min, m/z (ES+) = 450 $[M + H]^+$	—
7		3-Chloro-N-prop-2-ynyl-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.55 min, m/z (ES+) = 434 $[M + H]^+$	—
8		3-Chloro-N-propyl-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.70 min, m/z (ES+) = 438 $[M + H]^+$	—
9		N-(Cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS (method 1): R_t 2.34 min, m/z (ES+) = 417 $[M + H]^+$	Reaction time: 2 h

TABLE 2-continued

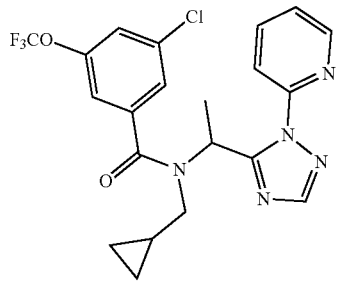
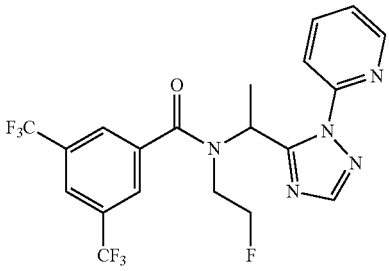
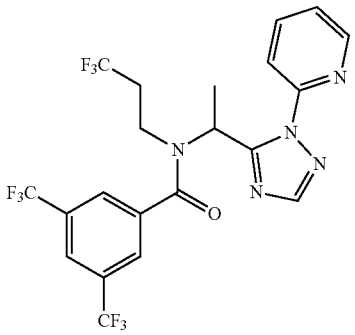
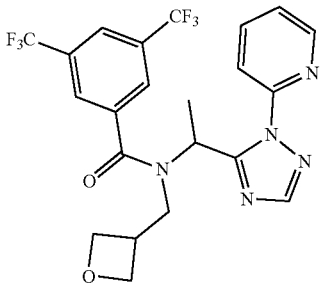
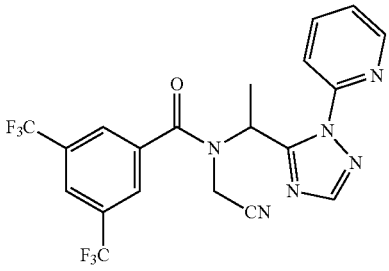
Example	Structure	Compound	LCMS method	Remarks
10		3-Chloro-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-5-(trifluoromethoxy)benzamide	LCMS (method 1): R_t 2.75 min, m/z (ES+) = 466 $[M + H]^+$	Reaction time: 2 h T = 50° C.
11		N-(2-Fluoroethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.63 min, m/z (ES+) = 476 $[M + H]^+$	—
12		N-[1-[2-(2-Pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)-N-(3,3,3-trifluoropropyl)benzamide	LCMS (method 1): R_t 2.77 min, m/z (ES+) = 526 $[M + H]^+$	—
13		N-(Oxetan-3-ylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.51 min, m/z (ES+) = 500 $[M + H]^+$	—
14		N-(Cyanomethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.58 min, m/z (ES+) = 469 $[M + H]^+$	—

TABLE 2-continued

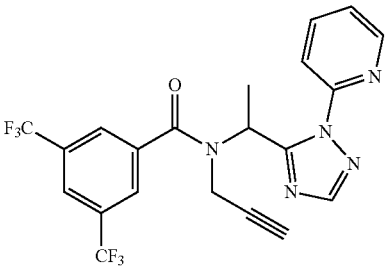
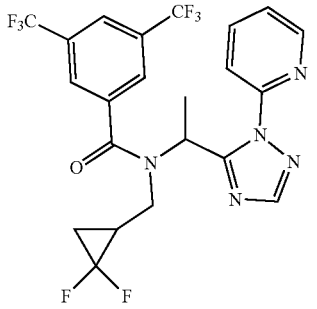
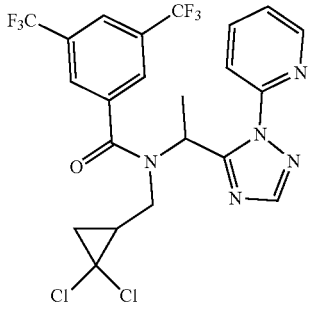
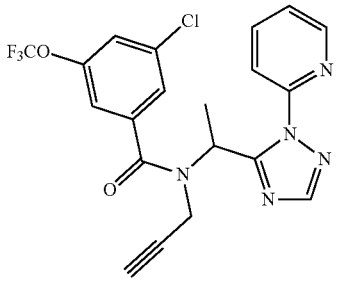
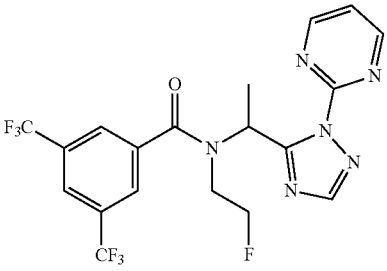
Example	Structure	Compound	LCMS method	Remarks
15		N-Prop-2-ynyl-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.60 min, m/z (ES+) = 468 $[M + H]^+$	Reaction time: 48 h
16		N-[(2,2-Difluorocyclopropyl)methyl]-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.72 min, m/z (ES+) = 520 $[M + H]^+$	—
17		N-[(2,2-Dichlorocyclopropyl)methyl]-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 1): R_t 2.83 min, m/z (ES+) = 552 $[M + H]^+$	—
18		3-Chloro-A-prop-2-ynyl-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-5-(trifluoromethoxy)benzamide	LCMS (method 1): R_t 2.60 min, m/z (ES+) = 450 $[M + H]^+$	T = 80° C.
19		N-(2-Fluoroethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 2): R_t 1.51 min, m/z (ES+) = 477 $[M + H]^+$	Triple amount of carboxylic acid and T3P ®

TABLE 2-continued

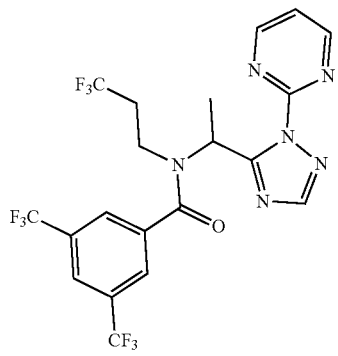
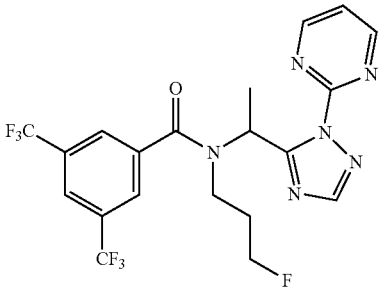
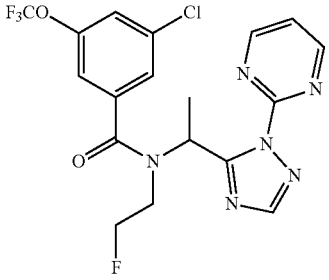
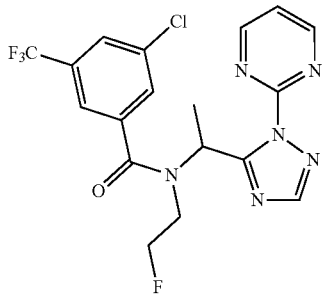
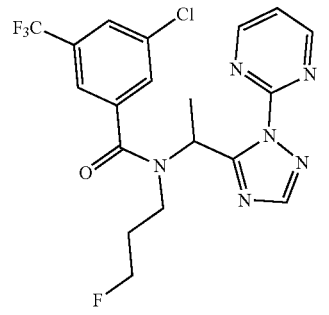
Example	Structure	Compound	LCMS method	Remarks
20		N-[1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)-N-(3,3,3-trifluoropropyl)benzamide	LCMS (method 2): R_t 1.73 min, m/z (ES+) = 527 $[M + H]^+$	Reaction time: 1 h
21		N-(3-Fluoropropyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 2): R_t 1.55 min, m/z (ES+) = 491 $[M + H]^+$	Reaction time: 1 h 45 min
22		3-Chloro-N-(2-fluoroethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethoxy)benzamide	LCMS (method 2): R_t 1.50 min, m/z (ES+) = 459 $[M + H]^+$	Reaction time: 1 h
23		3-Chloro-M-(2-fluoroethyl)-A-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.30 min, m/z (ES+) = 443 $[M + H]^+$	Double amount of carboxylic acid and T3P ®
24		3-Chloro-N-(3-fluoropropyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 5): R_t 2.41 min, m/z (ES+) = 457 $[M + H]^+$	—

TABLE 2-continued

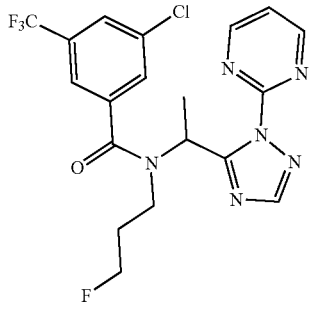
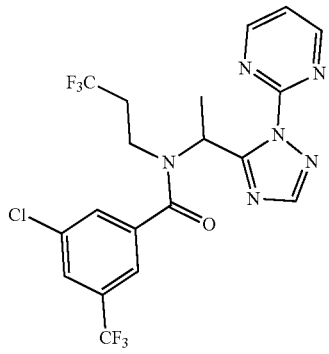
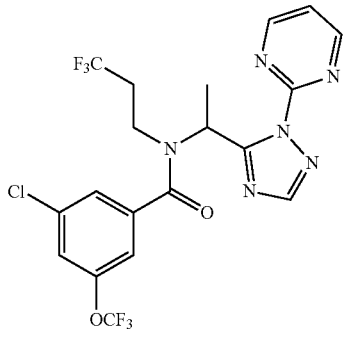
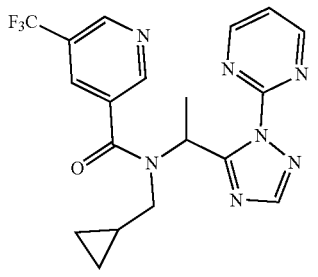
Example	Structure	Compound	LCMS method	Remarks
25		3-Chloro-N-(3-fluoropropyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethoxy)benzamide	LCMS (method 5): R_t 2.46 min, m/z (ES+) = 473 $[M + H]^+$	—
26		3-Chloro-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl] -5-(trifluoromethyl)-N-(3,3,3-trifluoropropyl)benzamide	LCMS (method 5): R_t 2.63 min, m/z (ES+) = 493 $[M + H]^+$	Reaction time: 3 h
27		3-Chloro-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl] -5-(trifluoromethoxy)-N-(3,3,3-trifluoropropyl)benzamide	LCMS (method 5): R_t 2.68 min, m/z (ES+) = 509 $[M + H]^+$	Reaction time: 3 h
28		N-(Cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS (method 4): R_t 0.74 min, m/z (ES+) = 418 $[M + H]^+$	—

TABLE 2-continued

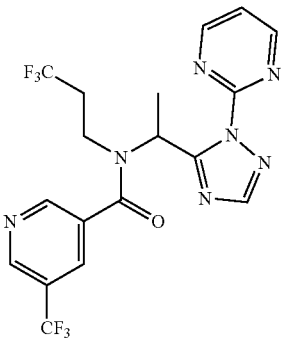
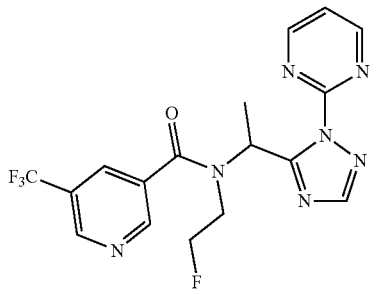
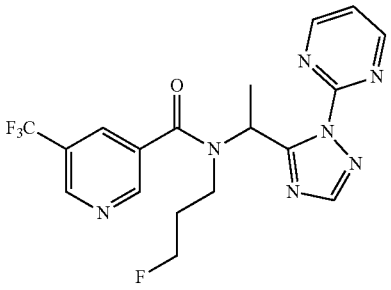
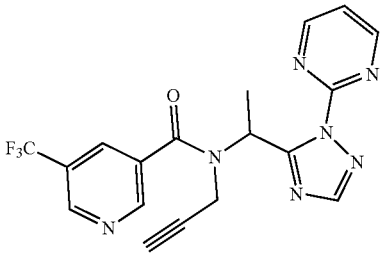
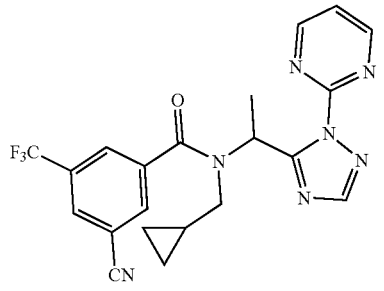
Example	Structure	Compound	LCMS method	Remarks
29		N-[1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]3-5-(trifluoromethyl)-N-(3,3,3-trifluoropropyl)pyridine-3-carboxamide	LCMS (method 5): R_t 2.28 min, m/z (ES+) = 460 $[M + H]^+$	Reaction time: 3 h
30		N-(2-Fluoroethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS (method 3): R_t 2.24 min, m/z (ES+) = 410 $[M + H]^+$	—
31		N-(3-Fluoropropyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS (method 3): R_t 2.28 min, m/z (ES+) = 424 $[M + H]^+$	Reaction time: 1 h
32		N-Prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS (method 4): R_t 0.67 min, m/z (ES+) = 402 $[M + H]^+$	Reaction time: 2 h; No work-up
50		3-Cyano-N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.47 min, m/z (ES+) = 442 $[M + H]^+$	Reaction time: 1.5 h; No work-up

TABLE 2-continued

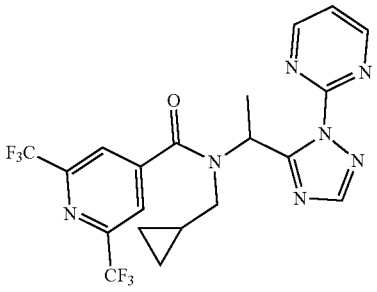
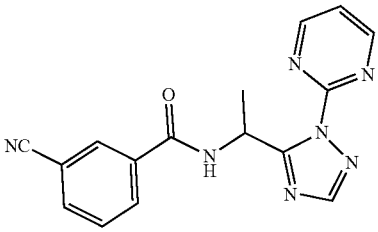
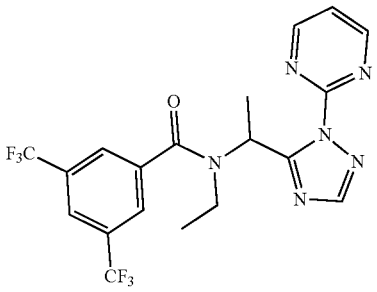
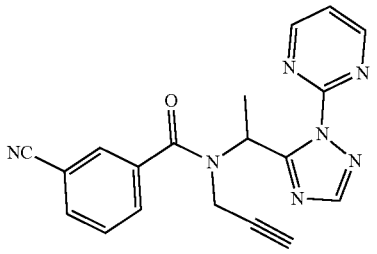
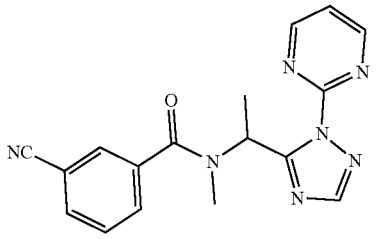
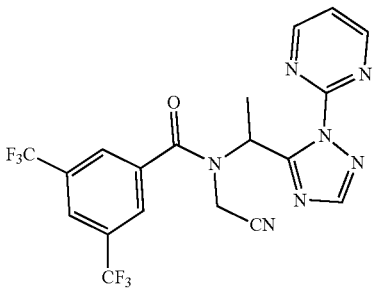
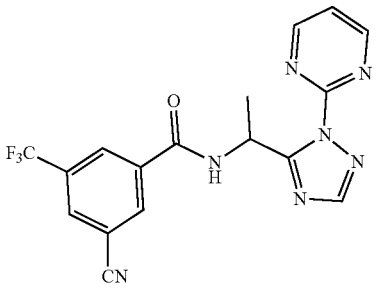
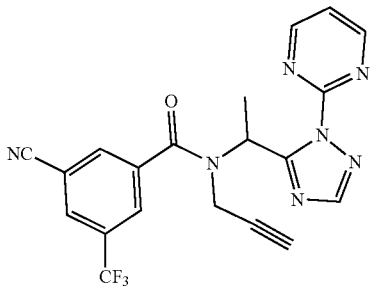
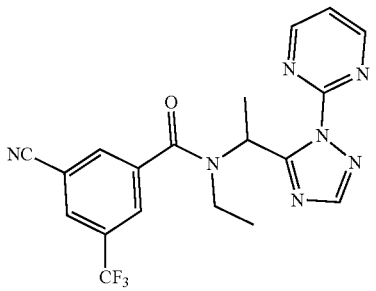
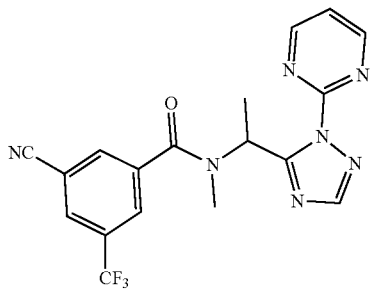
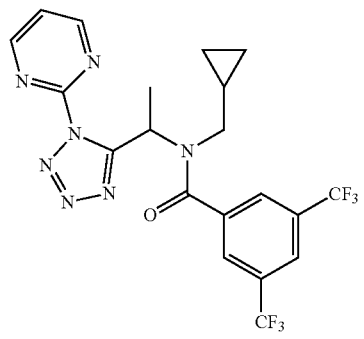
Example	Structure	Compound	LCMS method	Remarks
51		N-(Cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-2,6-bis(trifluoromethyl)pyridine-4-carboxamide	LCMS (method 4): R_t 1.72 min, m/z (ES+) = 486 $[M + H]^+$	—
52		3-Cyano-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]benzamide	LCMS (method 5): R_t 1.29 min, m/z (ES+) = 320 $[M + H]^+$	—
53		N-Ethyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.63 min, m/z (ES+) = 459 $[M + H]^+$	Double amount of T3P ®
54		3-Cyano-N-prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]benzamide	LCMS (method 4): R_t 0.54 min, m/z (ES+) = 358 $[M + H]^+$	Reaction time: 1 h; no work-up
55		3-Cyano-N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]benzamide	LCMS (method 4): R_t 0.48 min, m/z (ES+) = 334 $[M + H]^+$	Reaction time: 2.5 h

TABLE 2-continued

Example	Structure	Compound	LCMS method	Remarks
56		N-(Cyanomethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.60 min, m/z (ES+) = 470 $[M + H]^+$	—
57		3-Cyano-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.06 min, m/z (ES+) = 388 $[M + H]^+$	Reaction time: 3 h
58		3-Cyano-N-prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.24 min, m/z (ES+) = 426 $[M + H]^+$	Reaction time: 1.5 h; No work-up
59		3-Cyano-N-ethyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.24 min, m/z (ES+) = 416 $[M + H]^+$	Reaction time: 3 h
60		3-Cyano-N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS (method 4): R_t 1.04 min, m/z (ES+) = 402 $[M + H]^+$	Reaction time: 3 h

EXAMPLE 33

[0202]

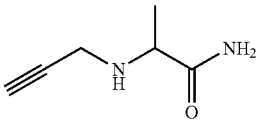


N-(Cyclopropylmethyl)-N-[1-(1-pyrimidin-2-yltetrazol-5-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide

[0203] Add 3,5-bis(trifluoromethyl)benzoic acid (43 mg) and T3P® (≥50 wt. % in EtOAc, 130 μL) to a solution of N-(cyclopropylmethyl)-1-(1-pyrimidin-2-yltetrazol-5-yl) ethanamine (30 mg) and DIPEA (73 μL) in EtOAc (1.5 mL) and stir at r.t. for 2.5 h. Partition between water and EtOAc, separate the layers and wash the organic phase sequentially with water, $NaHCO_3$ (aq. sat.) and NH_4Cl (aq. sat.). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-(cyclopropylmethyl)-N-[1-(1-pyrimidin-2-yltetrazol -5-yl)ethyl]-3,5-bis(trifluommethyl)benzamide (32 mg, 54%). LCMS (method 2): R_t 1.76 min, m/z (ES+)=486 $[M+H]^+$.

Preparation 26

[0204]

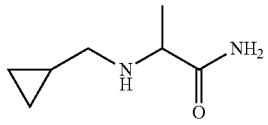


2-(Prop-2-ynylamino)propanamide

[0205] Add K_2CO_3 (55 g) and propargylamine (17 mL) to 2-bromopropanamide (20.2 g) in acetonitrile (320 mL) and stir at 80° C. for 3.5 h and at r.t. overnight. Concentrate under reduced pressure, partition the residue between water and EtOAc, separate the layers and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate under reduced pressure to provide 2-(prop-2-ynylamino)propanamide (15.7 g, 93%). ^1H NMR (400 MHz, $CDCl_3$) δppm 1.36 (3 H, d, J 7.0 Hz), 1.58 (1 H, br s), 2.23 (1 H, t, J 2.4 Hz), 3.34 (1 H, dd, J 17.1, 2.4 Hz), 3.41 (1 H, q, J 7.0 Hz), 3.49 (1 H, dd, J 17.1, 2.5 Hz), 5.39 (1 H, br s), 6.93 (1 H, br s).

Preparation 27

[0206]

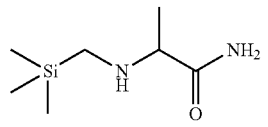


2-(Cyclopropylmethylamino)propanamide

[0207] Add K_2CO_3 (1.45 g) and cyclopropylmethanamine (560 μL) to 2-bromopropanamide (490 mg) and in acetonitrile (8 mL) and stir at 80° C. for 1 h. Cool to r.t., filter through Celite® and wash with acetonitrile. Partition the residue between water and EtOAc, separate the layers and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate under reduced pressure to provide 2-(cyclopropylmethylamino)propanamide (351 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.06-0.23 (2 H, m), 0.44-0.58 (2 H, m), 0.83-1.02 (1 H, m), 1.36 (3 H, d, J 6.9 Hz), 1.73 (1 H, br s), 2.42 (1 H, dd, J 12.4, 6.9 Hz), 2.55 (1 H, dd, J 12.1, 6.6 Hz), 3.24 (1 H, J 6.9 Hz), 5.39 (1 H, br s), 7.18 (1 H, br s).

Preparation 28

[0208]

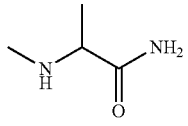


2-(Trimethylsilylmethylamino)propanamide

[0209] Add K_2CO_3 (628 mg) and (aminomethyl)trimethylsilane (341 mg) to 2-bromopropanamide (456 mg) in acetonitrile (5 mL) and stir at reflux overnight. Cool to r.t., filter, wash with acetonitrile and dry the resulting solid under reduced pressure to provide 2-(trimethylsilylmethylamino) propanamide (512 mg, 98%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.05 (9 H, s), 1.31 (3 H, d, J 6.9 Hz), 3.09 (1 H, q, J 6.9 Hz), 5.63 (1H, br s), 7.04 (1 H, br s).

Preparation 29

[0210]



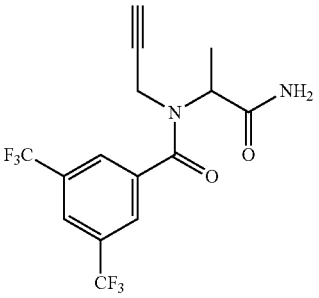
2-(Methylamino)propanamide

[0211] Add K_2CO_3 (4.15 g) and methylamine (2 M in THF, 10 mL) to 2-bromopropanamide (1.53 g) in acetonitrile (30 mL) and stir at 80° C. overnight. Cool to r.t., filter,

wash with MeOH and dry the resulting solid under reduced pressure to provide 2-(methylamino)propanamide (792 mg, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (3 H, d, J 6.9 Hz) 1.83 (1 H, br s) 2.18 (3 H, s) 2.77-2.90(1 H, m) 6.92(1 H, br s) 7.23 (1 H, br s).

Preparation 30

[0212]



N-(2-Amino-1-methyl-2-oxo-ethyl)-N-prop-2-ynyl-3,5-bis(trifluoromethyl)benzamide

[0213] Add DIPEA (73.7 g) to a solution of 2-(prop-2-ynylamino)propanamide (24.0 g) and 3,5-bis(trifluoromethyl)benzoic acid (58.9 g) in EtOAc (528 mL). Cool to 0° C. and add T3P® (≥50 wt. % in EtOAc, 170 mL) dropwise. Warm to r.t. and stir overnight. Partition between water and EtOAc, separate the layers, wash the organic phase with $NaHCO_3$ (aq. sat.) and NaOH (aq. 1 M). Dry the organic phase over Na_2SO_4, filter, concentrate under reduced pressure and purify the residue by trituration with pentane to provide N-(2-amino-1-methyl-2-oxo-ethyl)-N-prop-2-ynyl-3,5-bis(trifluoromethyl)benzamide (50 g, 72%). LCMS (method 7): R_t 2.17 min, m/z (ES+)=367 $[M+H]^+$.

[0214] The compounds of Preparations 31-40 set forth in table 3 may be prepared essentially as described in Preparation 30.

TABLE 3

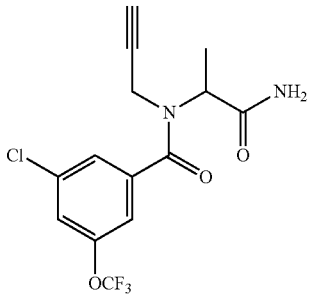
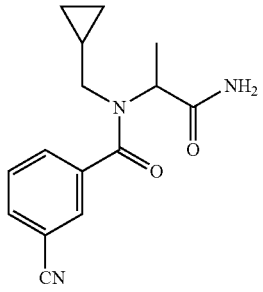
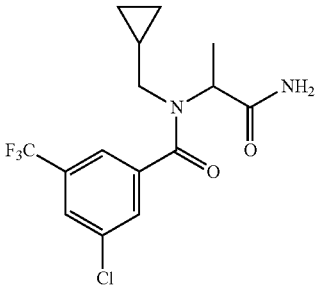
Prep.	Structure	Compound	Analytical data	Remarks
31		N-(2-amino-1-methyl-2-oxo-ethyl)-3-chloro-N-prop-2-ynyl-5-(trifluoromethoxy)benzamide	LCMS: (method 2) R_t 1.41 min, m/z (ES−) 347 $[M-H]^-$	Reaction time: 1 h 45 min; purification by chromatography
32		N-(2-Amino-1-methyl-2-oxo-ethyl)-3-cyano-A-(cyclopropylmethyl)benzamide	LCMS: (method 3) R_t 2.07 min, m/z (ES+) 272 $[M+H]^+$	Reaction time: 4 h; purification by chromatography
33		N-(2-Amino-1-methyl-2-oxo-ethyl)-3-chloro-N-(cyclopropylmethyl)-5-(trifluoromethyl)benzamide	LCMS: (method 2) R_t 1.46 min, m/z (ES+) 349 $[M+H]^+$	Reaction time: 30 min; purification by chromatography

TABLE 3-continued

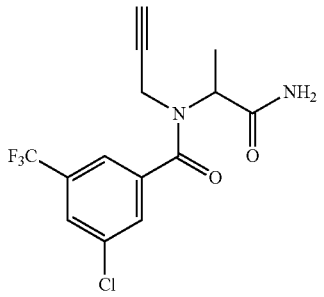
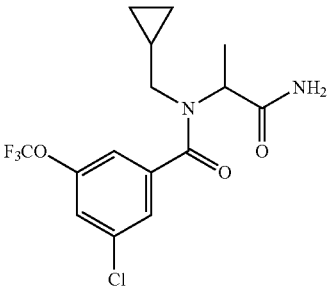
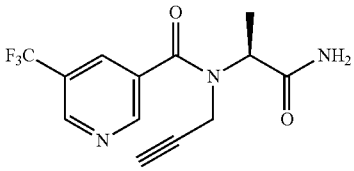
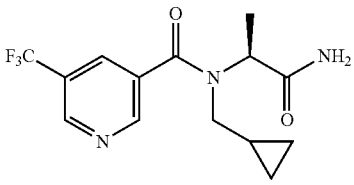
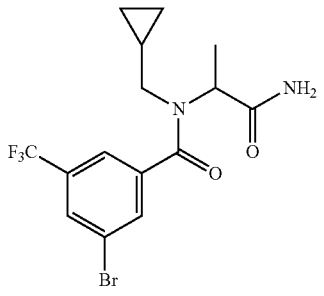
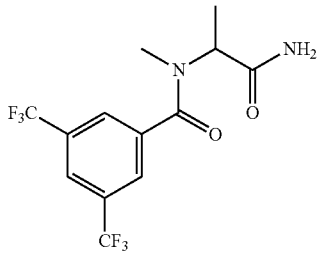
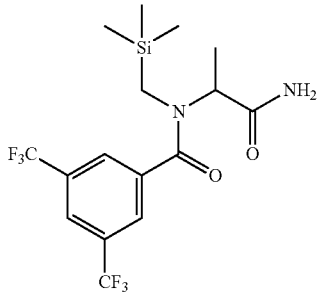
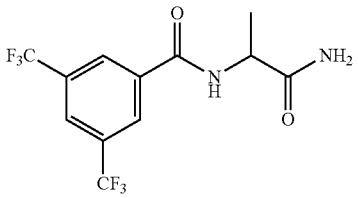
Prep.	Structure	Compound	Analytical data	Remarks
34		N-(2-Amino-1-methyl-2-oxo-ethyl)-3-chloro-N-prop-2-ynyl-5-(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.33 min, m/z (ES−) 331 $[M - H]^-$	—
35		N-(2-amino-1-methyl-2-oxo-ethyl)-3-chloro-A-(cyclopropylmethyl)-5-(trifluoromethoxy)benzamide	LCMS: (method 2) R_t 1.51 min, m/z (ES−) 363 $[M - H]^-$	Reaction time: 1 h 45 min; purification by chromatography
36		N-[(1S)-2-Amino-1-methyl-2-oxo-ethyl]-N-prop-2-ynyl-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS: (method 4) R_t 0.54 min, m/z (ES+) 300 $[M + H]^+$	Purification by chromatography
37		N-[(1S)-2-Amino-1-methyl-2-oxo-ethyl]-N-(cyclopropylmethyl)-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS: (method 4) R_t 0.64 min, m/z (ES+) 316 [M + H]+	Purification by chromatography
38		N-(2-Amino-1-methyl-2-oxo-ethyl)-3-bromo-N-(cyclopropylmethyl)-5-(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.55 min, m/z (ES−) 391 $[M - H]^-$	Reaction time: 3 days; no aq. work-up; purification by chromatography
39		N-(2-Amino-1-methyl-2-oxo-ethyl)-N-methyl-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.27 min, m/z (ES−) 341 $[M - H]^-$	Reaction time: overnight; double amount of T3P ® purification by chromatography

TABLE 3-continued

Prep.	Structure	Compound	Analytical data	Remarks
40		N-(2-Amino-1-methyl-2-oxo-ethyl)-3,5-bis(trifluoromethyl)-N-(trimethylsilylmethyl)benzamide	LCMS: (method 4) R_t 1.97 min, m/z (ES−) 413 $[M-H]^-$	Reaction time: overnight; purification by chromatography

Preparation 41

[0215]

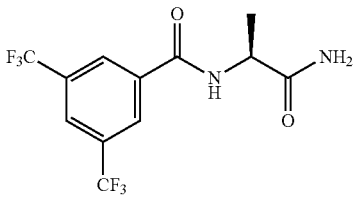


N-(2-Amino-1-methyl-2-oxo-ethyl)-3,5-bis(trifluoromethyl)benzamide

[0216] Add DIPEA (587 mg) to a solution of 2-aminopropanamide (661 mg) and 3,5-bis(trifluoromethyl)benzoic acid (387 mg) in DMF (7 mL). Add T3P® (≥50 wt. % in EtOAc, 1.79 mL) and stir at r.t. overnight. Concentrate under reduced pressure, partition between water and EtOAc, separate the layers, wash the organic phase with $NaHCO_3$ (aq. sat.) and NaCl (aq, sat.). Dry the organic phase over Na_2SO_4, filter, concentrate under reduced pressure to provide N-(2-amino-1-methyl-2-oxo-ethyl)-3,5-bis(trifluoromethyl)benzamide (387 mg, 79%). LCMS (method 4): R_t 1.27 min, m/z (ES−)=327 $[M-H]^-$.

Preparation 42

[0217]

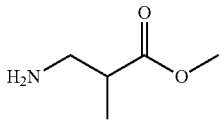


N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-3,5-bis(trifluoromethyl)benzamide

[0218] Add DIPEA (0.5 mL) to a solution of L-alaninamide (263 mg) and 3,5-bis(trifluoromethyl)benzoic acid (250 mg) in DMF (4 mL). Add T3P® (≥50 wt. % in EtOAc, 1.0 mL) and stir at r.t. overnight. Concentrate under reduced pressure, partition between water and EtOAc, separate the layers, wash the organic phase with $NaHCO_3$(aq. sat.) and NaCl (aq, sat.). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure to provide N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-3,5-bis(trifluoromethyl)benzamide (299 mg, 94%). LCMS (method 4): Rt 1.26 mm, m/z (ES+)=329 $[M+H]^+$.

Preparation 43

[0219]

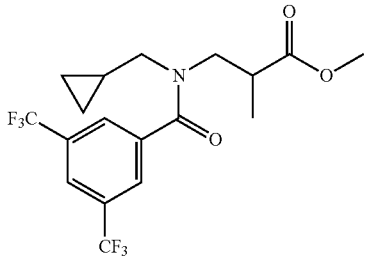


Methyl 3-amino-2-methyl-propanoate

[0220] Add thionyl chloride (1.41 mL) to a solution of 3-amino-2-methyl-propanoic acid (87% purity, 1.15 g) in MeOH (10 mL) and stir at r.t. overnight. Evaporate the solvent to provide methyl 3-amino-2-methyl-propanoate (1.13 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.35 (3 H, d, J 7.3 Hz), 2.95-3.36 (3 H, m), 3.80 (3 H, s), 8.46 (2 H, br s).

Preparation 44

[0221]

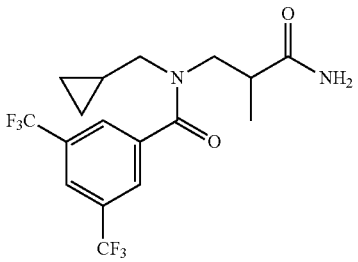


Methyl 3-[[3,5-bis(trifluoromethyl)benzoyl]-(cyclopropylmethyl)amino]-2-methyl-propanoate

[0222] Add methyl 3-amino-2-methyl-propanoate (1.13 g) to a mixture of cyclopropanecarboxaldehyde (867 μL) and Na_2SO_4 (13.8 g) in AcOH (10 mL) and stir at r.t. for 20 min. Add $NaBH(OAc)_3$ (6.16 g) and stir for 4 h. Partition between $NaHCO_3$ (aq. sat.) and EtOAc, adjusting the pH of the aqueous phase to >10 with NaOH (aq. 2 M), separate the layers, wash the organic phase with NaCl (aq. sat.), dry over Na_2SO_4, filter and concentrate under reduced pressure to provide methyl 3-(cyclopropylmethylamino)-2-methyl-propanoate. Dissolve the residue and 3,5-bis(trifluoromethyl) benzoic acid (3.73 g) in EtOAc (30 mL), add T3P® (≥50 wt. % in EtOAc,11.7 mL) and DIPEA (7.56 mL) and stir at 90° C. for 3 h. Partition between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers and extract the aqueous phase three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter, concentrate under reduced pressure and purify the residue by chromatography to provide methyl 3-[[3,5-bis(trifluoromethyl)benzoyl]-(cyclopropylmethyl) amino]-2-methyl-propanoate (100 mg, 2%). LCMS (method 1): R_t 2.75 min, m/z (ES+)=412 $[M+H]^+$.

Preparation 45

[0223]

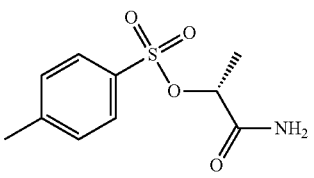


N-(3-Amino-2-methyl-3-oxo-propyl)-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide

[0224] Add Mg_3N_2 (123 mg) to a solution of methyl 3-[[3,5-bis(trifluoromethyl)benzoyl]-(cyclopropylmethyl) amino]-2-methyl-propanoate (100 mg) in MeOH (2.3 mL) at 0° C. and stir in a sealed tube for 1 h. Heat to 80° C. and stir for 4 days. Partition between water and $CHCl_3$, separate the layers, wash the organic phase with HCl (aq. 2 M), extract the aqueous phase three times with $CHCl_3$, dry the combined organic extracts over Na_2SO_4, filter and concentrate under reduced pressure to provide N-(3-amino-2-methyl-3-oxo-propyl)-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl) benzamide (55 mg, 57%). LCMS (method 1): R_t 2.42 min, m/z (ES+)=397 $[M+H]^+$.

Preparation 46

[0225]

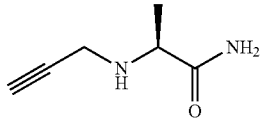


[(1R)-2-Amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate

[0226] Add p-toluene sulfonyl chloride (154 g) and DIPEA (113 mL) to (R)-(+)-lactamide (48.1 g) in CH_2Cl_2 (1.3 L) at 0° C., warm to r.t. and stir for 3 days. Concentrate under reduced pressure, partition between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers, dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and dissolve the residue in CH_2Cl_2. Add pentane, filter the precipitate and partition again between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers, dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure to provide [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (69.7 g, 48%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (3 H, d, J 6.9 Hz), 2.43 (3 H, s), 4.70 (1 H, q, J 6.9 Hz), 7.29 (1 H, br s), 7.43-7.54 (2 H, m), 7.80-7.85 (2 H, m).

Preparation 47

[0227]

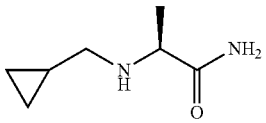


(2S)-2-(Prop-2-ynylamino)propanamide

[0228] Mix propargylamine (240 μL), [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (493 mg) and K_2CO_3 (790 mg) in acetonitrile (10 mL) and stir at 30° C. for 3 days. Filter through Celite® and wash with acetonitrile. Concentrate under reduced pressure and purify the residue by chromatography to provide (2S)-2-(prop-2-ynylamino)propanamide (49 mg, 21%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.37 (3 H, d, J 7.3 Hz,), 1.75 (1 H, br s), 2.24 (1 H, t, J 2.6 Hz), 3.36 (1 H, dd, J 17.2, 2.6 Hz), 3.42 (1 q, J 6.9 Hz) 3.49 (1 H, dd, J 17.2, 2.6 Hz), 5.48 (1 H, br s), 6.95 (1 H, br s).

Preparation 48

[0229]



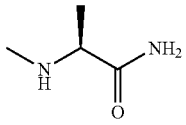
(2S)-2-(Cyclopropylmethylamino)propanamide

[0230] Mix cyclopropylmethanamine (44 mL), [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (69.3 g) and K_2CO_3 (107 g) in acetonitrile (700 mL) and stir at 30° C. for 6 h. Cool to r.t., filter through Celite® and wash with acetonitrile. Concentrate the filtrate under reduced pressure and purify the residue by chromatography to provide (2S)-2-(cyclopropylmethylamino)propanamide (29.7 g, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.09-0.18 (2 H,

m), 0.44-0.57 (2 H, m), 0.87-0.98 (1 H, m), 1.35 (3 H, d, J 6.9 Hz), 1.60 (1 H, br s), 2.40 (1 H, dd, J 12.1, 7.3 Hz), 2.54 (1 H, dd, J 12.1, 6.6 Hz), 3.21 (1 H, J 6.9 Hz), 5.31 (1 H, br s), 7.14 (1 H, br s).

Preparation 49

[0231]

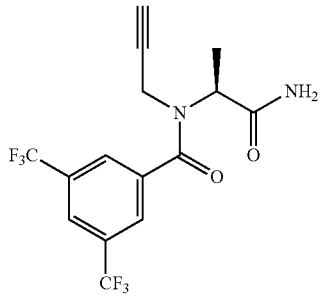


(2S)-2-(Methylamino)propanamide

[0232] Mix methylamine (2 M in THF, 1.0 mL), [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (243 mg) and K_2CO_3 (419 mg) in acetonitrile (1 mL) and stir at r.t. for 3 days. Filter through Celite® and wash with acetonitrile. Concentrate the filtrate under reduced pressure to provide (2S)-2-(methylamino)propanamide (50% w, 46 mg, 22%). ^{1}H NMR (400 MHz, DMSO-d6) δppm 1.09 (3 H, d, J 6.94 Hz), 1.84 (1 H, br s), 2.19 (3 H, s), 2.86 (1 H, q, J 6.81 Hz), 6.94 (1 H, br s), 7.25 (1 H, br s).

Preparation 50

[0233]

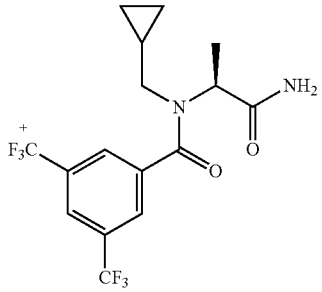


N-[(1S)-2-Amino-1-methyl-2-oxo-ethyl]-N-prop-2-ynyl-3,5-bis(trifluoromethyl)benzamide

[0234] Add T3P® (≥50 wt. % in EtOAc, 350 μL) and 3,5-bis(trifluoromethyl)benzoic acid (120 mg) to a solution of DIPEA (200 μL) and (2S)-2-(prop-2-ynylamino)propanamide (49 mg) in EtOAc (1.0 mL) and stir at r.t. overnight. Partition between water and EtOAc, separate the layers, wash the organic phase with water, NH_4Cl (aq. sat.) and NaOH (aq. 1 M). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-N-prop-2-ynyl-3,5-bis(trifluoromethyl)benzamide (58 mg, 38%). LCMS: (method 4) R_t 1.48 min, m/z (ES−) 365 $[M-H]^-$.

Preparation 51

[0235]

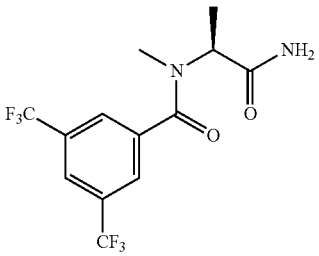


N-[(1.8)-2-Amino-1 -methyl-2-oxo-ethyl]-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide

[0236] Add T3P® (≥50 wt. % in EtOAc, 185 mL) and 3,5-bis(trifluoromethyl)benzoic acid (64.3 g) to a solution of DIPEA (109 mL) and (2S)-2-(cyclopropylmethylamino)propanamide (29.5 g) in EtOAc (590 mL) and stir at r.t. overnight. Partition between water and EtOAc, separate the layers, wash the organic phase with water, NH_4Cl (aq. sat.) and NaOH (aq. 1 M). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by precipitation from CH_2Cl_2 and pentane to provide N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide (49.1 g, 62%). LCMS: (method 4) R_t 1.61 min, m/z (ES+) 383 $[M+H]^+$.

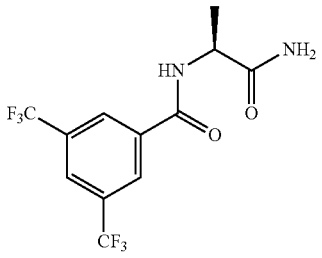
[0237] The compound of Preparation 52 set forth in table 4 may be prepared essentially as described in Preparation 51.

TABLE 4

Prep.	Structure	Compound	Analytical data	Remarks
52		N-[(1S)-2-Amino-1-methyl-2-oxo-ethyl]-N-methyl-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.28 min, m/z (ES−) 341 $[M-H]^-$	1 eq. of carboxylic acid and 1.5 eq. of T3P ®; purification by chromatography

Preparation 53

[0238]

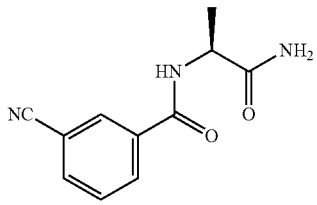


N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-3,5-bis(trifluoromethyl)benzamide

[0239] Add 3,5-bis(trifluoromethyl)benzoic acid (900 mg) and T3P® (≥50 wt. % in EtOAc, 4.2 mL) to a mixture of L-alaninamide (1.25 g) and DIPEA (1.9 mL) in DMF (15 mL). Stir at r.t. overnight. Partition between water and EtOAc, separate the layers, wash the organic phase $NaHCO_3$ (aq. sat.) and NaCl (aq. sat.). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure to provide N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-3,5-bis(trifluoromethyl)benzamide (1.05 g, 92%). LCMS: (method 4) R_t 1.27 min, m/z (ES+) 329 $[M+H]^+$.

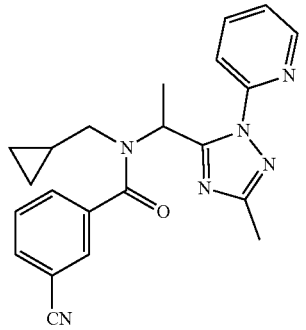
[0240] The compound of Preparation 54 set forth in table 5 may be prepared essentially as described in Preparation 53.

TABLE 5

Prep.	Structure	Compound	Analytical data	Remarks
54		N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-3-cyano-benzamide	LCMS: (method 4) R_t 0.39 min, m/z (ES+) 218 $[M + H]^+$	3 eq. of $_L$-alaninamide

EXAMPLE 34

[0241]

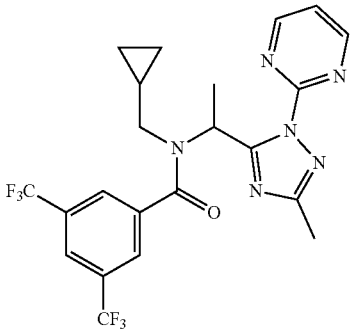


3-Cyano-N-(cyclopropylmethyl)-N-[1-[5-methyl-2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide

[0242] Add N,N-dimethylacetamide dimethylacetal (88 μL) to a solution of N-(2-amino-1-methyl-2-oxo-ethyl)-3-cyano-N-(cyclopropylmethyl)benzamide (108 mg) in CH_2Cl_2 (3.0 mL) and stir at reflux for 1 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (1 mL/1 mL) add 2-hydrazinopyridine (87 mg) and stir at 90° C. for 2 h. Cool to r.t., concentrate under reduced pressure, partition the residue between water and EtOAc. Separate the layers, wash the organic phase with $NaHCO_3$ (aq. sat.). Extract the combined aqueous phases twice with EtOAc, wash the combined organic extracts with NaCl (aq. sat.), dry over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 3-cyano-N-(cyclopropylmethyl)-N-[1-[5-methyl-2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide (104 mg, 68%). LCMS (method 3): R_t 2.66 min, m/z (ES+)=387 $[M+H]^+$.

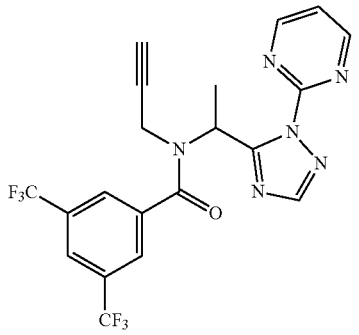
[0243] The compound of Example 61 set forth in table 6 may be prepared essentially as described in Example 34.

TABLE 6

Example	Structure	Compound	Analytical data	Remarks
61		N-(Cyclopropylmethyl)-N-[1-(5-methyl-2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.80 min, m/z (ES+) 499 $[M + H]^+$	2nd step: Reaction time: 16 h; T = 50° C.

EXAMPLE 35

[0244]

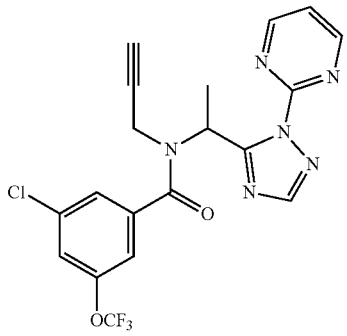


N-Prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide

[0245] Add N,N-dimethylamide dimethylacetal (2.8 mL) to a solution of N-(2-amino-1-methyl-2-oxo-ethyl)-N-prop-2-ynyl-3,5-bis(trifluoromethyl)benzamide (5.00 g) in CH_2Cl_2 (70 mL) and stir at reflux for 2 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (80 mL/8 mL), add 2-hydrazinopyrimidine (2.48 g) and stir at 50° C. overnight. Cool to r.t., concentrate under reduced pressure, partition the residue between $NaHCO_3$ (aq. sat.) and EtOAc. Separate the layers, extract the aqueous phase three times with EtOAc, dry the combined organic extracts over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide (2.97 g, 46%). LCMS (method 2): R_t 1.52 min, m/z (ES+) =469 $[M+H]^+$. Chiral HPLC: column Chiralpak AD-H (250×4.6 mm), heptane/iPrOH/dietbylamine 95:5:0.1, flow rate 1 mL/min, r.t., λ240 nm, R_t 13.8 and 16.6 min.

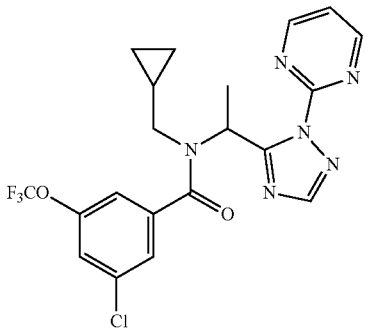
[0246] The compound of Example 36 set forth in table 7 may be prepared essentially as described in Example 35.

TABLE 7

Example	Structure	Compound	Analytical data	Remarks
36		3-Chloro-N-prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethoxy)-benzamide	LCMS: (method 2) R_t 1.49 min, m/z (ES+) 451 $[M + H]^+$	2nd step: Reaction time: 1 h; T = 90° C.

EXAMPLE 37

[0247]



3-chloro-N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethoxy) benzamide

[0248] Add N,N-dimethylamide dimethylacetal (60 μL) to a solution of N-(2-amino-1-methyl-2-oxo-ethyl)-3-chloro-N-(cyclopropylmethyl)-5-(trifluoromethoxy)-benzamide (106 mg) in CH_2-Cl_2 (5 mL) and stir at reflux for 1 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (1.5 mL/1.5 mL), add 2-hydrazinopyrimidine (48 mg) and stir at 90° C. for 1 h. Cool to r.t., concentrate under reduced pressure, partition the residue between $NaHCO_3$ (aq. sat.) and CH_2Cl_2. Separate the layers, extract the aqueous phase three times with CH_2Cl_2, dry the combined organic extracts over Na_2SO_4, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 3-chloro-N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl) ethyl]-5-(trifluoromethoxy)benzamide (101 mg, 59%). LCMS (method 2): R_t 1.64 min, m/z (ES+)=467 $[M+H]^+$.

[0249] The compounds of Examples 38-45 and 62-69 set forth in table 8 may be prepared essentially as described in Example 37.

TABLE 8

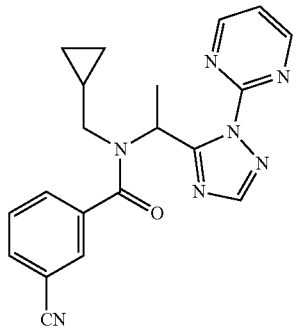
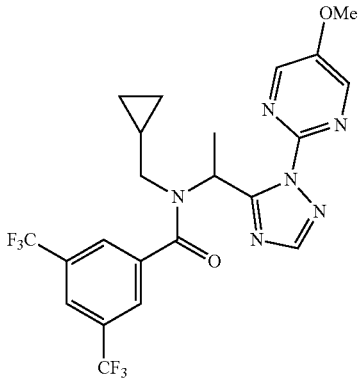
Example	Structure	Compound	Analytical data	Remarks
38		3-Cyano-N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]benzamide	LCMS: (method 2) R_t 1.11 min, m/z (ES+) 374 $[M + H]^+$	Reaction time: overnight; T = 80° C.
39		N-(Cyclopropylmethyl)-N-[1-[2-(5-methoxypyrimidin-2-yl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 2) R_t 1.71 min, m/z (ES+) 515 $[M + H]^+$	—

TABLE 8-continued

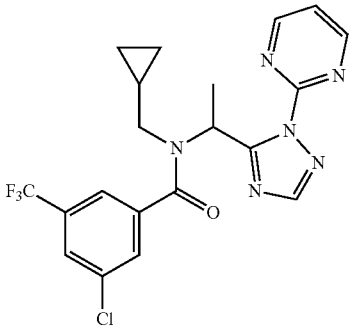
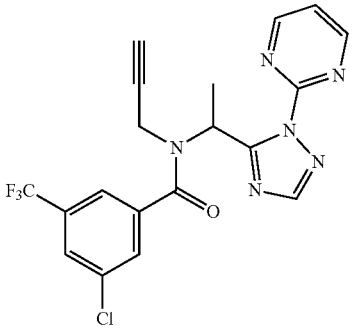
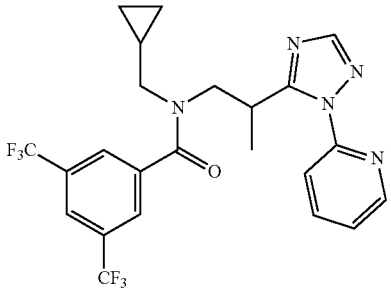
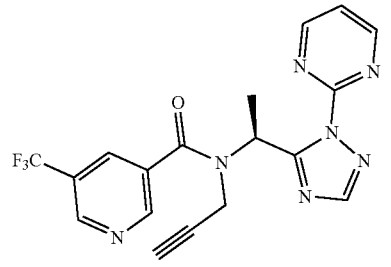
Example	Structure	Compound	Analytical data	Remarks
40		3-Chloro-N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS: (method 2) R_t 1.59 min, m/z (ES+) 451 $[M + H]^+$	—
41		3-Chloro-N-prop-2-ynyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS: (method 2) R_t 1.45 min, m/z (ES+) 435 $[M + H]^+$	—
42		N-(Cyclopropylmethyl)-N-[2-[2-(2-pyridyl)-1,2,4-triazol-3-yl]propyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 1) R_t 2.72 min, m/z (ES+) 498 $[M + H]^+$	Reaction time: overnight; T = 80° C.
43		N-Prop-2-ynyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS: (method 4) R_t 0.67 min, m/z (ES+) 402 $[M + H]^+$	Reaction time: overnight

TABLE 8-continued

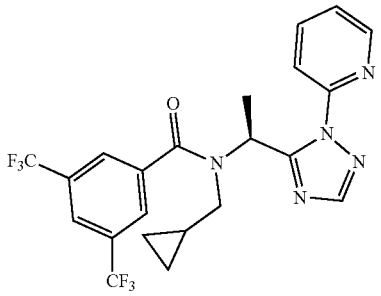
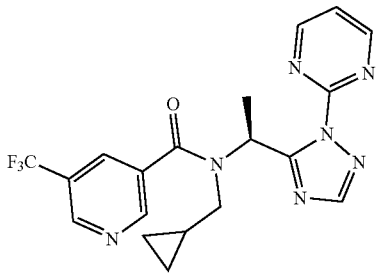
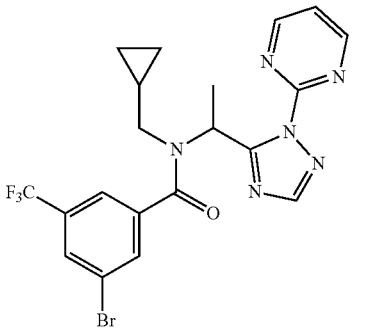
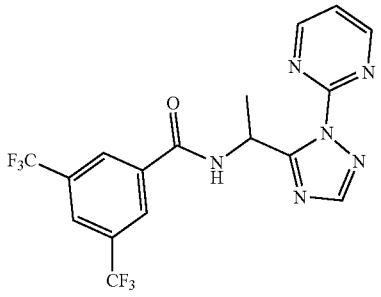
Example	Structure	Compound	Analytical data	Remarks
44		N-(Cyclopropylmethyl)-N-[(1S)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 2.05 min, m/z (ES+) 484 $[M + H]^+$	Reaction time: overnight
45		N-(Cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)pyridine-3-carboxamide	LCMS: (method 4) R_t 0.93 min, m/z (ES+) 418 $[M + H]^+$	Reaction time: overnight
62		3-Bromo-N-(cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.74 min, m/z (ES+) 495 $[M + H]^+$	2nd step: T = 50° C.
63		N-[1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.53 min, m/z (ES+) 431 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.

TABLE 8-continued

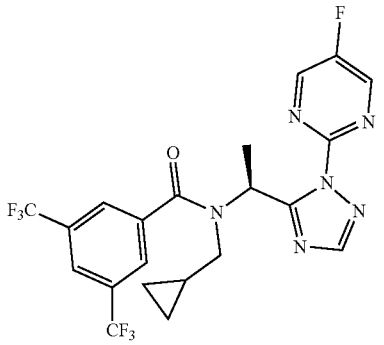
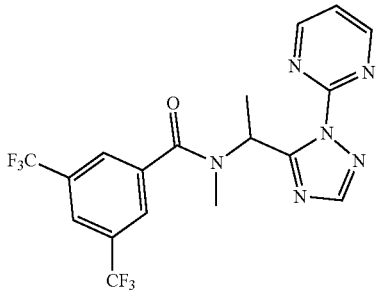
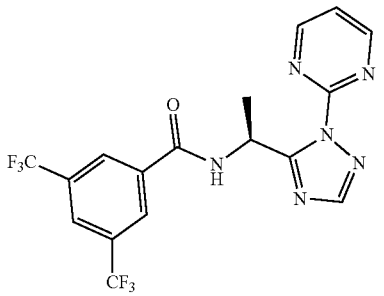
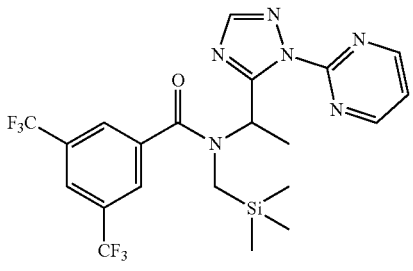
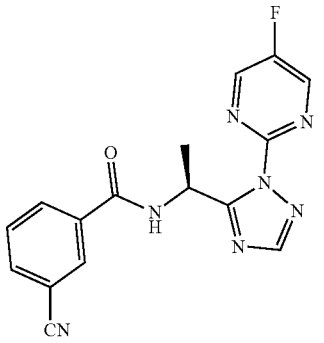
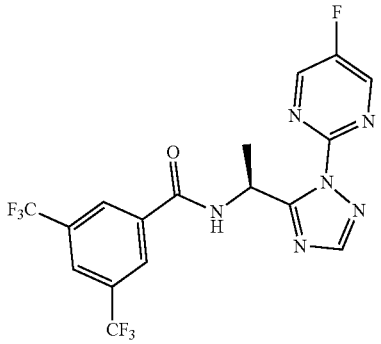
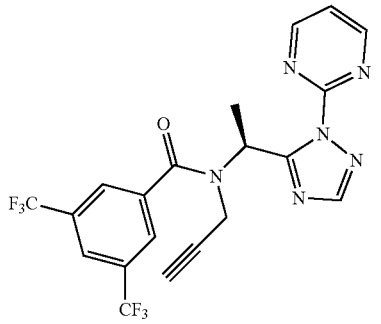
Example	Structure	Compound	Analytical data	Remarks
64		N-(Cyclopropylmethyl)-N-[(1S)-1-[2-(5-fluoropyrimidin-2-yl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.93 min, m/z (ES+) 503 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.
65		N-Methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.49 min, m/z (ES+) 445 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.
66		N-[(1S)-1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.53 min, m/z (ES+) 431 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.
67		N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)-N-(trimethylsilylmethyl)benzamide	LCMS: (method 4) R_t 2.19 min, m/z (ES+) 517 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.

TABLE 8-continued

Example	Structure	Compound	Analytical data	Remarks
68		3-Cyano-N-[(1S)-1-[2-(5-fluoropyrimidin-2-yl)-1,2,4-triazol-3-yl]ethyl]benzamide	LCMS: (method 4) R_t 0.57 min, m/z (ES+) 338 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.
69		N-[(1S)-1-[2-(5-Fluoropyrimidin-2-yl)-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide	LCMS: (method 4) R_t 1.67 min, m/z (ES+) 449 $[M + H]^+$	Reaction time 2nd step: overnight T = 50° C.

EXAMPLE 46

[0250]

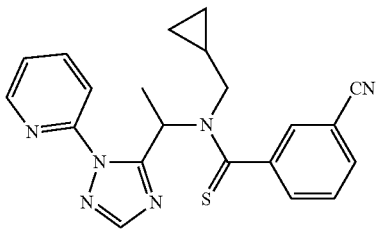


N-Prop-2-ynyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide

[0251] Add N,N-dimethylamide dimethylacetal (32 μL) to a solution of N-[1S)-2-amino-1-methyl-2-oxo-ethyl]-N-prop-2-ynyl-3,5-bis(trifluoromethyl)benzamide (58 mg) in CH_2Cl_2 (0.7 mL) and stir at reflux for 1 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (0.7 mL/0.7 mL), add 2-hydrazinopyrimidine (23 mg) and stir at 50° C. overnight. Cool to r.t., concentrate under reduced pressure, partition the residue between $NaHCO_3$ (aq. sat.) and EtOAc. Separate the layers, dry the organic phase over $MeSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-prop-2-ynyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide (38 mg, 58%). LCMS: (method 4) R_t 1.59 min, m/z (ES) 469 $[M+H]^+$. Chiral HPLC: column Chiralpak AD-H (250×4.6 mm), heptane/iPrOH/diethylamine 95:5:0.1, flow rate 1 mL/min, r.t., λ240 nm, R_t 14.1 min, ee>99%.

EXAMPLE 47

[0252]



3-Cyano-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzenecarbothioamide

(i) 3-Cyano-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide

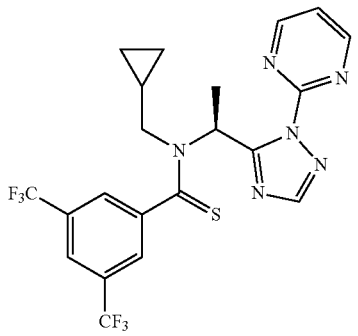
[0253] Add 3-cyanobenzoic acid (81 mg) to a solution of N-(cyclopropylmethyl)-1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethanamine (60 mg) and DIPEA (287μL) in EtOAc (6 mL) and stir the mixture at r.t. for 10 min. Add T3P® (≥50 wt. % in EtOAc, 534 μL) and stir at r.t. overnight. Partition the mixture between water and EtOAc, separate the layers and wash the organic phase sequentially with water, $NaHCO_3$ (aq. sat.) and NH_4Cl (aq. sat.). Dry over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 3-cyano-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide (160 mg, 85%). LCMS (method 1): R_t 2.32 min, m/z (ES+)=373 $[M+H]^+$.

(ii) 3-Cyano-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzenecarbothioamide

[0254] Add Lawesson's reagent (191 mg) to a solution of 3-cyano-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl]benzamide (160 mg) in toluene (10 mL) and stir at reflux overnight. Cool to r.t., concentrate under reduced pressure and purify the residue by chromatography and trituration with pentane to provide 3-cyano-N-(cyclopropylmethyl)-N-[1-[2-(2-pyridyl)-1,2,4-triazol-3-yl]ethyl] benzenecarbothioamide (145 mg, 87%). LCMS (method 1): R_t 2.58 min, m/z (ES+)=389 $[M+H]^+$.

EXAMPLE 70

[0255]

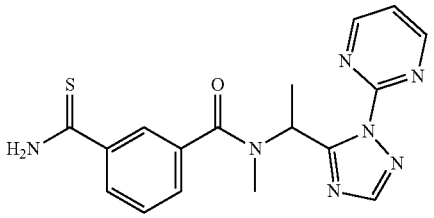


N-(Cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl) benzenecarbothioamide

[0256] Add Lawesson's reagent (92 mg) to a solution of N-(cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide (100 mg) in toluene (5 mL) and stir at reflux overnight. Cool to r.t., concentrate under reduced pressure and purify the residue by chromatography and trituration with pentane to provide N-(cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl) ethyl]-3,5-bis(trifluoromethyl)benzenecarbothioamide (61 mg, 59%). LCMS (method 4): R_t 2.19 min, m/z (ES+)=501 $[M+H]^+$.

EXAMPLE 71

[0257]

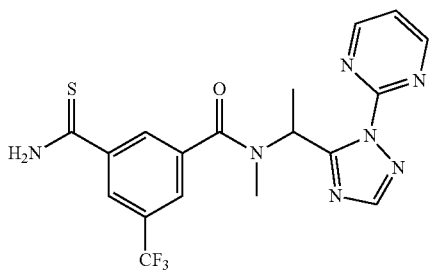


3-Carbamothioyl-N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]benzamide

[0258] Add triethylamine (0.1 mL) and ammonium sulfide (aq. 40-48wt. %, 126 mg) to a solution of 3-cyano-N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]benzamide (224 mg) in pyridine (2 mL) and stir at 50° C. for 1 h. Cool to r.t., partition the mixture between water and CH_2Cl_2, separate the layers and dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide 3-carbamothioyl-N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl) ethyl]benzamide (62 mg, 24%). LCMS (method 4): Rt 0.41 min, m/z (ES+)=368 $[M+H]^+$.

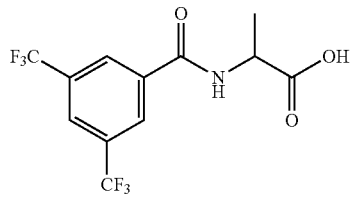
[0259] The compound of Example 72 set forth in table 9 may be prepared essentially as described in Example 71.

TABLE 9

Example	Structure	Compound	Analytical data	Remarks
72		3-Carbamothioyl-N-methyl-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-5-(trifluoromethyl)benzamide	LCMS: (method 4) R_t 0.81 min, m/z (ES+) 436 $[M + H]^+$	—

Preparation 55

[0260]

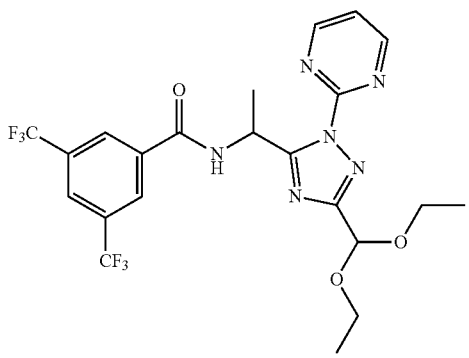


2-[[3,5-Bis(trifluoromethyl)benzoyl]amino]propanoic acid

[0261] Add DL-alanine (918 mg) to a solution of NaOH (1.74 g) in water (6.0 mL) and acetonitrile (2.0 mL). Cool the mixture to 0° C., add 3,5-bis(trifluoromethyl)benzoyl chloride (2.0 mL) and stiff at 0° C. for 30 min. Warm to r.t. and stir for 2 h. Concentrate under reduced pressure, add HCl (aq. 12 M, 1.0 mL) and filter the resulting solid. Dry the solid under vacuum to provide 2[[3,5-bis(trifluoromethyl) benzoyl]amino]propanoic acid (3.00 g, 54%). LCMS (method 4): Rt 1.52 min, m/z (ES+) 330 $[M+H]^+$.

EXAMPLE 73

[0262]

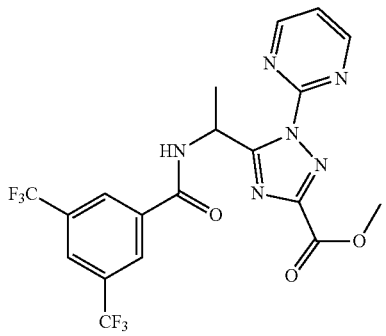


N-[1-[5-(Diethoxymethyl)-2-pyrimidin-2-yl-1,2,4-triazol-3-yl]ethyl]3,5-bis(trifluoromethyl)benzamide

[0263] Add N,N-diisopropylamine (3.84 mL) to a mixture of 2,2-dietboxyacetamidine hydrochloride (1.33 g), 2[[3,5-bis(trifluoromethyl)benzoyl]amino]propanoic acid (3.00 g) and HATU (3.05 g) in DMF (10 mL). Stiff at r.t. for 3 h. Add 2-hydrazinopyrimidine (1.20 g) followed by AcOH (4.18 mL) and stir at 80° C. for 1 h. Cool to r.t. and dilute with EtOAc (50 mL). Wash the organic phase sequentially with $NaHCO_3$ (aq. sat.) and water. Dry the organic phase over $MgSO_4$, filter and concentrate under reduced pressure to provide N-[1-[5-(diethoxymethyl)-2-pyrimidin-2-yl-1,2,4-triazol-3-yl]ethyl]-3,5-bis(trifluoromethyl)benzamide (900 mg, 23%). LCMS (method 4): R_t 1.96 min, m/z (ES−)=531 $[M-H]^-$.

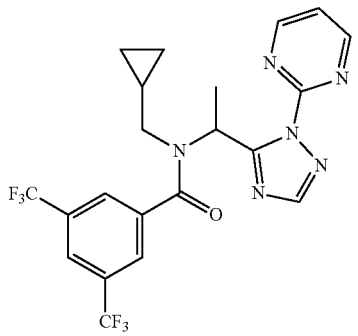
[0264] The compound of Example 74 set forth in table 10 may be prepared essentially as described in Example 73.

TABLE 10

Example	Structure	Compound	Analytical data	Remarks
74		Methyl 5-[1-[[3,5-bis (trifluoromethyl)benzoyl] amino]ethyl]-1-pyrimidin-2-yl-1,2,4-triazole-3-carboxylate	LCMS: (method 4) R_t 1.80 min, m/z (ES+) 499 $[M + H]^+$	

EXAMPLE 48

[0265]



N-(Cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide

(i) 2-(Cyclopropylmethylamino)propanamide

[0266] Add K_2CO_3 (1.45 g) and cyclopropylmethanamine (560 μL) to 2-bromopropanamide (490 mg) and in acetoni-

trile (8 mL) and stir at 80° C. for 1 h. Cool to r.t., filter through Celite® and wash with acetonitrile. Partition the residue between water and EtOAc, separate the layers and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate under reduced pressure to provide 2-(cyclopropylmethylamino)propanamide (351 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.06-0.23 (2 H, m), 0.44-0.58 (2 H, m), 0.83-1.02 (1 H, m), 1.36 (3 H, d, J 6.9 Hz), 1.73 (1 H, br s), 2.42 (1 H, dd, J 12.4, 6.9 Hz), 2.55 (1 H, dd, J 12.1, 6.6 Hz), 3.24 (1 H, q, J 6.9 Hz), 5.39 (1 H, br s), 7.18 (1 H, br s).

(ii) N-(2-Amino-1-methyl-2-oxo-ethyl)-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide

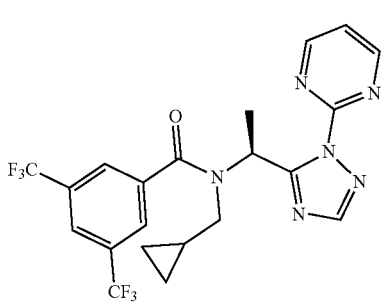
[0267] Add T3P® (≥50 wt. % in EtOAc, 6.2 mL) and DIPEA (4 mL) to a mixture of 2-(cyclopropylmethylamino) propanamide (990 mg) and 3,5-bis(trifluoromethyl)benzoic acid (2.02 g) in EtOAc (20 mL) and stir at r.t. overnight. Partition between water and EtOAc, separate the layers, extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with NaCl (aq. sat.), dry over Na_2SO_4, filter, concentrate under reduced pressure. Partition the residue between NaOH (aq. 1 M) and CH_2Cl_2, separate the layers, extract the aqueous phase three times with CH_2Cl_2, dry the combined organic extracts over Na_2SO_4, filter, concentrate under reduced pressure to provide N-(2-amino-1-methyl-2-oxo-ethyl)-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide (2.37 g, 78%). LCMS: (method 2) R_t 1.52 min, m/z (ES−)=381 $[M-H]^-$.

(iii) N-(Cyclopropylmethlyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl) benzamide

[0268] Add N,N-dimethylamide dimethylacetal (220 μL) to a solution of N-(2-amino-1-methyl-2-oxo-ethyl)-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide (408 mg) in CH_2Cl_2 (5 mL) and stir at reflux for 1.5 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (6 mL/0.6 mL), add 2-hydrazinopyrimidine (183 mg) and stir at 50° C. overnight. Cool to r.t., concentrate under reduced pressure, partition the residue between $NaHCO_3$ (aq. sat.) and EtOAc. Separate the layers, dry the organic phase over $MgSO_4$, concentrate under reduced pressure and purify the residue by chromatography to provide N-(Cyclopropylmethyl)-N-[1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide (173 mg, 33%). LCMS (method 5): Rt 2.16 min, m/z (ES+)=485 $[M+H]^+$. Chiral HPLC: column Chiralpak AD-H (250×4.6 mm), heptane/iPrOH/diethylamine 95:5:0.1, flow rate 1.3 mL/min, T=30° C., λ240 nm, R_t 13.5 and 16.9 min.

EXAMPLE 49

[0269]



N-(Cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl) benzamide

(i) [(1R)-2-Amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate

[0270] Add p-toluene sulfonyl chloride (154 g) and DIPEA (113 mL) to (R)-(+)-lactamide (48.1 g) in CH_2Cl_2 (1.3 L) at 0° C., warm to r.t. and stir for 3 days. Concentrate under reduced pressure, partition between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers, dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and dissolve the residue in CH_2Cl_2. Add pentane, filter the precipitate and partition again between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers, dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure to provide [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (69.7 g, 48%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (3 H, d, J 6.9 Hz), 2.43 (3 H, s), 4.70 (1 H, J 6.9 Hz), 7.29 (1 H, br s), 7.43-7.54 (2 H, m), 7.80-7.85 (2 H, m).

(ii) (2S)-2-(Cyclopropylmethylamino)propanamide

[0271] Mix cyclopropylmethanamine (44 mL), [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (69.3 g) and K_2CO_3 (107 g) in acetonitrile (700 mL) and stir at 30° C. for 6 h. Cool to r.t., filter through Celite® and wash with acetonitrile. Concentrate the filtrate under reduced pressure and purify the residue by chromatography to provide (2S)-2-(cyclopropylmethylamino)propanamide (29.7 g, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.09-0.18 (2 H, 0.44-0.57 (2 H, m), 0.87-0.98 (1 H, 1.35 (3 H, d, J 6.9 Hz), 1.60 (1 H, br s), 2.40 (1 H, dd, J 12.1, 7.3 Hz), 2.54 (1 H, dd, J 12.1, 6.6 Hz), 3.21 (1 H, q, J 6.9 Hz), 5.31 (1 H, br s), 7.14 (1 H, br s).

(iii) N-[(1S)-2-Amino-1-methyl-2-oxo-ethyl]-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide

[0272] Add T3P® (≥50 wt. % in EtOAc, 185 mL) and 3,5-bis(trifluoromethyl)benzoic acid (64.3 mg) to a solution of DIPEA (109 mL) and (2S)-2-(cyclopropylmethylamino) propanamide (29.5 g) in EtOAc (590 mL) and stir at r.t. overnight. Partition between water and EtOAc, separate the layers, wash the organic phase with water, NH4Cl (aq. sat.) and NaOH (aq. 1 M). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by precipitation from CH_2Cl_2 and pentane to provide N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide (49.1 g, 62%). LCMS: (method 4) R_t 1.61 min, m/z (ES+)=383 $[M+H]^+$.

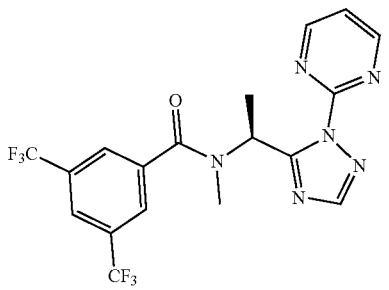
(iv) N-(Cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl) benzamide

[0273] Add N,N-dimethylamide dimethylacetal (25.5 mL) to a solution of N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-N-(cyclopropylmethyl)-3,5-bis(trifluoromethyl)benzamide (48.7 g) in CH_2Cl_2 (490 mL) and stir at reflux for 1 h 15 min. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (275 mL/275 mL), add 2-hydrazinopyrimidine (16.9 g) and stir at 50° C. overnight. Cool to r.t., concentrate under reduced pressure, and partition the residue between water and EtOAc. Filter through Celite®,

separate the layers, wash the organic phase with $NaHCO_3$ (aq. sat.), dry the organic phase over $MgSO_4$, concentrate under reduced pressure and purify the residue by chromatography and precipitation from diethyl ether and petroleum ether to provide N-(cyclopropylmethyl)-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide (29.7 g. 48%). LCMS: (method 4) R_t 1.79 min, m/z (ES)=485 $[M+H]^+$. Chiral HPLC: column Chiralpak AD-H (250×4.6 mm), heptane/iPrOH/diethylamine 95:5:0.1, flow rate 1.3 mL/min, T=30° C., λ240 nm, R_t 13.5 min, (R_t for R-enantiomer 16.9 min) ee>99%.

EXAMPLE 75

[0274]



N-Methyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide

(i) [(1R)-2-Amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate

[0275] Add p-toluene sulfonyl chloride (891 mg) and DIPEA (2.1 mL) to (R)-(+)-lactamide (891 mg) in CH_2Cl_2 (10 mL) and stir at r.t. for 2 days. Concentrate under reduced pressure, partition between $NaHCO_3$ (aq. sat.) and EtOAc, separate the layers, dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify by chromatography to provide [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (1.32 g, 54%). LCMS: (method 4) R_t 0.71 min, m/z (ES+)=244 $[M+H]^+$.

(ii) (2S)-2-(Methylamino)propanamide

[0276] Mix methanamine (2 M in THF, 1 mL), [(1R)-2-amino-1-methyl-2-oxo-ethyl] 4-methylbenzenesulfonate (243 mg) and K_2CO_3 (419 mg) in acetonitrile (1 mL) and stir at r.t. overnight. Filter through Celite® and wash with acetonitrile. Concentrate the filtrate under reduced pressure to provide (2S)-2-(methylamino)propanamide (50% w., 46 mg, 22%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (3 H, d, J 6.94 Hz), 1.84 (1 H, br s), 2.19 (3 H, s), 2.86 (1 H, q, 6.81 Hz), 6.94 (1 H, br s), 7.25 (1 H, br s).

(iii) N-[(1S)-2-Amino-1-methyl-2-oxo-ethyl]-N-methyl-3,5-bis(trifluoromethyl)benzamide

[0277] Add T3P® (≥50 wt. % in EtOAc, 320 μL) and 3,5-bis(trifluoromethyl)benzoic acid (70 mg) to a solution of DIPEA (140 μL) and (2S)-2-(methylamino)propanamide (50% w., 46 mg) in DMF (1.3 mL) and stir at r.t. overnight. Partition between water and EtOAc, separate the layers, extract the aqueous phase once with EtOAc, wash the combined organic extracts with NaCl (aq. sat.). Dry the organic phase over $MgSO_4$, filter, concentrate under reduced pressure and purify the residue by chromatography to provide N-[(1S)-2-amino-1-methyl-2-oxo-ethyl]-N-methyl-3,5-bis(trifluoromethyl)benzamide (90% w. purity, 82 mg, 80%). LCMS: (method 4) R_t 1.28 min, m/z (ES−)=341 $[M-H]^-$.

(iv) N-Methyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide

[0278] Add N,N-dimethylamide dimethylacetal (38 μL) to a solution of N-[(15)-2-amino-1-methyl-2-oxo-ethyl]-N-(methyl)-3,5-bis(trifluoromethyl)benzamide (90% w. purity, 72 mg) in CH_2Cl_2 (2 mL) and stir at reflux for 1.5 h. Cool to r.t., concentrate under reduced pressure, dissolve the residue in 1,4-dioxane/AcOH (0.5 mL/0.5 mL), add 2-hydrazinopyrimidine (25 mg) and stir at 50° C. overnight. Cool to r.t., concentrate under reduced pressure, and partition the residue between water and EtOAc. Filter through Celite®, separate the layers, wash the organic phase with NaCl (aq. sat.), dry the organic phase over $MgSO_4$, concentrate under reduced pressure and purify the residue by chromatography to provide N-methyl-N-[(1S)-1-(2-pyrimidin-2-yl-1,2,4-triazol-3-yl)ethyl]-3,5-bis(trifluoromethyl)benzamide (41 mg, 49%). LCMS: (method 4) R_t 1.50 min, m/z (ES+)=445 $[M+H]^+$. Chiral HPLC: column Diacel Chiralpak IC-3 (150×4.6 mm), 0.1% TFA in H_2O/0.1% TFA in MeCN 48:52, flow rate 0.3 mL/min, T=25° C., λ235 nm, R_t 16.4 min (R_t for R-enantiomer 15.4 min), ee 99.3%.

Analytical Methods

[0279] Analysis of the samples is in each case done using a Waters Autopurification (HPLC/MS) system or an Agilent Autopurification (HPLC/MS) system with a reversed phase column using one of the methods described below. The samples are characterized by m/z and retention time or by NMR spectroscopy using a Bruker Avance 400 spectrometer.

Method 1:

[0280] Column: Xterra MS $C_{18\ 5}$ μm×4.6 mm×50 min

[0281] Eluent: water (A) and acetonitrile (B)

[0282] Flow rate: 0.6 mL/min

[0283] Gradient:

Time [min]	A [%]	B [%]
0	90	10
2.0	5	95
4.0	5	95

Method 2:

[0284] Column: Xterra MS $C_{18\ 5}$ μm×4.6 mm×50 mm

[0285] Eluent: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

[0286] Flow rate: 2 mL/min

[0287] Gradient:

Time [min]	A [%]	B [%]
0	70	30
0.5	70	30
2.5	5	95
2.8	5	95
2.9	70	30
3.0	70	30

Method 3:

[0288] Column: Bischoff SC-03-150 Daisogel SP-120-ODS-AP 5.0 μm×3.0 mm×150 mm

[0289] Eluent: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

[0290] Flow rate: 2 mL/min

[0291] Gradient:

Time [min]	A [%]	B [%]
0	90	10
5.5	5	95
6.0	5	95
6.5	90	10
7.0	90	10

Method 4:

[0292] Column: Xterra MS $C_{18,\ 5}$ μm×4.6 mm×50 mm

[0293] Eluent: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

[0294] Flow rate: 2 mL/min

[0295] Gradient:

Time [min]	A [%]	B [%]
0	65	35
0.5	65	35
2.5	5	95
2.8	5	98
2.9	65	35
3.0	65	35

Method 5:

[0296] Column: XBridge C18 5 μm×2.1 mm×50 mm

[0297] Eluent: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

[0298] Flow rate: 0.6 mL/min

[0299] Gradient:

Time [min]	A [%]	B [%]
0	90	10
0.3	90	10
3.3	5	95
4.0	5	95

Method 6:

[0300] Column: XBridge $C_{18\ 2.5}$ μm×2.1 mm×50 mm

[0301] Eluent: 0.5% ammonia in water (A) and 0.5% ammonia in acetonitrile (B)

[0302] Flow rate: 0.6 mL/min

[0303] Gradient:

Time [min]	A [%]	B [%]
0	90	10
0.3	90	10
3.3	5	95
4.0	5	95

Method 7:

[0304] Column: BEH C18 1.7 μm×2.1 mm×50 mm

[0305] Eluent: 5 mM ammonium acetate+0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

[0306] Flow rate: 0.55 mL/min

[0307] Gradient:

Time [min]	A [%]	B [%]
0	95	5
0.4	95	5
0.8	65	35
1.2	45	55
2.5	0	100
3.3	0	100
3.31	95	5
4.0	95	5

Method 8:

[0308] Column: XBridge C18 3.5 μm×4.6 mm×50 mm

[0309] Eluent: 0.1% ammonia in water (A) and 0.1% ammonia in acetonitrile (B)

[0310] Flow rate: 1.00 mL/min

[0311] Gradient:

Time [min]	A [%]	B [%]
0.01	95	5
5.00	10	90
5.80	5	95
7.20	5	95
7.21	95	5
10.00	95	5

[0312] All of the exemplified compounds of Examples 1 to 49 exhibited one or more of the following: greater than 80% efficacy (EC_{80}) at 32 ppm in the in vitro cat flea assay (Assay A); greater than 80% efficacy (EC_{80}) at 3.2 ppm in the in vitro Australian sheep blow fly assay (Assay A); or greater than 80% efficacy (EC_{80}) at 10 ppm in the in vitro dog tick assay (Assay A). All of the exemplified compounds of Examples 50 to 75 exhibited one or more of the following: greater than 50% efficacy (EC_{50}) at 10 ppm in the in vitro cat flea assay (Assay B); greater than 50% efficacy (EC_{50}) at 10 ppm in the in vitro Australian sheep blow fly assay (Assay B); or greater than 50% efficacy (EC_{50}) at 20 ppm in the in vitro dog tick assay (Assay B).

Activity In Vitro Against *Ctenocephalides felis* (Cat Flea)—Assay A

[0313] A mixed adult population of fleas is placed in a suitably formatted 96-well plate allowing fleas to access and feed on treated blood via an artificial feeding system. Fleas are fed on treated blood for 24 h, after which the compound effect is recorded. Insecticidal activity is determined on the basis of the number of dead fleas recovered from the feeding system. In this test the following examples showed more than 80% (EC_{80}) efficacy at 100 ppm: 1 to 11, 13 to 22, 24 to 32 and 34 to 49.

In this test the compound of Example 18 showed an EC_{80} of 10 ppm.

Activity in Vitro Against *Ctenocephalides felis* (Cat Flea)—Assay B

[0314] Test compounds are added to organic bovine blood contained in an artificial feeding container. Compounds with known insecticidal activity are included to serve as positive controls. Newly emerged unfed adult fleas from a laboratory colony are aspirated into each vial. The test cages are maintained using the artificial feeding apparatus to allow ingestion of compound. Fleas are evaluated for % mortality at 48 hours post infestation. Fleas showing normal movement and/or jumping ability are considered viable and those showing no movement are scored as dead. In this test the following examples showed more than 50% (EC_{50}) efficacy at 10 ppm: 50 to 61, 63 to 73 and 75.

In this test the compound of Example 59 showed an EC_{50} of 1.6 ppm.

Activity In Vitro Against *Lucilia Cuprina* (Australian sheep Blowfly)—Assay A

[0315] Freshly laid blowfly eggs are used to seed a suitably formatted microplate containing the test substances to be evaluated for antiparasitic activity. Each compound is tested by serial dilution in order to determine its minimum efficacy dose. The test compounds are embedded in an agar-based nutritive medium allowing the full development of the eggs into 3rd instar larvae. The incubation lasts for 4 days at 28° C. and 60% relative humidity. Egg-hatching and ensuing larval development are also recorded to identify a possible growth-regulating activity. In this test the following examples showed more than 80% (EC_{80}) efficacy at 32 ppm: 1 to 4, 6 to 33, 35 to 46, 48 and 49.

In this test the compound of Example 41 showed an EC_{80} of 1 ppm.

Activity In Vitro Against *Lucilia Cuprina* (Australian Sheep Blowfly)—Assay B

[0316] Compound formulated in bovine serum is dispensed into scintillation. A dental cotton roll is added to each vial to absorb the compound solution. *L. cuprina* larvae are added to each treatment vial. The vials are capped and held for 24 hours in an environmental chamber at appropriate temperature, humidity and light/dark cycles. Evaluations are only made at 24 hours because dead larvae after 24 hours may be cannibalized by the remaining live ones. Vials are examined for percent mortality. In this test the following examples showed more than 50% (EC_{50}) efficacy at 10 ppm: 50, 51, 53, 56 to 70, 72 and 75.

In this test the compound of Example 59 showed and EC_{50} of 0.77 ppm.

Activity In Vitro Against *Rhipicephalus sanguineus* (Dog Tick)—Assay A

[0317] A contact test is performed by pre-coating microplate with serial dilution of compound allowing evaluating anti-parasitic activity by contact against ticks. A mixed adult tick population is then distributed to each well of the plate and incubated at 28° C. and 80% relative humidity for 7 days, during which the effect of the test compound is monitored. Acaricidal activity is confirmed if and when adult ticks are dead. In this test the following examples showed more than 80% (EC_{80}) efficacy at 100 ppm: 1 to 4, 6, 9 to 15, 19, 20, 24, 26 to 32, 34 to 43 and 47 to 49.

In this test the compound of Example 41 showed an EC_{80} of 32 ppm.

Activity In Vitro Against Rhipicephalus sanguineus (Dog Tick)—Assay B

[0318] A solution of the test compounds is used to coat the inner wall of glass vials containing a filter paper on the bottom of each vial. A second filter paper is also coated and placed in the cap of the vial. Vials and caps are allowed to dry overnight. Each treated vial is infested with ticks. Contact of the ticks with residues is induced by holding the vials in a controlled environment and assessment is performed at 48 hours after application in comparison with untreated glass vials and solvent-treated glass vials. In this test the following examples showed more than 50% (EC_{50}) efficacy at 20 ppm: 50, 54, 55, 58 to 63, 65, 67 to 70 and 73 to 75.

In this test the compound of Example 59 showed an EC_{50} of 14 ppm.

Activity in Vitro Against Engorged Female *Rhipicephalus microplus* (Cattle Tick)

[0319] A contact test is performed by pre-coating 6-well microplates with serial dilution of the compound to be evaluated for anti-parasitic activity. 10 engorged female ticks of the organophosphorous-resistant Ultimo strain are distributed to each well in triplicates. Plates are then incubated at 28° C. and 80% relative humidity. Evaluation takes place 28 days later based on mortality, oviposition and hatched larvae. An indication of the activity of the test compounds is shown by the number of females that:

[0320] die quickly before laying eggs,

[0321] survive for some time without laying eggs,

[0322] lay eggs in which no embryos are formed,

[0323] lay eggs in which embryos form, from which no larvae hatch, and

[0324] lay eggs in which embryos form, from which larvae normally hatch within 26 to 27 days

In this test the following examples showed more than 80% (EC_{80}) efficacy at 200 ppm: 1 to 4, 6 to 12, 14 to 25, 35 to 41, 44 to 46 and 48.

Activity In Vivo Against *Rhipicephalus sanguineus* Nymphs on Mongolian gerbils (*Meriones unguiculatus*) (Spray Application)

[0325] On day 0, gerbils are treated with the test compound at a given dose by pour on application. On day +1 (+2), the animals are infested with nymphs of *R.sanguineus*. Ticks are left on the animals until full repletion. Seven days after infestation nymphs dropped off fully engorged are collected and counted. They are kept until molting to also evaluate growth regulating activity of the test compound. Efficacy in killing (and growth regulating) is expressed as a tick number (and molted tick number) reduction in comparison with a placebo treated group, using the Abbott's formula:

$$\text{Corrected \%} = 100 \times \left(1 - \frac{n \text{ in } T \text{ after treatment}}{n \text{ in } Co \text{ after treatment}}\right)$$

[0326] n=number of live ticks, T=treated group, Co=control/placebo group.

In this test the following examples showed more than 90% (EC_{90}) efficacy at 32 mg/kg: 1, 8 to 12, 14, 16, 18 to 20, 23, 26, 28, 29, 31 35, 37, 39 to 41, 44, 45, 48 and 49.

Activity In Vivo Against *Rhipicephalus sanguineus* Ticks (Dog Tick) on Rabbits

[0327] On day 0, rabbits are treated with the test compound at a given dose by spray application on their ears only. On day +1, the animals are infested on their ears with adult *R. sanguineus* ticks (sex ratio 1:1). Evaluation of efficacy is performed 24 h, 48 h, and 72 h after infestation by counting the numbers of dead and live ticks recovered from the animals. Efficacy is expressed as comparison with a placebo treated group using the Abbott's formula:

$$\text{Corrected \%} = 100 \times \left(1 - \frac{n \text{ in } T \text{ after treatment}}{n \text{ in } Co \text{ after treatment}}\right)$$

[0328] n=number of ticks, T=treated group, Co=control /placebo group.

[0329] In this test the following examples showed more than 90% (EC_{90}) efficacy at 60 mg/m^2: 28, 32, 35, 40, 41 and 48.

Activity In Vivo Against Lice (*Polyplax serrata*) in Mice (Topical)

[0330] Mice naturally infected with *P. serrata* are treated with the formulated test compound on day 0 by pour-on application. On day +4 and +14, efficacy is evaluated by counting the number of live lice under a binocular. Efficacy at the two time points is expressed as a comparison of lice numbers counted on the same mouse before treatment, using the Henderson & Tilton formula, taking also into account lice numbers found on mice treated with the empty formulation (placebo group):

$$\text{Corrected \%} = 100 \times \left(1 - \frac{n \text{ in } Co \text{ before treatment} \times n \text{ in } T \text{ after treatment}}{n \text{ in } Co \text{ after treatment} \times n \text{ in } T \text{ before treatment}}\right)$$

[0331] n=number of lice, T=treated group, Co=control/placebo group.

[0332] In this test the following examples showed more than 90% (EC_{90}) efficacy at 32 mg/kg: 1, 7, 10 to 12, 15 to 21, 24, 25, 27, 28, 30, 35 to 41, 48 and 49.

Activity of Compounds Against Experimental Tick-Infestation with *Rhipicephalus* (*Boophilus*) *microplus* on Cattle

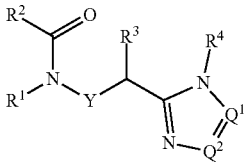
[0333] Studies are conducted to evaluate the curative and the prophylactic activity of the compounds against the cattle tick *R.* (*B.*) *microplus*, when administered as pour-on on experimentally infested cattle. Young adult cattle (approximately 80-250 kg, n=5 per group) are housed individually in roofed pens, but exposed to the ambient conditions .

[0334] During a 30-day acclimation phase all animals are infested three times per week in the dorsal region of the neck with approximately 5000 larvae of *R.* (*B.*) *microplus* per infestation. At the end of the acclimation-period the animals are treated with an experimental formulation that is poured on the back-line of each calf (Day 0). For the experimental formulation the compound is dissolved—as an example—in benzyl alcohol, propylene carbonate and isopropanol. The dose is set to achieve a point dose of ≤10 mg/kg bodyweight. After treatment, the infestation of the animals with *R.* (*B.*) *microplus*-larvae continues at a frequency of two infestations per week until the end of the study. Starting on Day 1 after treatment, adult engorged female ticks are collected daily from each animal according to Holdsworth et al. (W.A.A.V.P. guidelines for evaluating the efficacy of acaricides against ticks (Ixodidae) on ruminants, Vet Parasitol., 136(429-43(2005)). This setup allows evaluating the curative efficacy (onset of efficacy) as well as the residual protection. The infestation of the animals and the daily collection of the ticks continues until Study Day 77.

1.-16. (canceled)

17. A process for preparing a compound of formula

(I')



wherein:

Q^1 and Q^2 are independently CR^5 or N, provided at least one of Q^1 and Q^2 is N;

Y is a direct bond or CH_2;

R^1 is H; C_1-C_6alkyl optionally substituted with one substituent selected from: CN, $CONH_2$, COOH, NO_2 and —$Si(CH_3)_3$; C_1-C_6haloalkyl; C_2-C_6alkenyl; C_2-C_6haloalkenyl; C_2-C_6alkynyl; C_2-C_6haloalkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted with halo or C_1-C_3haloalkyl;

R^2 is phenyl, pyridine, pyrimidine, pyrazine or pyridazine, wherein the phenyl, pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one to three substituents, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group, each independently selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3thiohaloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halo, NO_2, SF_5, CN, $CONH_2$, COOH and $C(S)NH_2$;

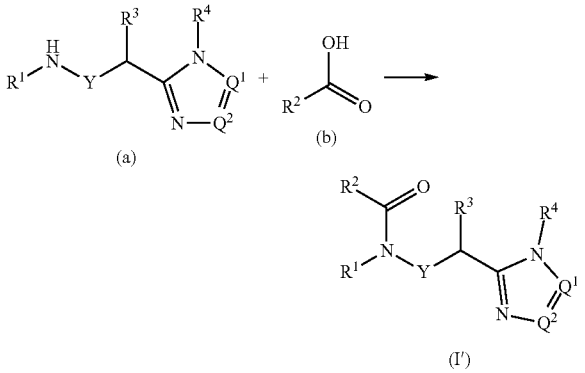
R^3 is C_1-C_3alkyl or C_1-C_3haloalkyl;

R^4 is pyridine, pyrimidine, pyrazine or pyridazine, wherein the pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one substituent selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_3-C_4cycloalkyl, halo or hydroxy; and

R^5 is H, C_1-C_3alkyl, C_1-C_3haloalkyl, C_3-C_4cycloalkyl, C_1-C_3alkoxy, C_1-C_3alkoxyC(O)— or (C_1-C_3alkoxy)$_2$CH—;

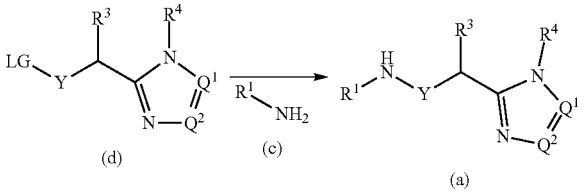
or a salt thereof;

the process comprising reacting an azole compound of formula (a) with a carboxylic acid of formula (b) to form a compound of formula (I'),



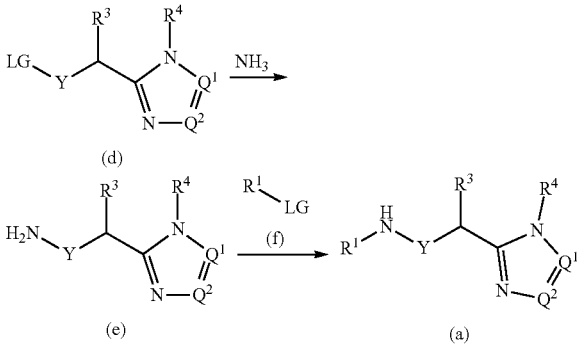
wherein R^1, R^2, R^3, R^4, Q^1, and Q^2 are as defined above.

18. The process of claim **17**, wherein the azole compound of formula (a) is prepared by reacting an amine of formula (c) with a substituted azole of formula (d),



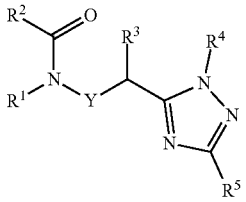
wherein LG is a suitable leaving group, and R^1, R^3, R^4, Q^1, and Q^2 are as defined in claim **17**.

19. The process of claim **17**, wherein the azole compound of formula (a) is prepared by reacting a substituted azole of formula (d) with ammonia to form a substituted azole of formula (e), and subsequently reacting the substituted azole of formula (e) with a compound of formula (f),



wherein LG is a suitable leaving group, and R^1, R^3, R^4, Q^1, and Q^2 are as defined in claim **17**.

20. A process for preparing a compound of formula



(I″)

wherein:

Y is a direct bond or CH_2;

R^1 is H; C_1-C_6alkyl optionally substituted with one substituent selected from: CN, $CONH_2$, COOH, NO_2 and —$Si(CH_3)_3$; C_1-C_6haloalkyl; C_2-C_6alkenyl; C_2-C_6haloalkenyl; C_2-C_6alkynyl; C_2-C_6haloalkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted with halo or C_1-C_3haloalkyl;

R^2 is phenyl, pyridine, pyrimidine, pyrazine or pyridazine, wherein the phenyl, pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one to three substituents, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group, each independently selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3thiohaloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halo, NO_2, SF_5, CN, $CONH_2$, COOH and $C(S)NH_2$;

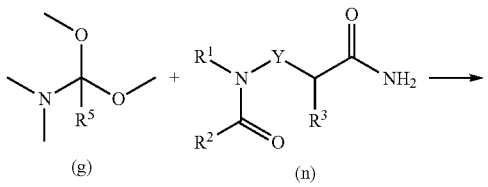
R^3 is C_1-C_3alkyl or C_1-C_3haloalkyl;

R^4 is pyridine, pyrimidine, pyrazine or pyridazine, wherein the pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one substituent selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_3-C_4cycloalkyl, halo or hydroxy; and

R^5 is H, C_1-C_3alkyl, C_1-C_3haloalkyl, C_3-C_4cycloalkyl, C_1-C_3alkoxy, C_1-C_3alkoxyC(O)— or (C_4-C_3alkoxy)$_2$CH—;

or a salt thereof;

the process comprising reacting an amide of formula (n) with an N,N-dimethylamide dimethyl acetal of formula (g) to a form compound of formula (o) which is subsequently reacted with a substituted hydrazine of formula (j) under acidic conditions to form a compound of formula (I"),



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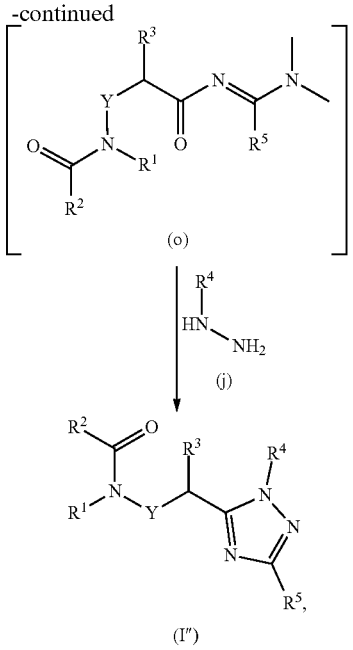
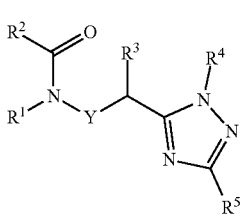


wherein R^1, R^2, R^3, R^4, R^5, and Y are as defined above.

21. The process of claim **20**, wherein the compound of formula (I") is N-[(1S) -1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl) ethyl]-3,5-bis (trifluoromethyl)benzamide or a salt thereof.

22. The process of claim **20**, wherein the compound of formula (I") is N-[(1S) -1-(2-Pyrimidin-2-yl-1,2,4-triazol-3-yl) ethyl]-3,5-bis (trifluoromethyl)benzamide.

23. A process for preparing a compound of formula



(I")

wherein:

Y is a direct bond or CH_2;

R^1 is H; C_1-C_6alkyl optionally substituted with one substituent selected from: CN, $CONH_2$, COOH, NO_2 and —$Si(CH_3)_3$; C_1-C_6haloalkyl; C_2-C_6alkenyl; C_2-C_6haloalkenyl; C_2-C_6alkynyl; C_2-C_6haloalkynyl; C_3-C_4cycloalkyl-C_1-C_2alkyl- wherein the C_3-C_4cycloalkyl is optionally substituted with 1 or 2 halo atoms; oxetan-3-yl-CH_2—; or benzyl optionally substituted with halo or C_1-C_3haloalkyl;

R^2 is phenyl, pyridine, pyrimidine, pyrazine or pyridazine, wherein the phenyl, pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one to three substituents, provided the substituent(s) are not on either carbon adjacent to the carbon bonded to the

group, each independently selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3thiohaloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halo, NO_2, SF_5, CN, $CONH_2$, COOH and $C(S)NH_2$;

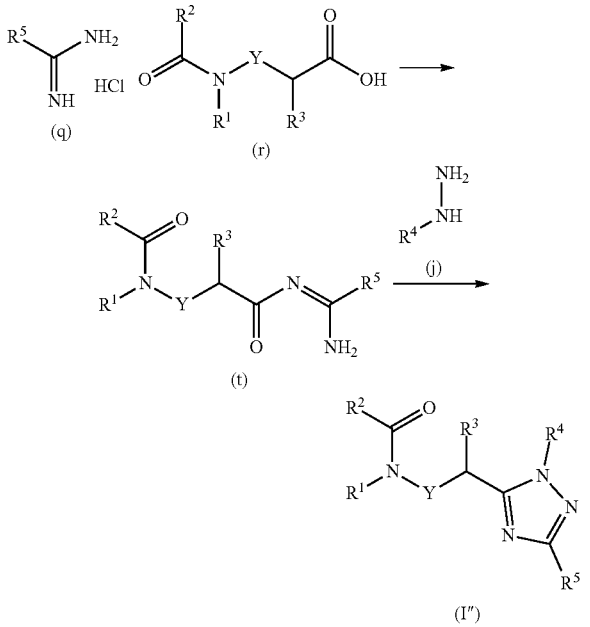
R^3 is C_1-C_3alkyl or C_1-C_3haloalkyl;

R^4 is pyridine, pyrimidine, pyrazine or pyridazine, wherein the pyridine, pyrimidine, pyrazine or pyridazine is optionally substituted with one substituent selected from: C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_3-C_4cycloalkyl, halo or hydroxy; and

R^5 is H, C_1-C_3alkyl, C_1-C_3haloalkyl, C_3-C_4cycloalkyl, C_1-C_3alkoxy, C_1-C_3alkoxyC(O)— or $(C_4$-C_3alkoxy$)_2CH$—;

or a salt thereof;

the process comprising reacting an amidine hydrochloride of formula (q) with an acid of formula (r) to form a compound of formula (t) which is subsequently reacted with a substituted hydrazine of formula (j) under acidic conditions to form a compound of formula (I"),



(I")

wherein R^1, R^2, R^3, R^4, R^5, and Y are as defined above.

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