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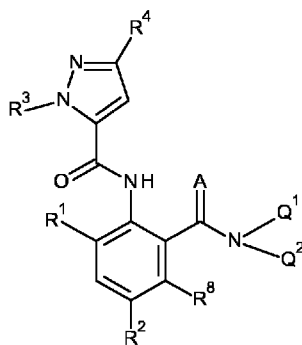
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(54) Title: METHOD FOR CONTROLLING DIAMIDE RESISTANT PESTS AND COMPOUNDS THEREFOR



(I)

(57) Abstract: A method for combating and controlling diamide-resistant insects to (i) reduce damage on a plant, which comprises applying to the insect, to a locus of the insect, or to a plant susceptible to attack by the insect, an effective amount of a compound of formula (I); or (ii) protect plant propagation material, which comprises treating the propagation material or the site, where the propagation material is planted, with an effective amount of a compound of formula (I); wherein the compound of formula (I) is I wherein the substituents are as defined in claim 1, and the agrochemically acceptable salts, stereoisomers, enantiomers, tautomers and N-oxides of those compounds, can be used as insecticides.

METHOD FOR CONTROLLING DIAMIDE RESISTANT PESTS & COMPOUNDS THEREFOR

The present invention relates to method of controlling diamide-resistant pests by use of certain pesticidally active, in particular insecticidally active, diamide compounds. Further, present invention
5 also relates to certain pesticidally active, in particular insecticidally active, diamide compounds, to processes for their preparation, to compositions comprising those compounds, and to their use for controlling animal pests, including arthropods and in particular insects or representatives of the order Lepidoptera, in particular diamide resistant Lepidoptera insects.

10 Diamide (or bisamide) derivatives with insecticidal action are known and described, for example, in WO2003015518, WO2004111030 and WO2007144100.

Bisamide insecticidal derivatives have been used widely during more than a decade and some insect populations have developed a level of resistance that renders them not susceptible enough to be
15 sufficiently controlled by compounds of the bisamide class available on the market. The consequence of this evolution is that a higher dose of protectant must be used and / or the protection of the crops might be insufficient.

Diamide insecticides target the ryanodine receptor in insects and lead to a depletion of the intracellular
20 calcium reservoirs (Ebbinghaus-Kintscher et al. 2006; Sattelle, Cordova, and Cheek 2008; Cordova et al. 2006). Commercial diamides can be attributed to two classes, the phthalic diamides with its sole representative being flubendiamide and the anthranilic diamides comprising chlorantraniliprole, cyantraniliprole, cyclaniliprole, and tetraniliprole. Other examples of phthalic diamides and anthranilic
25 diamides are cyhalodiamide, fluchlordiniliprole and tetrachlorantraniliprole. All diamides share the same mode of action and so are grouped in the IRAC MoA Group 28.

The diamides represent a fast-growing class of insecticides introduced to the market since the commercialization of neonicotinoids (Sparks and Nauen 2015; Richardson et al. 2020; Troczka et al.
30 2017) and are extremely valuable insect control agents not least because they had exhibited little or no cross-resistance to older insecticide classes, which suffer markedly from resistance problems. However, reports of insect resistance to the diamides class of insecticides are on the increase.

The increase in resistance of such insects to diamide insecticides thus poses a significant threat to the cultivation of a number of commercially important crops, fruits and vegetables, and there is thus a
35 need to find alternative insecticides capable of better controlling diamide resistant insects (e.g. to find insecticides that do not exhibit any cross-resistance with the diamide class).

Resistance may be defined as "a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species" (IRAC 2009).

- 5 Cross-resistance occurs when resistance to one insecticide confers resistance to another insecticide via the same biochemical mechanism. This can happen within insecticide chemical groups or between insecticide chemical groups. Cross-resistance may occur even if the resistant insect has never been exposed to one of the chemical classes of insecticide.
- 10 Two of the major mechanisms for diamide resistance include:
- (i) Target site resistance, whereby resistance is associated with replacement of one or more amino acids in the insecticide target protein (i.e. the ryanodine receptor); and
 - (ii) Metabolic resistance, such as enhanced oxidative detoxification of diamides due to overexpression of cytochrome P450 monooxygenases (P450) or conjugation of diamides due to overexpression of
- 15 UDP-dependent glycosyl transferases (UGT).

Target site resistance has been described in numerous Lepidopteran species incl. *Plutella xylostella* (Trocza et al. 2012; Steinbach et al. 2015; Guo et al. 2014), *Tuta absoluta* (Roditakis et al. 2017; Zimmer et al. 2019), *Spodoptera frugiperda* (Bolzan et al. 2019) *Spodoptera exigua* (Zuo et al. 2020, 2017), *Chilo suppressalis* (Yao et al. 2017; Yang et al. 2017). Similar to what has been described for target site resistance against other insecticides e.g. organochlorines affecting the GABA receptor (french-Constant et al. 1998) parallel evolution can also be observed for diamide resistance with certain mutations disclosed, e.g. I4970K, I4970M and G4946E (*P. xylostella* numbering) frequently described across species (Richardson et al. 2020; and Jouraku et al, Insect Biochemistry and

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25 Molecular Biology, Vol. 118, March 2020, 103308). However, that does not exclude that mutations in different positions in the target-site may cause high levels of diamide resistance.

The cytochrome P450 monooxygenases are an important metabolic system involved in the detoxification of xenobiotics in phase I i.e. modification (Dermauw, Van Leeuwen, and Feyereisen 2020; Bard 2000). As such, P450 monooxygenases play an important role in insecticide resistance. P450 monooxygenases have such a phenomenal array of metabolizable substrates because of the presence of numerous P450s (~26-261) arthropodal species, as well as the broad substrate specificity of some P450s (Dermauw, Van Leeuwen, and Feyereisen 2020). Studies of monooxygenase-mediated resistance have indicated that resistance can be due to increased gene expression of one

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35 P450 involved (quantitative changes) in detoxification of the insecticide and might also be due to a mutation in the gene itself altering the amino acid composition (qualitative changes) (Feyereisen, Dermauw, and Van Leeuwen 2015). As such, metabolic cross-resistance mechanisms affect not only insecticides from the given class (e.g. neonicotinoids) but also seemingly unrelated insecticides. For

example, cross-resistance relationships between the neonicotinoids and pymetrozine in *Bemisia tabaci* have been reported (Gorman et al. 2010; Nauen et al. 2013).

Apart from cytochrome P450s other enzyme and transport protein families may lead to insecticide resistance e.g. oxidases, hydrolases, transferases and ABC-transporters (Dermauw and Van Leeuwen 2014; Feyereisen, Dermauw, and Van Leeuwen 2015; Bass et al. 2014). P450s as well as other oxidases, transferases and ABC-transporters have been implicated in diamide resistance (Li et al. 2017; Mallott et al. 2019; Li et al. 2018; Shan et al. 2021).

Therefore, it is highly desirable to find classes of compounds offering a better control of the resistant insects.

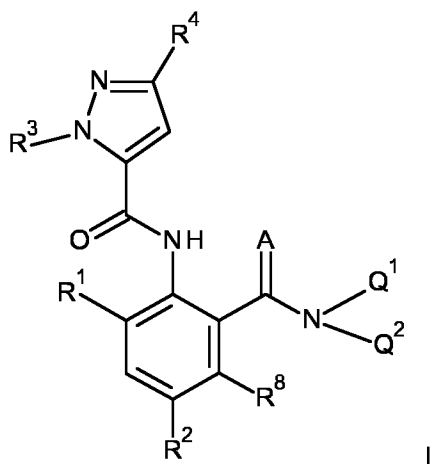
It has now been surprisingly found that certain diamide derivatives are able to better control diamide-resistant insects, as well as other relevant insects. In an embodiment of each aspect of the present invention, the diamide-resistant insect has a mutation corresponding to G4946E amino acid variant.

The present invention accordingly relates, in a first aspect, to a method for combating and controlling diamide-resistant insects to

(i) reduce damage on a plant, which comprises applying to the insect, to a locus of the insect, or to a plant susceptible to attack by the insect, an effective amount of a compound of formula I; or

(ii) protect plant propagation material, which comprises treating the propagation material or the site, where the propagation material is planted, with an effective amount of a compound of formula I;

wherein the compound of formula I is



wherein

A is O or S;

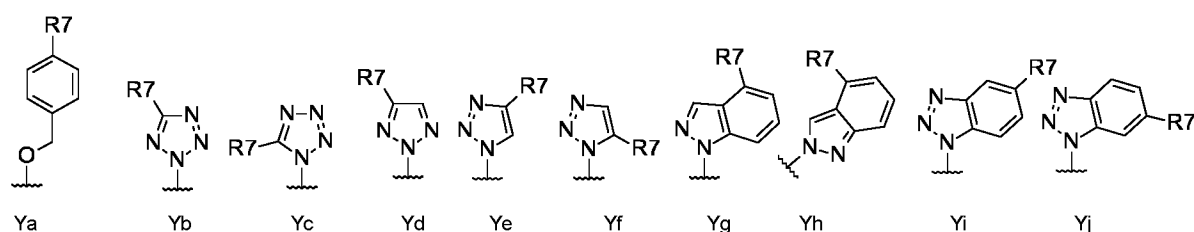
R¹ is halogen, or C₁-C₆alkyl;

R² is halogen, cyano, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R³ is C₃-C₆cycloalkyl, C₃-C₆cycloalkyl substituted by one to three substituents (selected from halogen, cyano, and C₁-C₃-alkyl), C₄-C₆heterocycloalkyl, C₃-C₆cycloalkenyl, C₂-C₈-alkyl, C₁-C₃-alkoxy-C₂-C₈-alkyl, C₂-C₈haloalkyl, C₅-C₈-alkenyl, or CH₂-Z, where Z is C₃-C₆cycloalkyl, C₃-C₆halocycloalkyl, C₁-C₃-alkoxy-C₁-C₃-alkoxy, C₁-C₃-alkoxy, phenoxy, halophenoxy, or 5-membered heteroaromatic ring, which is unsubstituted or substituted with one to three groups independently selected from R⁶;

R⁴ is hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, C₃-C₆halocycloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, or CH₂-Y, where Y is C₃-C₆cycloalkyl, C₃-C₆halocycloalkyl, benzyloxy,

halobenzyloxy, or any one of Y_a to Y_j;



R⁶ is independently selected from halogen, cyano, C₁-C₃alkyl, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy;

R⁷ is independently selected from halogen, cyano, C₁-C₃alkyl, C₁-C₃haloalkyl, C₃-C₆cycloalkyl, phenyl, and phenyl substituted with one to three independently selected substituents from halogen, cyano, C₁-C₃alkyl, and C₁-C₃haloalkyl;

R⁸ is hydrogen, or halogen;

Q¹ is hydrogen, C₁-C₄alkyl, C₃-C₆cycloalkyl, or C₁-C₃alkyl-C₃-C₆cycloalkyl;

Q² is hydrogen, C₁-C₄alkyl, or C₃-C₆cycloalkyl;

or an agronomically acceptable salt, isomer, enantiomer, tautomer and/or N-oxide of the compound of formula I.

It has further now been found that certain novel bisamide derivatives provide improved control over these diamide-resistant insects. Accordingly, a second aspect of the present invention relates to a compound of formula I as defined in the first aspect.

Through the use of a compound of formula I according to each aspect of the present invention the damage caused on plants, especially on useful plants and ornamentals in agriculture, in horticulture and in forests, or on organs, such as fruits, flowers, foliage, stalks, tubers or roots, of such plants, and in some cases even plant organs which are formed at a later point in time, by a diamide-resistant insect is controlled, reduced.

Compounds I which have at least one basic centre can form, for example, acid addition salts, for example with strong inorganic acids such as mineral acids, for example perchloric acid, sulfuric acid, nitric acid, nitrous acid, a phosphorus acid or a hydrohalic acid, with strong organic carboxylic acids,

such as C₁-C₄alkanecarboxylic acids which are unsubstituted or substituted, for example by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid or phthalic acid, such as hydroxycarboxylic acids, for example ascorbic acid, lactic acid, malic acid, tartaric acid or citric acid, or such as benzoic acid, or
5 with organic sulfonic acids, such as C₁-C₄alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Compounds I which have at least one acidic group can form, for example, salts with bases, for example mineral salts such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, piperidine, pyrrolidine, a mono-, di- or
10 tri-lower-alkylamine, for example ethyl-, diethyl-, triethyl- or dimethylpropylamine, or a mono-, di- or trihydroxy-lower-alkylamine, for example mono-, di- or triethanolamine. Where appropriate, the corresponding internal salts can furthermore be formed. Preferred within the scope of the invention are agrochemically advantageous salts; however, the invention also encompasses salts which have disadvantage for agrochemical use, for example salts which are toxic to bees or fish, and which are
15 employed, for example, for the isolation or purification of free compounds I or agrochemically utilizable salts thereof. Owing to the close relationship between the compounds I in free form and in the form of their salts, for the purposes of the invention the free compounds I or their salts hereinabove and hereinbelow are respectively to be understood as including, where appropriate, the corresponding salts or the free compounds I. The same applies analogously to tautomers of compounds I and salts
20 thereof. In general, the free form is preferred in each case.

N-oxides are oxidized forms of tertiary amines or oxidized forms of nitrogen containing heteroaromatic compounds. They are described for instance in the book "Heterocyclic N-oxides" by A. Albin and S. Pietra, CRC Press, Boca Raton 1991.

25 The compounds of formula I according to the invention also include hydrates which may be formed during the salt formation.

The term "C₁-C_nalkyl" as used herein refers to a saturated straight-chain or branched hydrocarbon radical attached via any of the carbon atoms having 1 to n carbon atoms, for example, any one of the
30 radicals methyl, ethyl, n-propyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2, 2-dimethylpropyl, 1-ethylpropyl, n-hexyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl,
35 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, or 1-ethyl-2-methylpropyl.

The term "C₁-C_nhaloalkyl" as used herein refers to a straight-chain or branched saturated alkyl radical attached via any of the carbon atoms having 1 to n carbon atoms (as mentioned above), where some or all of the hydrogen atoms in these radicals may be replaced by a halogen independently selected

from fluorine, chlorine, bromine and iodine, i.e., for example, any one of chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-

5 trichloroethyl, pentafluoroethyl, 2-fluoropropyl, 3-fluoropropyl, 2,2-difluoropropyl, 2,3-difluoropropyl, 2-chloropropyl, 3-chloropropyl, 2,3-dichloropropyl, 2-bromopropyl, 3-bromopropyl, 3,3,3-trifluoropropyl, 3,3,3-trichloropropyl, 2,2,3,3,3- pentafluoropropyl, heptafluoropropyl, 1-(fluoromethyl)-2-fluoroethyl, 1-(chloromethyl)-2-chloroethyl, 1-(bromomethyl)-2-bromoethyl, 4-fluorobutyl, 4-chlorobutyl, 4-bromobutyl or nonafluorobutyl. Accordingly, the term "C₁-C₂fluoroalkyl" would refer to a C₁-C₂alkyl radical which
10 carries 1, 2, 3, 4, or 5 fluorine atoms, for example, any one of difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 1,1,2,2-tetrafluoroethyl or pentafluoroethyl.

The term "C₁-C_nalkoxy" as used herein refers to a straight-chain or branched saturated alkyl radical
15 having 1 to n carbon atoms (as mentioned above) which is attached via an oxygen atom, i.e., for example, any one of the radicals methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy. The term "haloC₁-C_nalkoxy" as used herein refers to a C₁-C_nalkoxy radical where one or more hydrogen atoms on the alkyl radical is replaced by the same or different halo atom(s) - examples include trifluoromethoxy, 2-fluoroethoxy, 3-
20 fluoropropoxy, 3,3,3-trifluoropropoxy, 4-chlorobutoxy.

The term "C₃-C_ncycloalkyl" as used herein refers to 3-n membered cycloalkyl groups such as cyclopropane, cyclobutane, cyclopentane and cyclohexane.

25 The term "C₃-C_ncycloalkenyl" as used herein refers to 3-n membered cycloalkenyl groups and one or two double bonds, such as cyclohexenyl, and cyclobutenyl,

The term "C₁-C_malkyl-C₃-C_ncycloalkyl" as used herein refers to 3-n membered cycloalkyl group connected to a C₁-C_malkyl group, wherein the alkyl group is saturated straight-chain or branched
30 hydrocarbon radical attached, via any of the carbon atoms having 1 to m carbon atoms, to the rest of the compound.

The term "C₂-C_nhalocycloalkyl" as used herein refers to a C₃-C_ncycloalkyl moiety substituted with one or more halo atoms which may be the same or different.

35 The term "C₂-C_nalkenyl" as used herein refers to a straight or branched alkenyl chain having from two to n carbon atoms and one or two double bonds, for example, ethenyl, prop-1-enyl, but-2-enyl.

The term "C₂-C_nalkynyl" as used herein refers to a straight or branched alkynyl chain having from two to n carbon atoms and one triple bond, for example, ethynyl, prop-2-ynyl, but-3-ynyl.

Halogen or "halo" is generally fluorine, chlorine, bromine or iodine. This also applies, correspondingly, to halogen in combination with other meaning, such as haloalkyl

Examples of "5-membered heteroaromatic" refers to a 5 membered aromatic ring having 1 to 3 carbon atoms replaced independently by nitrogen, sulfur, or oxygen. Examples are pyrrolyl, pyrazolyl, imidazolyl, triazolyl (e.g. 1,2,4 triazolyl), furanyl, thiophenyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl and thiadiazolyl.

The term "C₄-C_nheterocycloalkyl" refers to a stable 4 to n-membered non-aromatic monocyclic ring radical which comprises 1 or 2 heteroatoms individually selected from nitrogen, oxygen and sulfur. The heterocyclyl radical may be bonded to the rest of the molecule via a carbon atom or heteroatom. Examples of such heterocycloalkyl (or heterocyclyl) include, but are not limited to, pyrrolidyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, piperaziny, tetrahydropyranyl, dioxolanyl, morpholinyl, oxetanyl, and azetidiny.

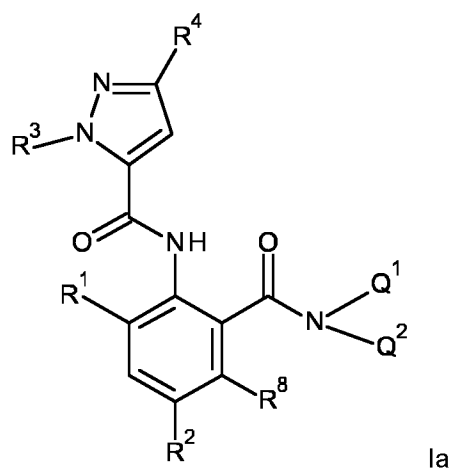
As used herein, the term "controlling" refers to reducing the number of pests (or insects), eliminating pests and/or preventing further pest damage such that damage to a plant or to a plant derived product is reduced. The insect encompasses all stages in the life cycle of the insect.

As used herein, the term "effective amount" refers to the amount of the compound, or a salt thereof, which, upon single or multiple applications provides the desired effect.

The staggered line as used herein, for example, in Ya1 to Ya18, represent the point of connection/attachment to the rest of the compound.

An effective amount is readily determined by the skilled person 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 including, but not limited to: the type of plant or derived product to be applied; the pest to be controlled & its lifecycle; the particular compound applied; the type of application; and other relevant circumstances.

In a preferred embodiment of each aspect of the present invention, compound of formula I is represented by formula Ia



where R^1 , R^2 , R^3 , R^4 , R^8 , Q^1 and Q^2 are as defined in the first aspect.

Embodiments according to the present invention are provided as set out below.

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In an embodiment of each aspect of the invention, A is

- A. sulfur; or
- B. oxygen.

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In an embodiment of each aspect of the invention, R^1 is

- A. halogen, or C_1 - C_3 alkyl; or
- B. methyl, F, Cl, Br, or I; or
- C. methyl, Cl, or Br; or
- D. methyl or chlorine; or

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- E. methyl.

In an embodiment of each aspect of the invention R^2 is

- A. halogen, cyano, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl; or
- B. chloro, bromo, fluoro, iodo, cyano, methyl, isopropyl, trifluoromethyl, or difluoromethyl; or
- C. chloro, bromo, fluoro, iodo, or cyano; or
- D. chloro, bromo, or cyano; or
- E. chloro, or cyano; or
- F. chloro; or
- G. cyano.

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In an embodiment of each aspect of the invention, R^3 is

- A. C_3 - C_4 cycloalkyl, C_3 - C_4 cycloalkyl substituted by one to three substituents (selected from halogen, cyano, and C_1 - C_3 -alkyl), C_4 - C_5 heterocycloalkyl, C_3 - C_4 cycloalkenyl, C_2 - C_6 -alkyl, C_1 - C_3 -alkoxy- C_2 - C_8 -alkyl, C_2 - C_6 haloalkyl, C_5 - C_6 -alkenyl, or CH_2 -Z, where Z is C_3 - C_4 cycloalkyl, C_3 -

C₄halocycloalkyl, C₁-C₃-alkoxy- C₁-C₃-alkoxy, C₁-C₃-alkoxy, phenoxy, halophenoxy, or 5-membered heteroaromatic ring, which is unsubstituted or substituted with one to three groups independently selected from R⁶; or

B. cyclopropyl, cyanocyclopropyl, halocyclopropyl, cyclobutyl, halocyclohexyl, haloethyl, halopropyl, halobutyl, ethyl, isopropyl, tert-butyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl, cyclohexen-1-yl, tetrahydrofuranyl, oxetanyl, pyrrolidyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, piperazinyl, tetrahydropyranyl, dioxolanyl, morpholinyl, azetidiny, methoxymethyl, cyclopropylmethyl, isoxazolylmethyl, or [3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl; or

C. cyclopropyl, cyanocyclopropyl, 2-fluorocyclopropyl, 2,2-difluorocyclopropyl, cyclobutyl, 4,4-difluorocyclohexyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3-difluoropropyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, ethyl, isopropyl, tert-butyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl, cyclohexen-1-yl, tetrahydrofuran-3-yl, oxetan-3-yl, methoxymethyl, cyclopropylmethyl, isoxazol-4-ylmethyl, or [3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl; or

D. cyclopropyl, 4,4-difluorocyclohexyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, ethyl, isopropyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl, cyclohexen-1-yl, methoxymethyl, cyclopropylmethyl, or isoxazol-4-ylmethyl; or

E. cyclopropyl, 2,2-difluoroethyl, or 2,2,2-trifluoroethyl.

In an embodiment of each aspect of the invention, R⁴ is

A. hydrogen, halogen, C₁-C₃alkyl, C₁-C₃haloalkyl, C₃-C₄cycloalkyl, C₃-C₄halocycloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is C₃-C₄cycloalkyl, C₃-C₄halocycloalkyl, benzyloxy, halobenzyloxy, or any one of Y_a to Y_j; or

B. halogen, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is any one of Y_a to Y_j; or

C. halogen, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is any one of from Y_{a1} to Y_{a18}; or

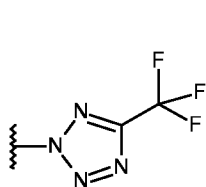
D. halogen, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is any one of from Y_{a1}, Y_{a2}, Y_{a3}, Y_{a4} or Y_{a18}; or

E. bromine, chlorine, methoxy, trifluoromethyl, difluoromethyl, pentafluoroethoxy, 2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, or CH₂-Y, where Y is any one of from Y_{a1}, Y_{a2}, Y_{a3}, Y_{a4} or Y_{a18}; or

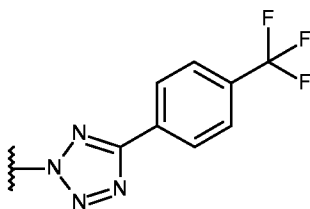
F. bromine, chlorine, methoxy, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, or CH₂-Y, where Y is any one of from Y_{a1}, Y_{a2}, Y_{a3}, Y_{a4} or Y_{a18}; or

G. bromine, methoxy, trifluoromethyl, or Y_{a18};

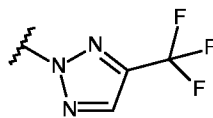
H. bromine, or trifluoromethyl.



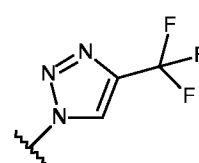
Ya1



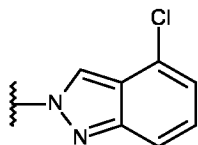
Ya2



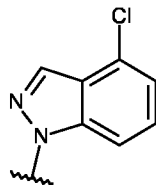
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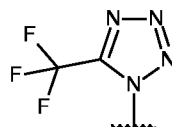
Ya4



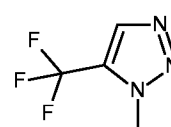
Ya5



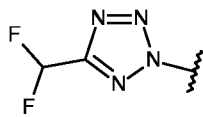
Ya6



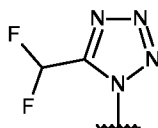
Ya7



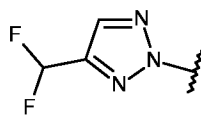
Ya8



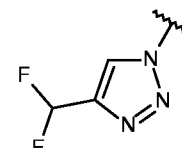
Ya9



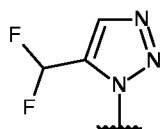
Ya10



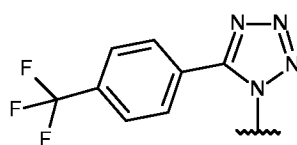
Ya11



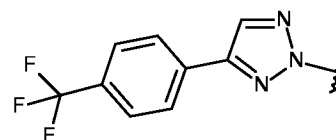
Ya12



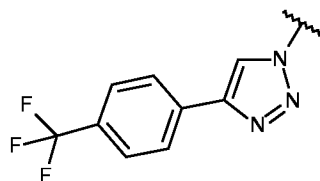
Ya13



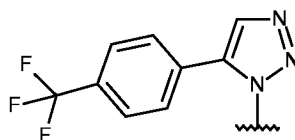
Ya14



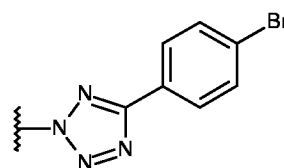
Ya15



Ya16



Ya17



Ya18

In an embodiment of each aspect of the invention, R⁶ is

- A. independently selected from halogen, cyano, C₁-C₃alkyl, C₁-C₃haloalkyl, and C₁-C₃haloalkoxy;
- or
- B. independently selected from halogen, cyano, C₁-C₃alkyl, and C₁-C₃haloalkyl; or

- C. independently selected from halogen, C₁-C₃alkyl, and C₁-C₃haloalkyl; or
- D. independently selected from chloro, fluoro, methyl, trifluoromethyl, and difluoromethyl; or
- E. independently selected from methyl, and difluoromethyl.

5 In an embodiment of each aspect of the invention, R₇ is

- A. independently selected from halogen, cyano, C₁-C₃alkyl, C₁-C₃haloalkyl, C₃-C₆cycloalkyl and phenyl substituted with one more selected from halogen, cyano, C₁-C₃alkyl, and C₁-C₃haloalkyl; or
- B. halogen, C₁-C₃alkyl, C₁-C₃haloalkyl, C₃-C₆cycloalkyl and phenyl substituted by chlorine, bromine, trifluoromethyl or difluoromethyl; or
- 10 C. halogen, C₁-C₃haloalkyl, C₃-C₆cycloalkyl and phenyl substituted by chlorine, bromine, trifluoromethyl or difluoromethyl or
- D. chlorine, bromine, fluorine, difluoromethyl, trifluoromethyl, cyclopropyl or phenyl substituted by trifluoromethyl or bromo; or
- 15 E. trifluoromethyl, or phenyl substituted by trifluoromethyl or bromo.

In an embodiment of each aspect of the invention, R⁸ is

- A. H, F, Cl, Br, I, or Me; or
- B. H, F, or Cl; or
- 20 C. H, or F; or
- D. hydrogen.

In an embodiment of each aspect of the invention, Q¹ is

- A. hydrogen, C₁-C₃alkyl, C₃-C₄cycloalkyl, or C₁-C₂alkyl-C₃-C₄cycloalkyl; or
- 25 B. hydrogen, methyl, isopropyl, cyclopropyl, or C₁-C₂alkyl-cyclopropyl; or
- C. hydrogen, methyl, isopropyl, cyclopropylmethyl, or CH(CH₃)-cyclopropyl.

In an embodiment of each aspect of the invention, Q² is

- A. hydrogen, C₁-C₃alkyl, or C₃-C₄cycloalkyl; or
- 30 B. hydrogen, methyl, isopropyl; or
- C. hydrogen.

The present invention, accordingly, makes available a compound of formula I having the substituents A, R¹, R², R³, R⁴, R⁸, Q¹ and Q² as defined above in all combinations / each permutation. Accordingly, made available, for example, is a compound of formula I with A being the first aspect (i.e. A is oxygen or sulfur); R¹ being embodiment D (i.e. methyl or chlorine); R² being an embodiment A (i.e. R² is halogen, cyano, C₁-C₃alkyl, or C₁-C₃haloalkyl); R³ being an embodiment D (i.e. R³ is cyclopropyl, 4,4-difluorocyclohexyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, ethyl, isopropyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl, cyclohexen-1-yl, methoxymethyl, cyclopropylmethyl, or isoxazol-4-ylmethyl); R⁴

being embodiment G (i.e. bromine, methoxy, trifluoromethyl, or Y_{a18}); R^8 being embodiment D (i.e. hydrogen); Q^1 being embodiment A (i.e. hydrogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_3\text{-C}_4$ cycloalkyl, or $\text{C}_1\text{-C}_2$ alkyl- $\text{C}_3\text{-C}_4$ cycloalkyl); and Q^2 being embodiment C (i.e. hydrogen).

- 5 In an embodiment of each aspect of the invention, the insects are those resistant to insecticides of the IRAC class 28 (<https://irac-online.org/moa-classification>), which act on the ryanodine receptors of the insects – such insecticides are generally referred to as diamides or phthalimide insecticides.

- 10 In an embodiment, the compounds of formula I control insects that demonstrate resistance to least one compound selected from chlorantraniliprole, cyantraniliprole, cyclantraniliprole, fluchlordiniliprole, tetrachlorantraniliprole, tetraniliprole, flubendiamide and cyhalodiamide.

- 15 The insects have developed target site resistance and have, for example, at least one of the mutations i.e. I4970K, I4970M and G4946E (P. xylostella numbering). A skilled person would however not exclude that mutations in different positions in the target-site may also cause high levels of diamide resistance.

The diamide-resistant insects are preferably from the order Lepidoptera.

- 20 Preferred species are *Plutella xylostella* (Trocza et al. 2012; Steinbach et al. 2015; Guo et al. 2014), *Tuta absoluta* (Roditakis et al. 2017; Zimmer et al. 2019), *Spodoptera frugiperda* (Bolzan et al. 2019) *Spodoptera exigua* (Zuo et al. 2020, 2017), *Chilo suppressalis* (Yao et al. 2017; Yang et al. 2017).

- 25 In an embodiment of the first aspect, the method for combating and controlling diamide-resistant insect is in a defined area /field of plants where the ratio of diamide-resistant insects to their corresponding sensitive strains is greater than 1:20 (based on number of insects), preferably greater than 1:10, especially greater than 1:5.

- 30 In an embodiment of the first aspect, a compound of formula I controls the diamide-resistant insect better compared to the secondary amide analog of the compound of formula I. The improvement in control can be more than 20, preferably more than 30, more preferably more than 40, and most preferably more than 50, percent. The improvement in the control is assessed at the same level, for example at 5 ppm.

- 35 In an embodiment of the first aspect, the method for combating and controlling diamide-resistant insect is by applying to a plant susceptible to attack by the insect an effective amount of a compound of formula I; or by treating the propagation material with an effective amount of a compound of formula I.

In an embodiment, the compounds of formula I are represented by compounds of formulae Ia, where the corresponding substituents are as defined for formula I in the first aspect.

In an embodiment of each aspect of the invention, the compound of formula Ia has R¹ as halogen, or C₁-C₃alkyl; R² as halogen, cyano, C₁-C₃alkyl, or C₁-C₃haloalkyl; R³ as C₃-C₄cycloalkyl, C₃-C₄cycloalkyl substituted by one to three substituents (selected from halogen, cyano, and C₁-C₃-alkyl), C₄-C₅heterocycloalkyl, C₃-C₄cycloalkenyl, C₂-C₆-alkyl, C₁-C₃alkoxy-C₂-C₆-alkyl, C₂-C₆haloalkyl, C₅-C₆-alkenyl, or CH₂-Z, where Z is C₃-C₄cycloalkyl, C₃-C₄halocycloalkyl, C₁-C₃alkoxy-C₁-C₃alkoxy, C₁-C₃alkoxy, phenoxy, halophenoxy, or 5-membered heteroaromatic ring, which is unsubstituted or substituted with one to three groups independently selected from R⁶; R⁴ as halogen, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is any one of from Ya1, Ya2, Ya3, Ya4 or Ya18; R⁶ as independently selected from chloro, fluoro, methyl, trifluoromethyl, and difluoromethyl; R⁸ as hydrogen; Q¹ as hydrogen, methyl, isopropyl, cyclopropyl, or C₁-C₂alkyl-cyclopropyl; and Q² as hydrogen.

In an embodiment of each aspect of the invention, the compound of formula Ia has R¹ as methyl, Cl, or Br; R² as chloro, bromo, fluoro, iodo, or cyano; R³ as C₃-C₄cycloalkyl, C₃-C₄cycloalkyl substituted by one to three substituents (selected from halogen, cyano, and C₁-C₃-alkyl), C₄-C₅heterocycloalkyl, C₃-C₄cycloalkenyl, C₂-C₆-alkyl, C₂-C₆haloalkyl, C₅-C₆-alkenyl, or CH₂-Z, where Z is C₃-C₄cycloalkyl, C₃-C₄halocycloalkyl, C₁-C₃alkoxy, phenoxy, halophenoxy, or 5-membered heteroaromatic ring, which is unsubstituted or substituted with one to three groups independently selected from R⁶; R⁴ as halogen, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is any one of from Ya1, Ya2, Ya3, Ya4 or Ya18; R⁶ as independently selected from chloro, fluoro, methyl, trifluoromethyl, and difluoromethyl; R⁸ as hydrogen; Q¹ as hydrogen, methyl, isopropyl, cyclopropyl, or C₁-C₂alkyl-cyclopropyl; and Q² as hydrogen.

In an embodiment of each aspect of the invention, the compound of formula Ia has R¹ as halogen, or C₁-C₃alkyl; R² as chloro, bromo, fluoro, iodo, or cyano; R³ as cyclopropyl, cyanocyclopropyl, 2,2-difluorocyclopropyl, cyclobutyl, 4,4-difluorocyclohexyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3-difluoropropyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, ethyl, isopropyl, tert-butyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl, cyclohexen-1-yl, tetrahydrofuran-3-yl, oxetan-3-yl, methoxymethyl, cyclopropylmethyl, isoxazol-4-ylmethyl, or [3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl; R⁴ as bromine, chlorine, methoxy, trifluoromethyl, difluoromethyl, pentafluoroethoxy, 2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, or CH₂-Y, where Y is any one of from Ya1, Ya2, Ya3, Ya4 or Ya18; R⁸ as hydrogen; Q¹ as hydrogen, methyl, isopropyl, or cyclopropylmethyl; and Q² as hydrogen.

In an embodiment of each aspect of the invention, the compound of formula Ia has R¹ as halogen, or C₁-C₃alkyl; R² as chloro, bromo, fluoro, iodo, or cyano; R³ as cyclopropyl, 4,4-difluorocyclohexyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, ethyl, isopropyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl,

cyclohexen-1-yl, methoxymethyl, cyclopropylmethyl, or isoxazol-4-ylmethyl; R⁴ as bromine, chlorine, methoxy, trifluoromethyl, difluoromethyl, pentafluoroethoxy, 2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, or CH₂-Y, where Y is any one of from Ya1, Ya2, Ya3, Ya4 or Ya18; R⁸ as hydrogen; Q¹ as hydrogen, methyl, isopropyl, or cyclopropylmethyl; and Q² as hydrogen.

5

In an embodiment of each aspect of the invention, the compound of formula Ia has R¹ as methyl, Cl, or Br; R² as chloro, bromo, fluoro, iodo, or cyano; R³ as cyclopropyl, 2,2-difluoroethyl, or 2,2,2-trifluoroethyl; R⁴ as bromine, chlorine, methoxy, trifluoromethyl, difluoromethyl, pentafluoroethoxy, 2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, or CH₂-Y, where Y is any one of from Ya1, Ya2, Ya3, Ya4 or Ya18; R⁸ as hydrogen; Q¹ as hydrogen, methyl, isopropyl, or cyclopropylmethyl; and Q² as hydrogen.

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In a third aspect, the present invention makes available a composition comprising a compound of formula I as defined in the second aspect, one or more auxiliaries and diluent, and optionally one or more other active ingredient.

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In a fourth aspect, the present invention makes available a method of combating and controlling insects, acarines, nematodes or molluscs which comprises applying to a pest, to a locus of a pest, or to a plant susceptible to attack by a pest an insecticidally, acaricidally, nematocidally or molluscicidally effective amount of a compound as defined in the second aspect or a composition as defined in the third aspect.

25

In a fifth aspect, the present invention makes available a method for the protection of plant propagation material from the attack by insects, acarines, nematodes or molluscs, which comprises treating the propagation material or the site, where the propagation material is planted, with an effective amount of a compound of formula I as defined in the second aspect or a composition as defined in the third aspect.

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In a sixth aspect, the present invention makes available a plant propagation material, such as a seed, comprising, or treated with or adhered thereto, a compound of formula I as defined in the second aspect or a composition as defined in the third aspect.

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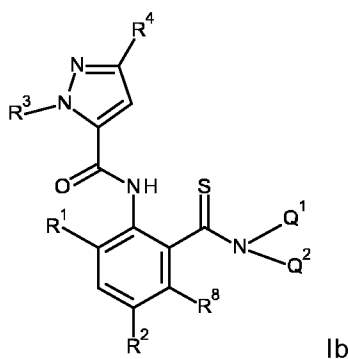
Compounds of formula I can be prepared by those skilled in the art following known methods. More specifically compounds of formula I, and intermediates therefor can be prepared as described below in the schemes and examples. Certain stereogenic centers have been left unspecified for the clarity and are not intended to limit the teaching of the schemes in any way.

The process according to the invention for preparing compounds of formula I is carried out by methods known to those skilled in the art. In particular, the process for preparing compounds of formula I or,

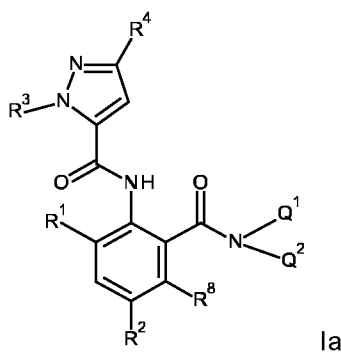
where appropriate, a tautomer and/or salt thereof, is carried out analogously to known processes, for example those described in WO 01/70671, WO 03/016284, WO 03/015518 and WO 04/033468. In the following section the substituents A, R¹, R², R³, R⁴, R⁸, Q¹ and Q² are defined as in formula I unless otherwise stated.

5

Processes for making compounds of formula Ib



in which R¹, R², R³, R⁴, R⁸, Q¹ and Q² are defined as in formula I, or, where appropriate, a tautomer and/or salt thereof, can be made from compounds of formula Ia

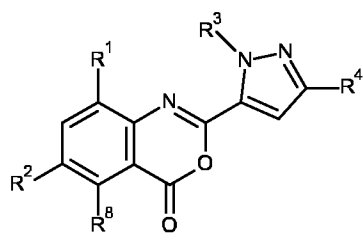


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by treatment with a thiation reagent such as Lawesson's reagent or phosphorus pentasulfide. The thiation of amides is well known and described for example in *Bioorganic & Medicinal Chemistry*, **2013**, 21, 1324-1332. The compounds of formula Ia may have to be separated from regioisomers in case the regioselectivity of the thiation is not sufficient.

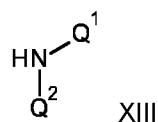
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A compound of formula Ia, or, where appropriate, a tautomer and/or salt thereof, can be obtained by reacting a compound of formula II



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in which R¹, R², R³, R⁴ and R⁸ are defined as in formula I, with an amine of formula XIII



In which, Q¹ and Q² are defined as in formula I in a solvent such as ethanol, tetrahydrofuran, or dioxane at a temperature that can preferentially range from room temperature to the boiling point of the reaction mixture.

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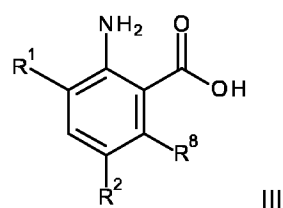
In the case of Q¹ and Q² are both hydrogen, XIII can be ammonia in either gaseous form, or a solution of ammonia in a solvent such as ethanol, tetrahydrofuran, or dioxane. Alternatively, any other form of ammonia, such as ammonium acetate or ammonium carbonate can replace compound XIII and the reaction is carried in a suitable solvent, such as ethyl acetate, tetrahydrofuran, or dioxane at a

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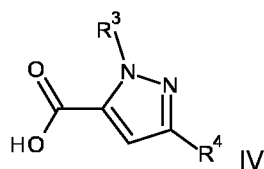
The compounds of formula II may be prepared by a person skilled in the art as described in WO2004/111030 or WO2004/067528.

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Compounds of formula II can be obtained by reaction of amino acids of formula III



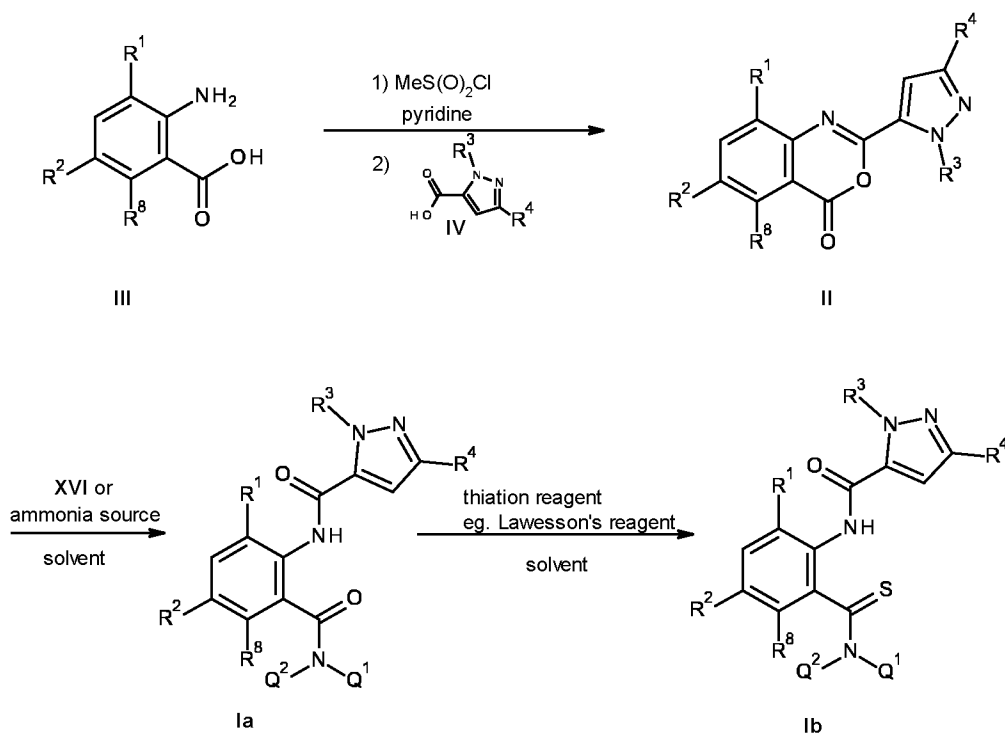
wherein R¹, R² and R³ are defined as in formula I, and pyrazole carboxylic acids of formula IV



wherein R³ and R⁴ are defined as in formula I, in the presence of a dehydrating reagent such as methanesulfonyl chloride, and a base like pyridine or a tertiary amine. This transformation is in many cases known in the literature or can be performed according to methods known to a person skilled in the art. Compounds of formula II can be isolated or used directly in the next step as a crude mixture.

The chemistry is described in more detail in Scheme 1.

25



Scheme 1

Many pyrazole carboxylic acids of formula IV can be purchased or are described in the literature and can be prepared by a person skilled in the art in a similar way as described for example in

5 WO2004/067528, WO2010/069502, WO2011/157664, WO2004/046129.

Alternatively, a compound of formula IV can be prepared from compounds of formula VI wherein R³ and R⁴ are defined as in formula I and R⁹ is a C₁-C₃alkyl group, under basic conditions that may include, for example lithium hydroxide or sodium hydroxide, in suitable solvents such as, tetrahydrofuram, methanol

10 or dioxane. Such processes have been described previously, for example, in WO2011/073101.

Compounds of formula VI (wherein R³ and R⁴ are as defined in formula I and R⁹ is a C₁-C₃alkyl group) can be prepared by reaction of compounds of formula XIV (wherein R⁴ is as defined in formula I and R⁹ is a C₁-C₃alkyl group) with compounds of formula XV (wherein R³ is as defined in formula I and Z₀ is a leaving group like, for example, chlorine, bromine, iodine, arylsulfonate, alkylsulfonate or trifluoromethanesulfonate) in presence of a base, like sodium carbonate or potassium carbonate, in a solvent, like, for example DMF preferably under inert atmosphere. The reaction temperature can preferentially range from room temperature to the boiling point of the reaction mixture. Such reactions are well known to those skilled in the art and have been reported, for example in WO2008034008.

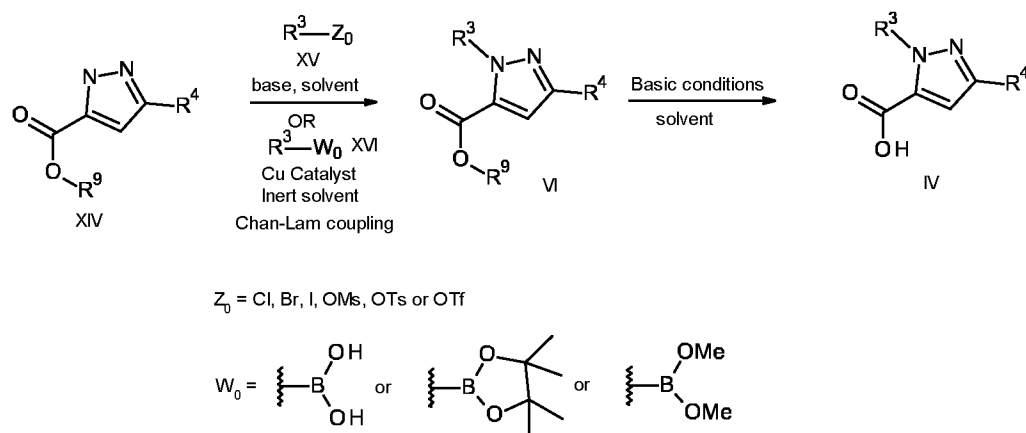
15 Alternatively, compounds of formula VI (wherein R³ and R⁴ are as defined in formula I and R⁹ is a C₁-C₃alkyl group) can also be prepared by a Chan-Lam reaction (Scheme 3), which involves for example, reacting compounds of formula XIV (wherein R⁴ is as defined in formula I and R⁹ is a C₁-C₃alkyl group) with compounds of formula XVI, wherein W₀ can be a boron-derived functional group, as for example B(OH)₂ or a pinacol boronic ester. The reaction can be catalyzed by a Copper catalyst, for example

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copper acetate, in presence of a ligand, like bipyridine and a base such as sodium carbonate in a solvent, like, for example dichloroethane preferably under air atmosphere. The reaction temperature can preferentially range from room temperature to the boiling point of the reaction mixture. Such Chan-Lam reactions are well known to those skilled in the art and have been reported, for example in Tetrahedron Letters (2010), 51(52), 6799-6801.

Many pyrazoles of formula XIV can be purchased or are described in the literature and can be prepared by a person skilled in the art in a similar way as described for example in CN109369615

A typical example of such a synthesis is shown in Scheme 2.



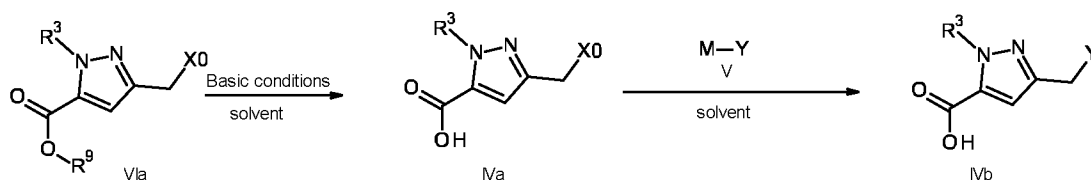
Scheme 2

Alternatively, compounds of formula IVb may be prepared by reaction between compounds of formula V, wherein Y is defined as above and M is an alkali metal such as lithium, sodium, potassium, and compounds of formula IVa, wherein R^3 is as defined in formula I and X_0 is chlorine, bromine or iodine, in suitable solvents that may include, for example, acetone or tetrahydrofuran, optionally in the presence of potassium iodide as catalyst.

Compounds of formula IVa, wherein R^3 is as defined in formula I and X_0 is chlorine, bromine or iodine, can be prepared from compounds of formula VIa, wherein R_3 has the meaning given for formula I, R^9 is a C_1 - C_3 alkyl group and X_0 is chlorine, bromine or iodine, under basic conditions that may include, for example lithium hydroxide or sodium hydroxide, in suitable solvents such as, tetrahydrofuran, methanol or dioxane. Such processes have been described previously, for example, in WO2011/073101.

Compounds of formula VIa are generally known or can be easily prepared by those skilled in the art by a similar way than described above for the synthesis of compounds VI.

A typical example of such a synthesis is shown in Scheme 3.



What has been said above for tautomers and/or salts of compounds of formula I applies analogously to starting materials mentioned hereinabove and hereinbelow with regard to the tautomers and/or salts thereof.

The reactions described hereinabove and hereinbelow are carried out in a manner known per se, for example in the absence or, normally, in the presence of a suitable solvent or diluent or of a mixture of these, the process being carried out, as required, with cooling, at room temperature or with heating, for example in a temperature range of from approximately -80°C to the boiling point of the reaction mixture, preferably from approximately -20°C to approximately $+150^{\circ}\text{C}$, and, if required, in a sealed vessel, under reduced, normal or elevated pressure, in an inert gas atmosphere and/or under anhydrous conditions. Especially advantageous reaction conditions can be seen from the examples.

Unless otherwise specified, the starting materials mentioned hereinabove and hereinbelow, which are used for the preparation of the compounds of formula I or, where appropriate, the tautomers thereof, in each case in free form or in salt form, are known or can be prepared by methods known per se, for example in accordance with the information given below.

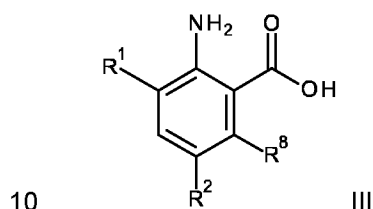
Depending on the procedure or the reaction conditions, the reactants can be reacted in the presence of a base. Examples of suitable bases are alkali metal or alkaline earth metal hydroxides, alkali metal or alkaline earth metal hydrides, alkali metal or alkaline earth metal amides, alkali metal or alkaline earth metal alkoxides, alkali metal or alkaline earth metal acetates, alkali metal or alkaline earth metal carbonates, alkali metal or alkaline earth metal dialkylamides or alkali metal or alkaline earth metal alkylsilylamides, alkylamines, alkylenediamines, free or N-alkylated saturated or unsaturated cycloalkylamines, basic heterocycles, ammonium hydroxides and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium acetate, sodium carbonate, potassium tert-butoxide, potassium hydroxide, potassium carbonate, potassium hydride, lithium diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, triethylamine, diisopropylethylamine, triethylenediamine, cyclohexylamine, N-cyclohexyl-N,N-dimethylamine, N,N-diethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, quinuclidine, N-methylmorpholine, benzyltrimethylammonium hydroxide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The reactants can be reacted with each other as such, i.e. without adding a solvent or diluent. In most cases, however, it is advantageous to add an inert solvent or diluent or a mixture of these. If the reaction is carried out in the presence of a base, bases which are employed in excess, such as triethylamine, pyridine, N-methylmorpholine or N,N-diethylaniline, may also act as solvents or diluents.

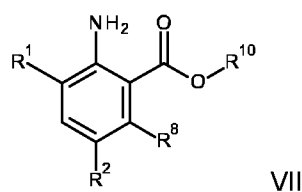
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Processes for making compounds of formula III, are generally known, or can be easily prepared by those skilled in the art. Many compounds of formula III can also be purchased.

Alternatively, a compound of formula III,

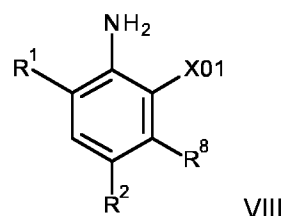


in which R¹, R² and R⁸ are as defined in formula I can be prepared from compound of formula VII,



15 wherein R¹, R² and R⁸ are as defined in formula I and R¹⁰ is a C₁-C₃alkyl group, under basic conditions that may include, for example lithium hydroxide or sodium hydroxide, in suitable solvents such as, tetrahydrofuran, methanol or dioxane. Such processes have been described previously, for example, in WO2015060373.

Compound of formula VII can be prepared from compound of formula VIII,



20 wherein R¹, R² and R⁸ are as defined in formula I and X01 is Cl, Br or I. For example, compound of formula VII is obtained via a carbonylation step under carbon monoxide atmosphere (up to 20 bars), in the presence of a palladium catalyst (for example Pd(OAc)₂, (1,1'-bis(diphenylphosphino)-ferrocene) or PdCl₂(dppf)), the relevant alcohol R₁₀OH, in suitable solvents that may include, for example, DMSO, and a tertiary amine as base such as triethylamine or diisopropylethylamine. Such processes have been
25 described previously, for example, in WO2012/067663.

Compound of formula VIII may be prepared by treatment of compounds of formula IX wherein R¹, R² and R⁸ are as defined in formula I, with a halogenation agent such as N-chlorosuccinimide, N-

bromosuccinimide, iodine in suitable solvent that may include, for example, acetic acid, ethanol or DMSO. Such kind of processes have been described previously, for example, in WO2017102275.

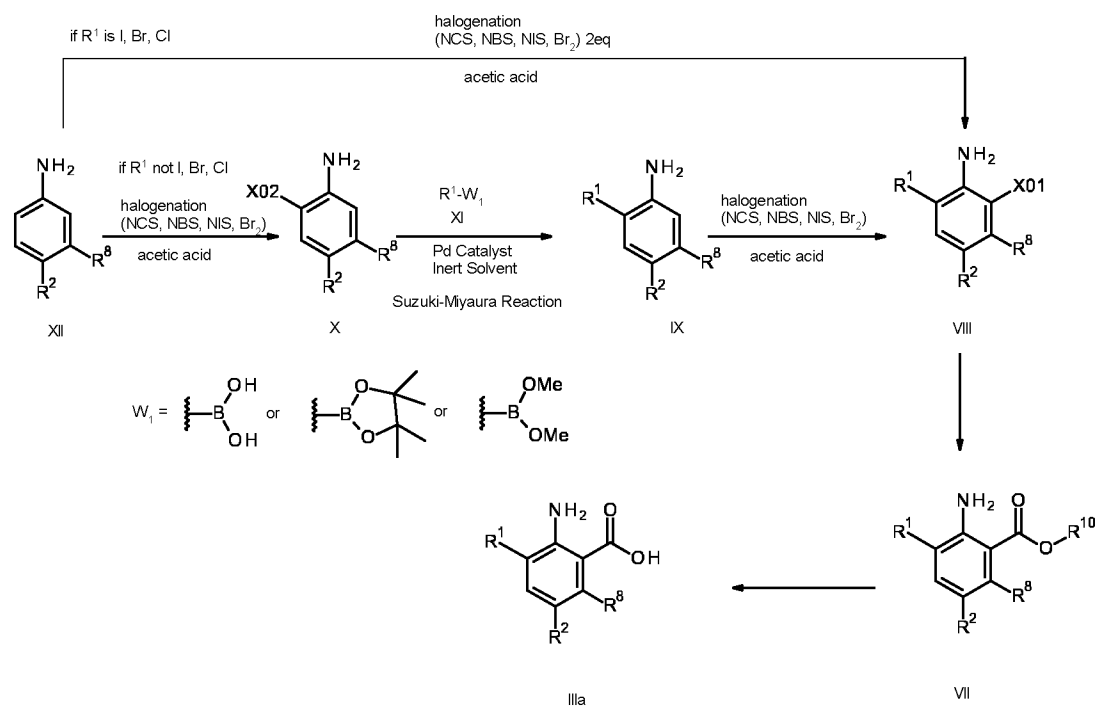
Compound of formula IX wherein R^1 , R^2 and R^8 are as defined in formula I, can be prepared a Suzuki reaction (Scheme 4), which involves for example, reacting compounds of formula X (R^1 is as defined in formula I but not an halogen, R^2 and R^8 are as defined in formula I and XO_2 is a leaving group like, for example, chlorine, bromine, iodine, arylsulfonate, alkylsulfonate or trifluoromethanesulfonate) with compounds of formula XI, wherein W_1 can be a boron-derived functional group, as for example $B(OH)_2$ or a pinacol boronic ester and R^1 is as defined in formula I but not an halogen atom. The reaction can be catalyzed by a palladium based catalyst, for example tetrakis(triphenylphosphine)-palladium or (1,1'-bis(diphenylphosphino)-ferrocene)dichloropalladium-dichloromethane (1:1 complex), in presence of a base, like sodium carbonate or cesium fluoride, in a solvent or a solvent mixture, like, for example a mixture of 1,2-dimethoxyethane and water, dioxane and water, or DMF and water preferably under inert atmosphere. The reaction temperature can preferentially range from room temperature to the boiling point of the reaction mixture. In the case of R^1 is a methylene group, trimethylboroxine can be used as reagent XI. Such Suzuki reactions are well known to those skilled in the art and have been reported, for example in J. Organomet. Chem. 576, 1999, 147–168, Science of Synthesis 2010, 45b, 547, Eur. J. Org. Chem. 2012, (31), 6248 and Synthesis 2017, 49, 4372.

Compound of formula X may be prepared by treatment of compounds of formula XII wherein R^2 and R^8 are as defined in formula I, with a halogenation agent such as N-chlorosuccinimide, N-bromosuccinimide, iodine in suitable solvent that may include, for example, acetic acid, ethanol or DMSO. Such kind of processes have been described previously, for example, in WO2017/102275.

Processes for making compounds of formula XII, are generally known, or can be easily prepared by those skilled in the art. Many compounds of formula XII can also be purchased.

Alternatively, in the case of R^1 is Chlorine, bromine or iodine, compound of formula VIII can be prepared directly from compound of formula XII by a bis-halogenation step involving 2 equivalents of halogenation agent such as N-chlorosuccinimide, N-bromosuccinimide, iodine in suitable solvent that may include, for example, acetic acid, ethanol or DMSO.

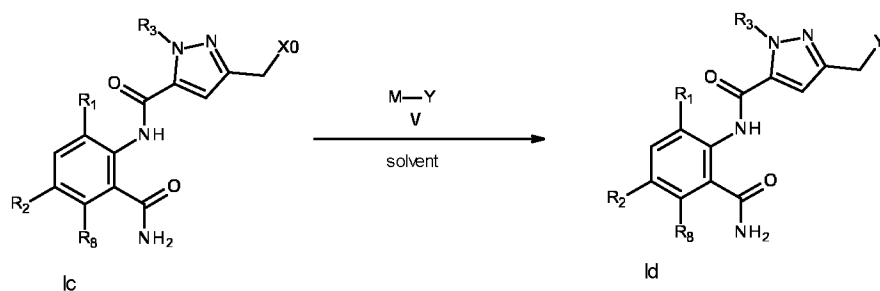
A typical example of such a synthesis is shown in Scheme 4.



Scheme 4

A compound of formula I can be converted in a manner known per se into another compound of formula I respectively by replacing one or more substituents of the starting compound of formula I in the customary manner by (an)other substituent(s) according to the invention.

For example, compounds of formula Ic in which R^1 , R^2 , R^3 , and R^8 are as defined in formula I and X0 is iodine, bromine or chlorine, can be converted into compounds of formula Id respectively, in which R^1 , R^2 , R^3 , and R^8 are as defined in formula I and Y is as defined in formula I. A typical example of such a synthesis is shown in Scheme 5.



Scheme 5

For example, compounds of formula Id may be prepared by reaction between compounds of formula V, wherein Y is defined as above and M is an alkali metal such as lithium, sodium, potassium, and compounds of formula Ic wherein R^1 , R^2 , R^3 , and R^8 are as defined in formula I and X0 is iodine, bromine or chlorine, in suitable solvents that may include, for example, acetone or tetrahydrofuran, optionally in the presence of potassium iodide as catalyst.

Processes for making compounds of formula V, are generally known or can be easily prepared by those skilled in the art.

Compounds of formula Ic can be made by a similar method than described in Scheme 1 with R⁴ is specifically -CH₂Cl, -CH₂Br or -CH₂I in this case.

Salts of compounds of formula I can be prepared in a manner known *per se*. Thus, for example, acid addition salts of compounds of formula I are obtained by treatment with a suitable acid or a suitable ion exchanger reagent and salts with bases are obtained by treatment with a suitable base or with a suitable ion exchanger reagent.

Salts of compounds of formula I can be converted in the customary manner into the free compounds I, acid addition salts, for example, by treatment with a suitable basic compound or with a suitable ion exchanger reagent and salts with bases, for example, by treatment with a suitable acid or with a suitable ion exchanger reagent.

Salts of compounds of formula I can be converted in a manner known *per se* into other salts of compounds of formula I, acid addition salts, for example, into other acid addition salts, for example by treatment of a salt of inorganic acid such as hydrochloride with a suitable metal salt such as a sodium, barium or silver salt, of an acid, for example with silver acetate, in a suitable solvent in which an inorganic salt which forms, for example silver chloride, is insoluble and thus precipitates from the reaction mixture.

Depending on the procedure or the reaction conditions, the compounds of formula I, which have salt-forming properties can be obtained in free form or in the form of salts.

The compounds of formula I and, where appropriate, the tautomers thereof, in each case in free form or in salt form, can be present in the form of one of the isomers which are possible or as a mixture of these, for example in the form of pure isomers, such as antipodes and/or diastereomers, or as isomer mixtures, such as enantiomer mixtures, for example racemates, diastereomer mixtures or racemate mixtures, depending on the number, absolute and relative configuration of asymmetric carbon atoms which occur in the molecule and/or depending on the configuration of non-aromatic double bonds which occur in the molecule; the invention relates to the pure isomers and also to all isomer mixtures which are possible and is to be understood in each case in this sense hereinabove and hereinbelow, even when stereochemical details are not mentioned specifically in each case.

Diastereomer mixtures or racemate mixtures of compounds of formula I, in free form or in salt form, which can be obtained depending on which starting materials and procedures have been chosen can be separated in a known manner into the pure diastereomers or racemates on the basis of the

physicochemical differences of the components, for example by fractional crystallization, distillation and/or chromatography.

Enantiomer mixtures, such as racemates, which can be obtained in a similar manner can be resolved into the optical antipodes by known methods, for example by recrystallization from an optically active solvent, by chromatography on chiral adsorbents, for example high-performance liquid chromatography (HPLC) on acetyl cellulose, with the aid of suitable microorganisms, by cleavage with specific, immobilized enzymes, via the formation of inclusion compounds, for example using chiral crown ethers, where only one enantiomer is complexed, or by conversion into diastereomeric salts, for example by reacting a basic end-product racemate with an optically active acid, such as a carboxylic acid, for example camphor, tartaric or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separating the diastereomer mixture which can be obtained in this manner, for example by fractional crystallization based on their differing solubilities, to give the diastereomers, from which the desired enantiomer can be set free by the action of suitable agents, for example basic agents.

Pure diastereomers or enantiomers can be obtained according to the invention not only by separating suitable isomer mixtures, but also by generally known methods of diastereoselective or enantioselective synthesis, for example by carrying out the process according to the invention with starting materials of a suitable stereochemistry.

N-oxides can be prepared by reacting a compound of the formula I with a suitable oxidizing agent, for example the H_2O_2 /urea adduct in the presence of an acid anhydride, e.g. trifluoroacetic anhydride. Such oxidations are known from the literature, for example from *J. Med. Chem.*, 32 (12), 2561-73, 1989 or WO 2000/15615.

It is advantageous to isolate or synthesize in each case the biologically more effective isomer, for example enantiomer or diastereomer, or isomer mixture, for example enantiomer mixture or diastereomer mixture, if the individual components have a different biological activity.

The compounds of formula I and, where appropriate, the tautomers thereof, in each case in free form or in salt form, can, if appropriate, also be obtained in the form of hydrates and/or include other solvents, for example those which may have been used for the crystallization of compounds which are present in solid form.

The compounds of formula I represented in Tables A-1 to A-10 can be prepared according to the methods described above. The examples which follow are intended to illustrate the invention and show preferred compounds of formula I, in the form of a compound of formula IAA.

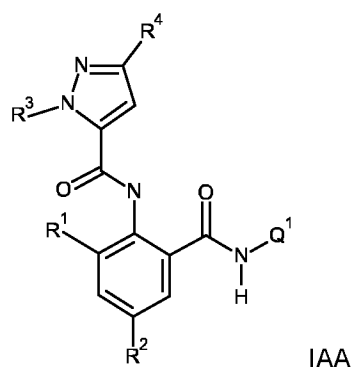


Table A-1 provides 72 compounds A-1.001 to A-1.072 of formula IAA wherein R^4 is CHF_2 and R^1 , R^2 , R^3 , Q^1 are as defined in table X.

5

Table A-2 provides 72 compounds A-2.001 to A-2.072 of formula IAA wherein R^4 is Br and R^1 , R^2 , R^3 , Q^1 are as defined in table X.

Table A-3 provides 72 compounds A-3.001 to A-3.072 of formula IAA wherein R^4 is Cl and R^1 , R^2 , R^3 , Q^1 are as defined in table X.

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Table A-4 provides 72 compounds A-4.001 to A-4.072 of formula IAA wherein R^4 is CF_3 and R^1 , R^2 , R^3 , Q^1 are as defined in table X.

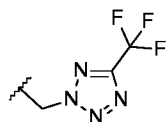
Table A-5 provides 72 compounds A-5.001 to A-5.072 of formula IAA wherein R^4 is OCH_2CF_3 and R^1 , R^2 , R^3 , Q^1 are as defined in table X.

15

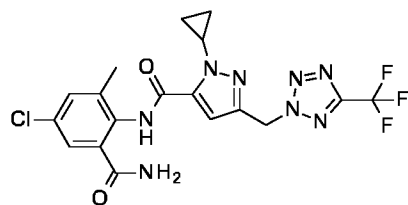
Table A-6 provides 72 compounds A-6.001 to A-6.072 of formula IAA wherein R^4 is OCH_2CHF_2 and R^1 , R^2 , R^3 , Q^1 are as defined in table X.

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Table A-7 provides 72 compounds A-7.001 to A-7.072 of formula IAA wherein R^4 is

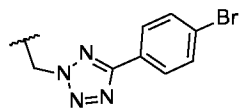


wherein the staggered line indicates the point of attachment of R^4 to the rest of the molecule, and R^1 , R^2 , R^3 , Q^1 are as defined in table X. For example, compound A-7.005 has the following structure:



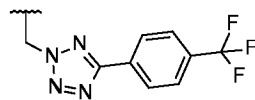
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Table A-8 provides 72 compounds A-8.001 to A-8.072 of formula IAA wherein R⁴ is



and R¹, R², R³, Q¹ are as defined in table X.

5 Table A-9 provides 72 compounds A-9.001 to A-9.072 of formula IAA wherein R⁴ is



and R¹, R², R³, Q¹ are as defined in table X.

Table A-10 provides 72 compounds A-10.001 to A-10.072 of formula IAA wherein R⁴ is OCH₃ and R¹, R², R³, Q¹ are as defined in table X.

10

Table X: Substituent definitions of R¹, R², R³ and Q¹:

Index	R ²	R ³	Q ¹	R ¹
1	Cl	CH ₂ CHF ₂	H	Me
2	Cl	CH ₂ CHF ₂	Me	Me
3	Cl	CH ₂ CF ₃	H	Me
4	Cl	CH ₂ CF ₃	Me	Me
5	Cl	Cyclopropyl	H	Me
6	Cl	Cyclopropyl	Me	Me
7	Br	CH ₂ CHF ₂	H	Me
8	Br	CH ₂ CHF ₂	Me	Me
9	Br	CH ₂ CF ₃	H	Me
10	Br	CH ₂ CF ₃	Me	Me
11	Br	Cyclopropyl	H	Me
12	Br	Cyclopropyl	Me	Me
13	I	CH ₂ CHF ₂	H	Me
14	I	CH ₂ CHF ₂	Me	Me
15	I	CH ₂ CF ₃	H	Me
16	I	CH ₂ CF ₃	Me	Me
17	I	Cyclopropyl	H	Me
18	I	Cyclopropyl	Me	Me
19	CN	CH ₂ CHF ₂	H	Me
20	CN	CH ₂ CHF ₂	Me	Me
21	CN	CH ₂ CF ₃	H	Me
22	CN	CH ₂ CF ₃	Me	Me
23	CN	Cyclopropyl	H	Me
24	CN	Cyclopropyl	Me	Me
25	Cl	CH ₂ CHF ₂	H	Br
26	Cl	CH ₂ CHF ₂	Me	Br
27	Cl	CH ₂ CF ₃	H	Br
28	Cl	CH ₂ CF ₃	Me	Br

29	Cl	Cyclopropyl	H	Br
30	Cl	Cyclopropyl	Me	Br
31	Br	CH ₂ CHF ₂	H	Br
32	Br	CH ₂ CHF ₂	Me	Br
33	Br	CH ₂ CF ₃	H	Br
34	Br	CH ₂ CF ₃	Me	Br
35	Br	Cyclopropyl	H	Br
36	Br	Cyclopropyl	Me	Br
37	I	CH ₂ CHF ₂	H	Br
38	I	CH ₂ CHF ₂	Me	Br
39	I	CH ₂ CF ₃	H	Br
40	I	CH ₂ CF ₃	Me	Br
41	I	Cyclopropyl	H	Br
42	I	Cyclopropyl	Me	Br
43	CN	CH ₂ CHF ₂	H	Br
44	CN	CH ₂ CHF ₂	Me	Br
45	CN	CH ₂ CF ₃	H	Br
46	CN	CH ₂ CF ₃	Me	Br
47	CN	Cyclopropyl	H	Br
48	CN	Cyclopropyl	Me	Br
49	Cl	CH ₂ CHF ₂	H	Cl
50	Cl	CH ₂ CHF ₂	Me	Cl
51	Cl	CH ₂ CF ₃	H	Cl
52	Cl	CH ₂ CF ₃	Me	Cl
53	Cl	Cyclopropyl	H	Cl
54	Cl	Cyclopropyl	Me	Cl
55	Br	CH ₂ CHF ₂	H	Cl
56	Br	CH ₂ CHF ₂	Me	Cl
57	Br	CH ₂ CF ₃	H	Cl
58	Br	CH ₂ CF ₃	Me	Cl
59	Br	Cyclopropyl	H	Cl
60	Br	Cyclopropyl	Me	Cl
61	I	CH ₂ CHF ₂	H	Cl
62	I	CH ₂ CHF ₂	Me	Cl
63	I	CH ₂ CF ₃	H	Cl
64	I	CH ₂ CF ₃	Me	Cl
65	I	Cyclopropyl	H	Cl
66	I	Cyclopropyl	Me	Cl
67	CN	CH ₂ CHF ₂	H	Cl
68	CN	CH ₂ CHF ₂	Me	Cl
69	CN	CH ₂ CF ₃	H	Cl
70	CN	CH ₂ CF ₃	Me	Cl
71	CN	Cyclopropyl	H	Cl
72	CN	Cyclopropyl	Me	Cl

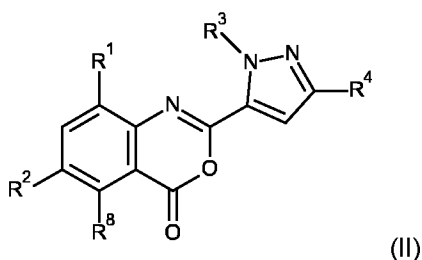
Also made available are certain intermediate compounds, some of which are novel. For example,

- a compound of formula II, where R¹, R², R³, R⁴ and R⁸ are as defined in Tables A1 to A10; and.

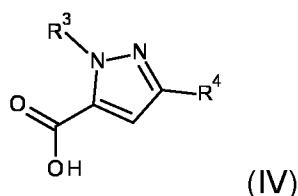
- a compound of formula IV, where R^3 , and R^4 are as defined in Tables A1 to A10;
- a compound of formula VI, where R^3 , and R^4 are as defined in Tables A1 to A10, and R^9 is methyl.

5 Accordingly, the present invention further makes available

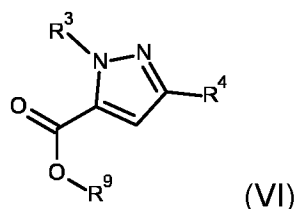
- a compound of formula II, where R^1 , R^2 , R^3 , R^4 and R^8 are as defined in the first aspect; and.



- a compound of formula IV, where R^3 , and R^4 are as defined in the first aspect;



- 10
- a compound of formula VI, where R^3 , and R^4 are as defined in the first aspect, and R^9 is C₁-C₃alkyl group, such as methyl.



15 The compounds of formula I according to the invention are preventively and/or curatively valuable active ingredients in the field of pest control, even at low rates of application, which have a very favorable biocidal spectrum and are well tolerated by warm-blooded species, fish and plants. The active ingredients according to the invention act against all or individual developmental stages of normally sensitive, but also resistant, animal pests, such as insects or representatives of the order Acarina. The insecticidal or acaricidal activity of the active ingredients according to the invention can manifest itself

20 directly, i. e. in destruction of the pests, which takes place either immediately or only after some time has elapsed, for example during ecdysis, or indirectly, for example in a reduced oviposition and/or hatching rate.

Examples of the above mentioned animal pests are:

25 from the order *Acarina*, for example,

- Acalitus spp, Aculus spp, Acaricalus spp, Aceria spp, Acarus siro, Amblyomma spp., Argas spp., Boophilus spp., Brevipalpus spp., Bryobia spp, Calipitimerus spp., Chorioptes spp., Dermanyssus gallinae, Dermatophagoides spp, Eotetranychus spp, Eriophyes spp., Hemitarsonemus spp, Hyalomma spp., Ixodes spp., Olygonychus spp, Ornithodoros spp., Polyphagotarsonus latus, Panonychus spp., Phyllocoptruta oleivora, Phytoneumus spp, Polyphagotarsonemus spp, Psoroptes spp., Rhipicephalus spp., Rhizoglyphus spp., Sarcoptes spp., Steneotarsonemus spp, Tarsonemus spp. and Tetranychus spp.;
- from the order *Anoplura*, for example,
Haematopinus spp., Linognathus spp., Pediculus spp., Pemphigus spp. and Phylloxera spp.;
- from the order *Coleoptera*, for example,
Agriotes spp., Amphimallon majale, Anomala orientalis, Anthonomus spp., Aphodius spp, Astylus atromaculatus, Ataenius spp, Atomaria linearis, Chaetocnema tibialis, Cerotoma spp, Conoderus spp, Cosmopolites spp., Cotinis nitida, Curculio spp., Cyclocephala spp, Dermestes spp., Diabrotica spp., Diloboderus abderus, Epilachna spp., Eremnus spp., Heteronychus arator, Hypothenemus hampei, Lagria vilosa, Leptinotarsa decemlineata, Lissorhoptrus spp., Liogenys spp, Maecolaspis spp, Maladera castanea, Megascelis spp, Meligethes aeneus, Melolontha spp., Myochrous armatus, Orycaephilus spp., Otiorhynchus spp., Phyllophaga spp, Phlyctinus spp., Popillia spp., Psylliodes spp., Rhyssomatus aubtilis, Rhizopertha spp., Scarabeidae, Sitophilus spp., Sitotroga spp., Somaticus spp, Sphenophorus spp, Sternechus subsignatus, Tenebrio spp., Tribolium spp. and Trogoderma spp.;
- from the order *Diptera*, for example,
Aedes spp., Anopheles spp, Antherigona soccata, Bactrocea oleae, Bibio hortulanus, Bradysia spp, Calliphora erythrocephala, Ceratitis spp., Chrysomyia spp., Culex spp., Cuterebra spp., Dacus spp., Delia spp, Drosophila melanogaster, Fannia spp., Gastrophilus spp., Geomyza tripunctata, Glossina spp., Hypoderma spp., Hyppobosca spp., Liriomyza spp., Lucilia spp., Melanagromyza spp., Musca spp., Oestrus spp., Orseolia spp., Oscinella frit, Pegomyia hyoscyami, Phorbia spp., Rhagoletis spp, Rivelia quadrifasciata, Scatella spp, Sciara spp., Stomoxys spp., Tabanus spp., Tannia spp. and Tipula spp.;
- from the order *Hemiptera*, for example,
Acanthocoris scabrator, Acrosternum spp, Adelphocoris lineolatus, Aleurodes spp., Amblypelta nitida, Bathycoelia thalassina, Blissus spp, Cimex spp., Clavigralla tomentosicollis, Creontiades spp, Distantiella theobroma, Dichelops furcatus, Dysdercus spp., Edessa spp, Euschistus spp., Eurydema pulchrum, Eurygaster spp., Halyomorpha halys, Horcias nobilellus, Leptocoris spp., Lygus spp, Margarodes spp, Murgantia histrionic, Neomegalotomus spp, Nesidiocoris tenuis, Nezara spp., Nysius simulans, Oebalus insularis, Piesma spp., Piezodorus spp, Rhodnius spp., Sahlbergella singularis, Scaptocoris castanea, Scotinophara spp. , Thyanta spp , Triatoma spp., Vatica illudens;
- Acyrtosium pisum, Adalges spp, Agalliana ensigera, Agonoscena targionii, Aleurodicus spp, Aleurocanthus spp, Aleurolobus barodensis, Aleurothrix floccosus, Aleyrodes brassicae, Amarasca biguttula, Amritodus atkinsoni, Aonidiella spp., Aphididae, Aphis spp., Aspidiotus spp., Aulacorthum solani, Bactericera cockerelli, Bemisia spp, Brachycaudus spp, Brevicoryne brassicae, Cacopsylla

- spp, *Cavariella aegopodii* Scop., *Ceroplaster* spp., *Chrysomphalus aonidium*, *Chrysomphalus dictyospermi*, *Cicadella* spp, *Cofana spectra*, *Cryptomyzus* spp, *Cicadulina* spp, *Coccus hesperidum*, *Dalbulus maidis*, *Dialeurodes* spp, *Diaphorina citri*, *Diuraphis noxia*, *Dysaphis* spp, *Empoasca* spp., *Eriosoma larigerum*, *Erythroneura* spp., *Gascardia* spp., *Glycaspis brimblecombei*, *Hyadaphis*
- 5 *pseudobrassicae*, *Hyalopterus* spp, *Hyperomyzus pallidus*, *Idioscopus clypealis*, *Jacobiasca lybica*, *Laodelphax* spp., *Lecanium corni*, *Lepidosaphes* spp., *Lopaphis erysimi*, *Lyogenys maidis*, *Macrosiphum* spp., *Mahanarva* spp, *Metcalfa pruinosa*, *Metopolophium dirhodum*, *Myndus crudus*, *Myzus* spp., *Neotoxoptera* sp, *Nephotettix* spp., *Nilaparvata* spp., *Nippolachnus piri* Mats, *Odonaspis ruthae*, *Oregma lanigera* Zehnter, *Parabemisia myricae*, *Paratrioza cockerelli*, *Parlatoria* spp.,
- 10 *Pemphigus* spp., *Peregrinus maidis*, *Perkinsiella* spp, *Phorodon humuli*, *Phylloxera* spp, *Planococcus* spp., *Pseudaulacaspis* spp., *Pseudococcus* spp., *Pseudatomoscelis seriatus*, *Psylla* spp., *Pulvinaria aethiopica*, *Quadraspidotus* spp., *Quesada gigas*, *Recilia dorsalis*, *Rhopalosiphum* spp., *Saissetia* spp., *Scaphoideus* spp., *Schizaphis* spp., *Sitobion* spp., *Sogatella furcifera*, *Spissistilus festinus*, *Tarophagus Proserpina*, *Toxoptera* spp, *Trialeurodes* spp, *Tridiscus sporoboli*, *Trionymus* spp, *Trioza*
- 15 *erytraeae* , *Unaspis citri*, *Zygina flammigera*, *Zyginidia scutellaris* , ;
from the order *Hymenoptera*, for example,
Acromyrmex, *Arge* spp, *Atta* spp., *Cephus* spp., *Diprion* spp., *Diprionidae*, *Gilpinia polytoma*, *Hoplocampa* spp., *Lasius* spp., *Monomorium pharaonis*, *Neodiprion* spp., *Pogonomymex* spp, *Slenopsis invicta*, *Solenopsis* spp. and *Vespa* spp.;
- 20 from the order *Isoptera*, for example,
Coptotermes spp, *Cornitermes cumulans*, *Incisitermes* spp, *Macrotermes* spp, *Mastotermes* spp, *Microtermes* spp, *Reticulitermes* spp.; *Solenopsis geminate*
from the order *Lepidoptera*, for example,
Acleris spp., *Adoxophyes* spp., *Aegeria* spp., *Agrotis* spp., *Alabama argillaceae*, *Amylois* spp.,
- 25 *Anticarsia gemmatilis*, *Archips* spp., *Argyresthia* spp, *Argyrotaenia* spp., *Autographa* spp., *Bucculatrix thurberiella*, *Busseola fusca*, *Cadra cautella*, *Carposina nipponensis*, *Chilo* spp., *Choristoneura* spp., *Chrysoteuchia topiaria*, *Clysia ambiguella*, *Cnaphalocrocis* spp., *Cnephasia* spp., *Cochylis* spp., *Coleophora* spp., *Colias lesbia*, *Cosmophila flava*, *Crambus* spp, *Crocidolomia binotalis*, *Cryptophlebia leucotreta*, *Cydalima perspectalis*, *Cydia* spp., *Diaphania perspectalis*, *Diatraea* spp., *Diparopsis*
- 30 *castanea*, *Earias* spp., *Elasmopalpus lignosellus*, *Eldana saccharina*, *Ephestia* spp., *Epinotia* spp, *Estigmene acrea*, *Etiella zinckinella*, *Eucosma* spp., *Eupoecilia ambiguella*, *Euproctis* spp., *Euxoa* spp., *Feltia jaculiferia*, *Grapholita* spp., *Hedya nubiferana*, *Heliothis* spp., *Hellula undalis*, *Herpetogramma* spp, *Hyphantria cunea*, *Keiferia lycopersicella*, *Lasmopalpus lignosellus*, *Leucoptera scitella*, *Lithocollethis* spp., *Lobesia botrana*, *Loxostege bifidalis*, *Lymantria* spp., *Lyonetia* spp.,
- 35 *Malacosoma* spp., *Mamestra brassicae*, *Manduca sexta*, *Mythimna* spp, *Noctua* spp, *Operophtera* spp., *Orniodes indica*, *Ostrinia nubilalis*, *Pammene* spp., *Pandemis* spp., *Panolis flammea*, *Papaipema nebris*, *Pectinophora gossypiella*, *Perileucoptera coffeella*, *Pseudaletia unipuncta*, *Phthorimaea operculella*, *Pieris rapae*, *Pieris* spp., *Plutella xylostella*, *Prays* spp., *Pseudoplusia* spp, *Rachiplusia* nu, *Richia albicosta*, *Scirpophaga* spp., *Sesamia* spp., *Sparganothis* spp., *Spodoptera* spp., *Sylepta*

derogate, *Synanthedon* spp., *Thaumetopoea* spp., *Tortrix* spp., *Trichoplusia* ni, *Tuta absoluta*, and *Yponomeuta* spp.;

from the order *Mallophaga*, for example,

Damalinea spp. and *Trichodectes* spp.;

5 from the order *Orthoptera*, for example,

Blatta spp., *Blattella* spp., *Grylotalpa* spp., *Leucophaea maderae*, *Locusta* spp., *Neocurtilla hexadactyla*, *Periplaneta* spp., *Scapteriscus* spp, and *Schistocerca* spp.;

from the order *Psocoptera*, for example,

Liposcelis spp.;

10 from the order *Siphonaptera*, for example,

Ceratophyllus spp., *Ctenocephalides* spp. and *Xenopsylla cheopis*;

from the order *Thysanoptera*, for example,

Calliothrips phaseoli, *Frankliniella* spp., *Heliothrips* spp, *Hercinothrips* spp., *Parthenothrips* spp, *Scirtothrips aurantii*, *Sericothrips variabilis*, *Taeniothrips* spp., *Thrips* spp;

15 from the order *Thysanura*, for example, *Lepisma saccharina*.

In a further aspect, the invention may also relate to a method of controlling damage to plant and parts thereof by plant parasitic nematodes (Endoparasitic-, Semiendoparasitic- and Ectoparasitic

nematodes), especially plant parasitic nematodes such as root knot nematodes, *Meloidogyne hapla*,

20 *Meloidogyne incognita*, *Meloidogyne javanica*, *Meloidogyne arenaria* and other *Meloidogyne* species;

cyst-forming nematodes, *Globodera rostochiensis* and other *Globodera* species; *Heterodera avenae*, *Heterodera glycines*, *Heterodera schachtii*, *Heterodera trifolii*, and other *Heterodera* species; Seed gall

nematodes, *Anguina* species; Stem and foliar nematodes, *Aphelenchoides* species; Sting nematodes, *Belonolaimus longicaudatus* and other *Belonolaimus* species; Pine nematodes, *Bursaphelenchus*

25 *xylophilus* and other *Bursaphelenchus* species; Ring nematodes, *Criconema* species, *Criconemella*

species, *Criconemoides* species, *Mesocriconema* species; Stem and bulb nematodes, *Ditylenchus*

destructor, *Ditylenchus dipsaci* and other *Ditylenchus* species; Awl nematodes, *Dolichodorus* species;

Spiral nematodes, *Helicotylenchus multicinctus* and other *Helicotylenchus* species; Sheath and

sheathoid nematodes, *Hemicyclophora* species and *Hemicriconemoides* species; *Hirshmanniella*

30 species; Lance nematodes, *Hoploaimus* species; false rootknot nematodes, *Nacobbus* species;

Needle nematodes, *Longidorus elongatus* and other *Longidorus* species; Pin nematodes,

Pratylenchus species; Lesion nematodes, *Pratylenchus neglectus*, *Pratylenchus penetrans*,

Pratylenchus curvatus, *Pratylenchus goodeyi* and other *Pratylenchus* species; Burrowing nematodes,

Radopholus similis and other *Radopholus* species; Reniform nematodes, *Rotylenchus robustus*,

35 *Rotylenchus reniformis* and other *Rotylenchus* species; *Scutellonema* species; Stubby root

nematodes, *Trichodorus primitivus* and other *Trichodorus* species, *Paratrachodorus* species; Stunt

nematodes, *Tylenchorhynchus claytoni*, *Tylenchorhynchus dubius* and other *Tylenchorhynchus*

species; Citrus nematodes, *Tylenchulus* species; Dagger nematodes, *Xiphinema* species; and other

plant parasitic nematode species, such as *Subanguina* spp., *Hypsoperine* spp., *Macroposthonia* spp., *Melinius* spp., *Punctodera* spp., and *Quinisulcius* spp..

The compounds of the invention may also have activity against the molluscs. Examples of which include, for example, Ampullariidae; Arion (*A. ater*, *A. circumscriptus*, *A. hortensis*, *A. rufus*); Bradybaenidae (*Bradybaena fruticum*); Cepaea (*C. hortensis*, *C. Nemoralis*); ochlodina; Deroceras (*D. agrestis*, *D. empiricorum*, *D. laeve*, *D. reticulatum*); Discus (*D. rotundatus*); Euomphalia; Galba (*G. trunculata*); Helicelia (*H. itala*, *H. obvia*); Helicidae *Helicigona arbustorum*); Helicodiscus; Helix (*H. aperta*); Limax (*L. cinereoniger*, *L. flavus*, *L. marginatus*, *L. maximus*, *L. tenellus*); Lymnaea; Milax (*M. gagates*, *M. marginatus*, *M. sowerbyi*); Opeas; Pomacea (*P. canaticulata*); Vallonia and Zanioides.

The active ingredients according to the invention can be used for controlling, i. e. containing or destroying, pests of the abovementioned type which occur in particular on plants, especially on useful plants and ornamentals in agriculture, in horticulture and in forests, or on organs, such as fruits, flowers, foliage, stalks, tubers or roots, of such plants, and in some cases even plant organs which are formed at a later point in time remain protected against these pests.

Suitable target plant or crops are, in particular, cereals, such as wheat, barley, rye, oats, rice, maize or sorghum; beet, such as sugar or fodder beet; fruit, for example pomaceous fruit, stone fruit or soft fruit, such as apples, pears, plums, peaches, almonds, cherries or berries, for example strawberries, raspberries or blackberries; leguminous crops, such as beans, lentils, peas or soya; oil crops, such as oilseed rape, mustard, poppies, olives, sunflowers, coconut, castor, cocoa or ground nuts; cucurbits, such as pumpkins, cucumbers or melons; fibre plants, such as cotton, flax, hemp or jute; citrus fruit, such as oranges, lemons, grapefruit or tangerines; vegetables, such as spinach, lettuce, asparagus, cabbages, carrots, onions, tomatoes, potatoes or bell peppers; Lauraceae, such as avocado, Cinnamomum or camphor; and also tobacco, nuts, coffee, eggplants, sugarcane, tea, pepper, grapevines, hops, the plantain family and latex plants.

The compositions and/or methods of the present invention may be also used on any ornamental and/or vegetable crops, including flowers, shrubs, broad-leaved trees and evergreens.

For example the invention may be used on any of the following ornamental species: *Ageratum* spp., *Alonsoa* spp., *Anemone* spp., *Anisodonteia capensis*, *Anthemis* spp., *Antirrhinum* spp., *Aster* spp., *Begonia* spp. (e.g. *B. elatior*, *B. semperflorens*, *B. tuberosa*), *Bougainvillea* spp., *Brachycome* spp., *Brassica* spp. (ornamental), *Calceolaria* spp., *Capsicum annuum*, *Catharanthus roseus*, *Canna* spp., *Centaurea* spp., *Chrysanthemum* spp., *Cineraria* spp. (*C. maritime*), *Coreopsis* spp., *Crassula coccinea*, *Cuphea ignea*, *Dahlia* spp., *Delphinium* spp., *Dicentra spectabilis*, *Dorotheantus* spp., *Eustoma grandiflorum*, *Forsythia* spp., *Fuchsia* spp., *Geranium gnaphalium*, *Gerbera* spp., *Gomphrena globosa*, *Heliotropium* spp., *Helianthus* spp., *Hibiscus* spp., *Hortensia* spp., *Hydrangea*

spp., *Hypoestes phyllostachya*, *Impatiens* spp. (*I. Walleriana*), *Iresines* spp., *Kalanchoe* spp., *Lantana camara*, *Lavatera trimestris*, *Leonotis leonurus*, *Lilium* spp., *Mesembryanthemum* spp., *Mimulus* spp., *Monarda* spp., *Nemesia* spp., *Tagetes* spp., *Dianthus* spp. (carnation), *Canna* spp., *Oxalis* spp., *Bellis* spp., *Pelargonium* spp. (*P. peltatum*, *P. Zonale*), *Viola* spp. (pansy), *Petunia* spp., *Phlox* spp.,
 5 *Plecthranthus* spp., *Poinsettia* spp., *Parthenocissus* spp. (*P. quinquefolia*, *P. tricuspidata*), *Primula* spp., *Ranunculus* spp., *Rhododendron* spp., *Rosa* spp. (rose), *Rudbeckia* spp., *Saintpaulia* spp., *Salvia* spp., *Scaevola aemola*, *Schizanthus wisetonensis*, *Sedum* spp., *Solanum* spp., *Surfinia* spp., *Tagetes* spp., *Nicotinia* spp., *Verbena* spp., *Zinnia* spp. and other bedding plants.

10 For example the invention may be used on any of the following vegetable species: *Allium* spp. (*A. sativum*, *A. cepa*, *A. oschaninii*, *A. Porrum*, *A. ascalonicum*, *A. fistulosum*), *Anthriscus cerefolium*, *Apium graveolus*, *Asparagus officinalis*, *Beta vulgaris*, *Brassica* spp. (*B. Oleracea*, *B. Pekinensis*, *B. rapa*), *Capsicum annuum*, *Cicer arietinum*, *Cichorium endivia*, *Cichorium* spp. (*C. intybus*, *C. endivia*), *Citrillus lanatus*, *Cucumis* spp. (*C. sativus*, *C. melo*), *Cucurbita* spp. (*C. pepo*, *C. maxima*), *Cyanara*
 15 spp. (*C. scolymus*, *C. cardunculus*), *Daucus carota*, *Foeniculum vulgare*, *Hypericum* spp., *Lactuca sativa*, *Lycopersicon* spp. (*L. esculentum*, *L. lycopersicum*), *Mentha* spp., *Ocimum basilicum*, *Petroselinum crispum*, *Phaseolus* spp. (*P. vulgaris*, *P. coccineus*), *Pisum sativum*, *Raphanus sativus*, *Rheum rhaponticum*, *Rosemarinus* spp., *Salvia* spp., *Scorzonera hispanica*, *Solanum melongena*, *Spinacea oleracea*, *Valerianella* spp. (*V. locusta*, *V. eriocarpa*) and *Vicia faba*.

20 Preferred ornamental species include African violet, *Begonia*, *Dahlia*, *Gerbera*, *Hydrangea*, *Verbena*, *Rosa*, *Kalanchoe*, *Poinsettia*, *Aster*, *Centaurea*, *Coreopsis*, *Delphinium*, *Monarda*, *Phlox*, *Rudbeckia*, *Sedum*, *Petunia*, *Viola*, *Impatiens*, *Geranium*, *Chrysanthemum*, *Ranunculus*, *Fuchsia*, *Salvia*, *Hortensia*, rosemary, sage, St. Johnswort, mint, sweet pepper, tomato and cucumber.

25 The active ingredients according to the invention are especially suitable for controlling Aphis craccivora, Diabrotica balteata, Heliothis virescens, Myzus persicae, Plutella xylostella and Spodoptera littoralis in cotton, vegetable, maize, rice and soya crops. The active ingredients according to the invention are further especially suitable for controlling Mamestra (preferably in vegetables),
 30 Cydia pomonella (preferably in apples), Empoasca (preferably in vegetables, vineyards), Leptinotarsa (preferably in potatoes) and Chilo suppressalis (preferably in rice).

The compounds of formula I are particularly suitable for control of

- a pest of the order Lepidoptera, for example, one or more of the species Spodoptera littoralis, Spodoptera frugiperda, Plutella xylostella, Cnaphalocrocis medinalis, Cydia pomonella, Chrysodeixis includens, Chilo suppressalis, Elasmopalpus lignosellus, Pseudoplusia includens, and Tuta absoluta (preferably in vegetables and corn).

The term "crops" is to be understood as including also crop plants which have been so transformed by the use of recombinant DNA techniques that they are capable of synthesising one or more selectively acting toxins, such as are known, for example, from toxin-producing bacteria, especially those of the genus *Bacillus*.

5

Toxins that can be expressed by such transgenic plants include, for example, insecticidal proteins, for example insecticidal proteins from *Bacillus cereus* or *Bacillus popilliae*; or insecticidal proteins from *Bacillus thuringiensis*, such as d-endotoxins, e.g. Cry1Ab, Cry1Ac, Cry1F, Cry1Fa2, Cry2Ab, Cry3A, Cry3Bb1 or Cry9C, or vegetative insecticidal proteins (Vip), e.g. Vip1, Vip2, Vip3 or Vip3A; or
10 insecticidal proteins of bacteria colonising nematodes, for example *Photorhabdus* spp. or *Xenorhabdus* spp., such as *Photorhabdus luminescens*, *Xenorhabdus nematophilus*; toxins produced by animals, such as scorpion toxins, arachnid toxins, wasp toxins and other insect-specific neurotoxins; toxins produced by fungi, such as *Streptomyces* toxins, plant lectins, such as pea lectins, barley lectins or snowdrop lectins; agglutinins; proteinase inhibitors, such as trypsin inhibitors,
15 serine protease inhibitors, patatin, cystatin, papain inhibitors; ribosome-inactivating proteins (RIP), such as ricin, maize-RIP, abrin, luffin, saporin or bryodin; steroid metabolism enzymes, such as 3-hydroxysteroidoxidase, ecdysteroid-UDP-glycosyl-transferase, cholesterol oxidases, ecdysone inhibitors, HMG-CoA-reductase, ion channel blockers, such as blockers of sodium or calcium channels, juvenile hormone esterase, diuretic hormone receptors, stilbene synthase, bibenzyl
20 synthase, chitinases and glucanases.

In the context of the present invention there are to be understood by d-endotoxins, for example Cry1Ab, Cry1Ac, Cry1F, Cry1Fa2, Cry2Ab, Cry3A, Cry3Bb1 or Cry9C, or vegetative insecticidal proteins (Vip), for example Vip1, Vip2, Vip3 or Vip3A, expressly also hybrid toxins, truncated toxins
25 and modified toxins. Hybrid toxins are produced recombinantly by a new combination of different domains of those proteins (see, for example, WO 02/15701). Truncated toxins, for example a truncated Cry1Ab, are known. In the case of modified toxins, one or more amino acids of the naturally occurring toxin are replaced. In such amino acid replacements, preferably non-naturally present protease recognition sequences are inserted into the toxin, such as, for example, in the case of
30 Cry3A055, a cathepsin-G-recognition sequence is inserted into a Cry3A toxin (see WO 03/018810).

Examples of such toxins or transgenic plants capable of synthesising such toxins are disclosed, for example, in EP-A-0 374 753, WO 93/07278, WO 95/34656, EP-A-0 427 529, EP-A-451 878 and WO 03/052073.

35

The processes for the preparation of such transgenic plants are generally known to the person skilled in the art and are described, for example, in the publications mentioned above. CryI-type deoxyribonucleic acids and their preparation are known, for example, from WO 95/34656, EP-A-0 367 474, EP-A-0 401 979 and WO 90/13651.

The toxin contained in the transgenic plants imparts to the plants tolerance to harmful insects. Such insects can occur in any taxonomic group of insects, but are especially commonly found in the beetles (Coleoptera), two-winged insects (Diptera) and moths (Lepidoptera).

5

Transgenic plants containing one or more genes that code for an insecticidal resistance and express one or more toxins are known and some of them are commercially available. Examples of such plants are: YieldGard® (maize variety that expresses a Cry1Ab toxin); YieldGard Rootworm® (maize variety that expresses a Cry3Bb1 toxin); YieldGard Plus® (maize variety that expresses a Cry1Ab and a
10 Cry3Bb1 toxin); Starlink® (maize variety that expresses a Cry9C toxin); Herculex I® (maize variety that expresses a Cry1Fa2 toxin and the enzyme phosphinothricine N-acetyltransferase (PAT) to achieve tolerance to the herbicide glufosinate ammonium); NuCOTN 33B® (cotton variety that expresses a Cry1Ac toxin); Bollgard I® (cotton variety that expresses a Cry1Ac toxin); Bollgard II® (cotton variety that expresses a Cry1Ac and a Cry2Ab toxin); VipCot® (cotton variety that expresses a
15 Vip3A and a Cry1Ab toxin); NewLeaf® (potato variety that expresses a Cry3A toxin); NatureGard®, Agrisure® GT Advantage (GA21 glyphosate-tolerant trait), Agrisure® CB Advantage (Bt11 corn borer (CB) trait) and Protecta®.

Further examples of such transgenic crops are:

- 20 1. **Bt11 Maize** from Syngenta Seeds SAS, Chemin de l'Hobit 27, F-31 790 St. Sauveur, France, registration number C/FR/96/05/10. Genetically modified *Zea mays* which has been rendered resistant to attack by the European corn borer (*Ostrinia nubilalis* and *Sesamia nonagrioides*) by transgenic expression of a truncated Cry1Ab toxin. Bt11 maize also transgenically expresses the enzyme PAT to achieve tolerance to the herbicide glufosinate ammonium.
- 25 2. **Bt176 Maize** from Syngenta Seeds SAS, Chemin de l'Hobit 27, F-31 790 St. Sauveur, France, registration number C/FR/96/05/10. Genetically modified *Zea mays* which has been rendered resistant to attack by the European corn borer (*Ostrinia nubilalis* and *Sesamia nonagrioides*) by transgenic expression of a Cry1Ab toxin. Bt176 maize also transgenically expresses the enzyme PAT to achieve tolerance to the herbicide glufosinate ammonium.
- 30 3. **MIR604 Maize** from Syngenta Seeds SAS, Chemin de l'Hobit 27, F-31 790 St. Sauveur, France, registration number C/FR/96/05/10. Maize which has been rendered insect-resistant by transgenic expression of a modified Cry3A toxin. This toxin is Cry3A055 modified by insertion of a cathepsin-G-protease recognition sequence. The preparation of such transgenic maize plants is described in WO 03/018810.
- 35 4. **MON 863 Maize** from Monsanto Europe S.A. 270-272 Avenue de Tervuren, B-1150 Brussels, Belgium, registration number C/DE/02/9. MON 863 expresses a Cry3Bb1 toxin and has resistance to certain Coleoptera insects.

5. **IPC 531 Cotton** from Monsanto Europe S.A. 270-272 Avenue de Tervuren, B-1150 Brussels, Belgium, registration number C/ES/96/02.

6. **1507 Maize** from Pioneer Overseas Corporation, Avenue Tedesco, 7 B-1160 Brussels, Belgium, registration number C/NL/00/10. Genetically modified maize for the expression of the protein Cry1F for achieving resistance to certain Lepidoptera insects and of the PAT protein for achieving tolerance to the herbicide glufosinate ammonium.

7. **NK603 × MON 810 Maize** from Monsanto Europe S.A. 270-272 Avenue de Tervuren, B-1150 Brussels, Belgium, registration number C/GB/02/M3/03. Consists of conventionally bred hybrid maize varieties by crossing the genetically modified varieties NK603 and MON 810. NK603 × MON 810

Maize transgenically expresses the protein CP4 EPSPS, obtained from *Agrobacterium sp.* strain CP4, which imparts tolerance to the herbicide Roundup® (contains glyphosate), and also a Cry1Ab toxin obtained from *Bacillus thuringiensis subsp. kurstaki* which brings about tolerance to certain Lepidoptera, include the European corn borer.

Transgenic crops of insect-resistant plants are also described in BATS (Zentrum für Biosicherheit und Nachhaltigkeit, Zentrum BATS, Clarastrasse 13, 4058 Basel, Switzerland) Report 2003, (<http://bats.ch>).

The term "crops" is to be understood as including also crop plants which have been so transformed by the use of recombinant DNA techniques that they are capable of synthesising antipathogenic substances having a selective action, such as, for example, the so-called "pathogenesis-related proteins" (PRPs, see e.g. EP-A-0 392 225). Examples of such antipathogenic substances and transgenic plants capable of synthesising such antipathogenic substances are known, for example, from EP-A-0 392 225, WO 95/33818 and EP-A-0 353 191. The methods of producing such transgenic plants are generally known to the person skilled in the art and are described, for example, in the publications mentioned above.

Crops may also be modified for enhanced resistance to fungal (for example Fusarium, Anthracnose, or Phytophthora), bacterial (for example Pseudomonas) or viral (for example potato leafroll virus, tomato spotted wilt virus, cucumber mosaic virus) pathogens.

Crops also include those that have enhanced resistance to nematodes, such as the soybean cyst nematode.

Crops that are tolerance to abiotic stress include those that have enhanced tolerance to drought, high salt, high temperature, chill, frost, or light radiation, for example through expression of NF-YB or other proteins known in the art.

Antipathogenic substances which can be expressed by such transgenic plants include, for example, ion channel blockers, such as blockers for sodium and calcium channels, for example the viral KP1,

KP4 or KP6 toxins; stilbene synthases; bibenzyl synthases; chitinases; glucanases; the so-called "pathogenesis-related proteins" (PRPs; see e.g. EP-A-0 392 225); antipathogenic substances produced by microorganisms, for example peptide antibiotics or heterocyclic antibiotics (see e.g. WO 95/33818) or protein or polypeptide factors involved in plant pathogen defence (so-called "plant disease resistance genes", as described in WO 03/000906).

Further areas of use of the compositions according to the invention are the protection of stored goods and store rooms and the protection of raw materials, such as wood, textiles, floor coverings or buildings, and also in the hygiene sector, especially the protection of humans, domestic animals and productive livestock against pests of the mentioned type.

The present invention provides a compound of the second aspect for use in therapy. The present invention provides a compound of the first aspect, for use in controlling parasites in or on an animal. The present invention further provides a compound of the first aspect, for use in controlling ectoparasites on an animal. The present invention further provides a compound of the first aspect, for use in preventing and/or treating diseases transmitted by ectoparasites.

The present invention provides the use of a compound of the second aspect, 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 first aspect, for the manufacture of a medicament for controlling ectoparasites on an animal. The present invention further provides the use of a compound of the first aspect, for the manufacture of a medicament for preventing and/or treating diseases transmitted by ectoparasites.

The present invention provides the use of a compound of the first aspect, in controlling parasites in or on an animal. The present invention further provides the use of a compound of the second aspect, in controlling ectoparasites on an animal.

The term "controlling" when used in context of parasites in or on an animal refers to reducing the number of pests or parasites, eliminating pests or parasites and/or preventing further pest or parasite infestation.

The term "treating" when used in context of parasites in or on an animal refers to restraining, slowing, stopping or reversing the progression or severity of an existing symptom or disease. The term "preventing" when used in context of parasites in or on an animal refers to the avoidance of a symptom or disease developing in the animal.

The term "animal" when used in context of parasites in or on an 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.

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: *Rhipicaphalus*, for example, *Rhipicaphalus* (*Boophilus*) *microplus* and *Rhipicephalus sanguineus*; *Amblyomrma*; *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 ovis*; *Cheyletiella*; *Dermanyssus*; for example *Dermanyssus gallinae*; *Ornithonyssus*; *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 *Tabanus spp.*; *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*.

The term "effective amount" when used in context of parasites in or on an animal 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. The effective amount can be 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 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.

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.

Salt forms of the compounds of the invention include both pharmaceutically acceptable salts and veterinary acceptable salts, which can be different to agrochemically 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.

The present invention also provides a method for controlling pests (such as mosquitoes and other disease vectors; see also http://www.who.int/malaria/vector_control/irs/en/). In one embodiment, the method for controlling pests comprises applying the compositions of the invention to the target pests, to their locus or to a surface or substrate by brushing, rolling, spraying, spreading or dipping. By way of example, an IRS (indoor residual spraying) application of a surface such as a wall, ceiling or floor surface is contemplated by the method of the invention. In another embodiment, it is contemplated to apply such compositions to a substrate such as non-woven or a fabric material in the form of (or which can be used in the manufacture of) netting, clothing, bedding, curtains and tents.

In one embodiment, the method for controlling such pests comprises applying a pesticidally effective amount of the compositions of the invention to the target pests, to their locus, or to a surface or substrate so as to provide effective residual pesticidal activity on the surface or substrate. Such application may be made by brushing, rolling, spraying, spreading or dipping the pesticidal composition of the invention. By way of example, an IRS application of a surface such as a wall, ceiling or floor surface is contemplated by the method of the invention so as to provide effective residual pesticidal activity on the surface. In another embodiment, it is contemplated to apply such compositions for residual control of pests on a substrate such as a fabric material in the form of (or which can be used in the manufacture of) netting, clothing, bedding, curtains and tents.

Substrates including non-woven, fabrics or netting to be treated may be made of natural fibres such as cotton, raffia, jute, flax, sisal, hessian, or wool, or synthetic fibres such as polyamide, polyester, polypropylene, polyacrylonitrile or the like. The polyesters are particularly suitable. The methods of

textile treatment are known, e.g. WO 2008/151984, WO 2003/034823, US 5631072, WO 2005/64072, WO2006/128870, EP 1724392, WO 2005113886 or WO 2007/090739.

Further areas of use of the compositions according to the invention are the field of tree injection/trunk treatment for all ornamental trees as well all sort of fruit and nut trees.

In the field of tree injection/trunk treatment, the compounds according to the present invention are especially suitable against wood-boring insects from the order *Lepidoptera* as mentioned above and from the order *Coleoptera*, especially against woodborers listed in the following tables A and B:

Table A. Examples of exotic woodborers of economic importance.

Family	Species	Host or Crop Infested
Buprestidae	<i>Agrilus planipennis</i>	Ash
Cerambycidae	<i>Anoplura glabripennis</i>	Hardwoods
Scolytidae	<i>Xylosandrus crassiusculus</i>	Hardwoods
	<i>X. mutilatus</i>	Hardwoods
	<i>Tomicus piniperda</i>	Conifers

Table B. Examples of native woodborers of economic importance.

Family	Species	Host or Crop Infested
Buprestidae	<i>Agrilus anxius</i>	Birch
	<i>Agrilus politus</i>	Willow, Maple
	<i>Agrilus sayi</i>	Bayberry, Sweetfern
	<i>Agrilus vittaticollis</i>	Apple, Pear, Cranberry, Serviceberry, Hawthorn
	<i>Chrysobothris femorata</i>	Apple, Apricot, Beech, Boxelder, Cherry, Chestnut, Currant, Elm, Hawthorn, Hackberry, Hickory, Horsechestnut, Linden, Maple, Mountain-ash, Oak, Pecan, Pear, Peach, Persimmon, Plum, Poplar, Quince, Redbud, Serviceberry, Sycamore, Walnut, Willow
	<i>Texania campestris</i>	Basswood, Beech, Maple, Oak, Sycamore, Willow, Yellow-poplar
Cerambycidae	<i>Goes pulverulentus</i>	Beech, Elm, Nuttall, Willow, Black oak, Cherrybark oak, Water oak, Sycamore

Family	Species	Host or Crop Infested
	<i>Goes tigrinus</i>	Oak
	<i>Neoclytus acuminatus</i>	Ash, Hickory, Oak, Walnut, Birch, Beech, Maple, Eastern hophornbeam, Dogwood, Persimmon, Redbud, Holly, Hackberry, Black locust, Honeylocust, Yellow-poplar, Chestnut, Osage-orange, Sassafras, Lilac, Mountain-mahogany, Pear, Cherry, Plum, Peach, Apple, Elm, Basswood, Sweetgum
	<i>Neoptychodes trilineatus</i>	Fig, Alder, Mulberry, Willow, Netleaf hackberry
	<i>Oberea ocellata</i>	Sumac, Apple, Peach, Plum, Pear, Currant, Blackberry
	<i>Oberea tripunctata</i>	Dogwood, Viburnum, Elm, Sourwood, Blueberry, Rhododendron, Azalea, Laurel, Poplar, Willow, Mulberry
	<i>Oncideres cingulata</i>	Hickory, Pecan, Persimmon, Elm, Sourwood, Basswood, Honeylocust, Dogwood, Eucalyptus, Oak, Hackberry, Maple, Fruit trees
	<i>Saperda calcarata</i>	Poplar
	<i>Strophiona nitens</i>	Chestnut, Oak, Hickory, Walnut, Beech, Maple
Scolytidae	<i>Corthylus columbianus</i>	Maple, Oak, Yellow-poplar, Beech, Boxelder, Sycamore, Birch, Basswood, Chestnut, Elm
	<i>Dendroctonus frontalis</i>	Pine
	<i>Dryocoetes betulae</i>	Birch, Sweetgum, Wild cherry, Beech, Pear
	<i>Monarthrum fasciatum</i>	Oak, Maple, Birch, Chestnut, Sweetgum, Blackgum, Poplar, Hickory, Mimosa, Apple, Peach, Pine
	<i>Phloeotribus liminaris</i>	Peach, Cherry, Plum, Black cherry, Elm, Mulberry, Mountain-ash

Family	Species	Host or Crop Infested
	<i>Pseudopityophthorus pruinus</i>	Oak, American beech, Black cherry, Chickasaw plum, Chestnut, Maple, Hickory, Hornbeam, Hophornbeam
Sesiidae	<i>Paranthrene simulans</i>	Oak, American chestnut
	<i>Sannina uroceriformis</i>	Persimmon
	<i>Synanthedon exitiosa</i>	Peach, Plum, Nectarine, Cherry, Apricot, Almond, Black cherry
	<i>Synanthedon pictipes</i>	Peach, Plum, Cherry, Beach, Black Cherry
	<i>Synanthedon rubrofascia</i>	Tupelo
	<i>Synanthedon scitula</i>	Dogwood, Pecan, Hickory, Oak, Chestnut, Beech, Birch, Black cherry, Elm, Mountain-ash, Viburnum, Willow, Apple, Loquat, Ninebark, Bayberry
	<i>Vitacea polistiformis</i>	Grape

The present invention may be also used to control any insect pests that may be present in turfgrass, including for example beetles, caterpillars, fire ants, ground pearls, millipedes, sow bugs, mites, mole crickets, scales, mealybugs, ticks, spittlebugs, southern chinch bugs and white grubs. The present invention may be used to control insect pests at various stages of their life cycle, including eggs, larvae, nymphs and adults.

In particular, the present invention may be used to control insect pests that feed on the roots of turfgrass including white grubs (such as *Cyclocephala* spp. (e.g. masked chafer, *C. lurida*), *Rhizotrogus* spp. (e.g. European chafer, *R. majalis*), *Cotinus* spp. (e.g. Green June beetle, *C. nitida*), *Popillia* spp. (e.g. Japanese beetle, *P. japonica*), *Phyllophaga* spp. (e.g. May/June beetle), *Ataenius* spp. (e.g. Black turfgrass ataenius, *A. spretulus*), *Maladera* spp. (e.g. Asiatic garden beetle, *M. castanea*) and *Tomarus* spp.), ground pearls (*Margarodes* spp.), mole crickets (tawny, southern, and short-winged; *Scapteriscus* spp., *Gryllotalpa africana*) and leatherjackets (European crane fly, *Tipula* spp.).

The present invention may also be used to control insect pests of turfgrass that are thatch dwelling, including armyworms (such as fall armyworm *Spodoptera frugiperda*, and common armyworm *Pseudaletia unipuncta*), cutworms, billbugs (*Sphenophorus* spp., such as *S. venatus verstitus* and *S. parvulus*), and sod webworms (such as *Crambus* spp. and the tropical sod webworm, *Herpetogramma phaeopteralis*).

The present invention may also be used to control insect pests of turfgrass that live above the ground and feed on the turfgrass leaves, including chinch bugs (such as southern chinch bugs, *Blissus insularis*), Bermudagrass mite (*Eriophyes cynodoniensis*), rhodesgrass mealybug (*Antonina graminis*), two-lined spittlebug (*Prospapia bicincta*), leafhoppers, cutworms (*Noctuidae* family), and greenbugs.

5

The present invention may also be used to control other pests of turfgrass such as red imported fire ants (*Solenopsis invicta*) that create ant mounds in turf.

10

In the hygiene sector, the compositions according to the invention are active against ectoparasites such as hard ticks, soft ticks, mange mites, harvest mites, flies (biting and licking), parasitic fly larvae, lice, hair lice, bird lice and fleas.

Examples of such parasites are:

15

Of the order Anoplurida: Haematopinus spp., Linognathus spp., Pediculus spp. and Phtirus spp., Solenopotes spp..

Of the order Mallophagida: Trimenopon spp., Menopon spp., Trinoton spp., Bovicola spp., Werneckiella spp., Lepikentron spp., Damalina spp., Trichodectes spp. and Felicola spp..

20

Of the order Diptera and the suborders Nematocerina and Brachycerina, for example Aedes spp., Anopheles spp., Culex spp., Simulium spp., Eusimulium spp., Phlebotomus spp., Lutzomyia spp., Culicoides spp., Chrysops spp., Hybomitra spp., Atylotus spp., Tabanus spp., Haematopota spp., Philipomyia spp., Braula spp., Musca spp., Hydrotaea spp., Stomoxys spp., Haematobia spp., Morellia spp., Fannia spp., Glossina spp., Calliphora spp., Lucilia spp., Chrysomyia spp., Wohlfahrtia spp., Sarcophaga spp., Oestrus spp., Hypoderma spp., Gasterophilus spp., Hippobosca spp., Lipoptena spp. and Melophagus spp..

25

Of the order Siphonaptera, for example Pulex spp., Ctenocephalides spp., Xenopsylla spp., Ceratophyllus spp..

30

Of the order Heteropterida, for example Cimex spp., Triatoma spp., Rhodnius spp., Panstrongylus spp..

35

Of the order Blattarida, for example Blatta orientalis, Periplaneta americana, Blattella germanica and Supella spp..

Of the subclass Acaria (Acarida) and the orders Meta- and Meso-stigmata, for example Argas spp., Ornithodoros spp., Otobius spp., Ixodes spp., Amblyomma spp., Boophilus spp., Dermacentor spp.,

Haemophysalis spp., Hyalomma spp., Rhipicephalus spp., Dermanyssus spp., Raillietia spp., Pneumonyssus spp., Sternostoma spp. and Varroa spp..

Of the orders Actinedida (Prostigmata) and Acaridida (Astigmata), for example Acarapis spp.,

- 5 Cheyletiella spp., Ornithocheyletia spp., Myobia spp., Psorergatesspp., Demodex spp., Trombicula spp., Listrophorus spp., Acarus spp., Tyrophagus spp., Caloglyphus spp., Hypodectes spp., Pterolichus spp., Psoroptes spp., Chorioptes spp., Otodectes spp., Sarcoptes spp., Notoedres spp., Knemidocoptes spp., Cytodites spp. and Laminosioptes spp..

- 10 The compositions according to the invention may be also suitable for protecting against insect infestation in the case of materials such as wood, textiles, plastics, adhesives, glues, paints, paper and card, leather, floor coverings and buildings.

The compositions according to the invention can be used, for example, against the following pests:

- 15 beetles such as Hylotrupes bajulus, Chlorophorus pilosis, Anobium punctatum, Xestobium rufovillosum, Ptilinuspecticornis, Dendrobium pertinex, Ernobius mollis, Priobium carpini, Lyctus brunneus, Lyctus africanus, Lyctus planicollis, Lyctus linearis, Lyctus pubescens, Trogoxylon aequale, Minthesrugicollis, Xyleborus spec., Tryptodendron spec., Apate monachus, Bostrychus capucins, Heterobostrychus brunneus, Sinoxylon spec. and Dinoderus minutus, and also hymenopterans such
- 20 as Sirex juvencus, Urocerus gigas, Urocerus gigas taignus and Urocerus augur, and termites such as Kaloterme flavicollis, Cryptoterme brevis, Heteroterme indicola, Reticuliterme flavipes, Reticuliterme santonensis, Reticuliterme lucifugus, Mastoterme darwiniensis, Zootermopsis nevadensis and Coptoterme formosanus, and bristletails such as Lepisma saccharina.

- 25 The compounds of formula I, or salts thereof, are especially suitable for controlling one or more pests selected from order Lepidoptera, especially one or more of the species Spodoptera littoralis, Spodoptera frugiperda, Plutella xylostella, Cnaphalocrocis medinalis, Cydia pomonella, Chrysodeixis includens, Chilo suppressalis, Elasmopalpus lignosellus, Pseudoplusia includens, and Tuta absoluta (preferably in vegetables and corn). In a preferred embodiment of each aspect, a compound TX
- 30 (where the abbreviation "TX" means "one compound selected from the compounds defined in Tables A-1 to A10 and P") controls one or more of pests selected from the species Spodoptera littoralis, Spodoptera frugiperda, Plutella xylostella, Cnaphalocrocis medinalis, Cydia pomonella, Chrysodeixis includens, Chilo suppressalis, Elasmopalpus lignosellus, Pseudoplusia includens, and Tuta absoluta (preferably in vegetables and corn).

- 35 The compounds of formula I, or salts thereof, are especially suitable for controlling one or more of the insects having diamide resistance selected from: Spodoptera littoralis, Spodoptera frugiperda, Plutella xylostella, Cnaphalocrocis medinalis, Cydia pomonella, Chrysodeixis includens, Chilo suppressalis, Elasmopalpus lignosellus, Pseudoplusia includens, and Tuta absoluta. In a preferred embodiment of

each aspect, a compound TX (where the abbreviation "TX" means "one compound selected from the compounds defined in Tables A-1 to A-10 and P") controls one or more of the insects having diamide resistance selected from: *Spodoptera littoralis*, *Spodoptera frugiperda*, *Plutella xylostella*, *Cnaphalocrocis medinalis*, *Cydia pomonella*, *Chrysodeixis includens*, *Chilo suppressalis*,

5 *Elasmopalpus lignosellus*, *Pseudoplusia includens*, and *Tuta absoluta*.

The compounds of formula I, or salts thereof, are especially suitable for controlling one or more of insects having diamide resistance selected from: *Plutella xylostella*, *Chilo suppressalis*, and *Tuta absoluta*.

10

In a preferred embodiment of each aspect, a compound TX (where the abbreviation "TX" means "one compound selected from the compounds defined in Tables A-1 to A-10 and P") controls one or more insect selected from *Plutella xylostella*, *Chilo suppressalis*, and *Tuta absoluta*, which insect

demonstrates resistance against IRAC MoA Group 28 insecticides, such as *Plutella xylostella* + TX,

15 *Chilo suppressalis* + TX, and *Tuta absoluta* + TX.

Compounds according to the invention may possess any number of benefits including, inter alia, advantageous levels of biological activity for protecting plants against insects or superior properties for use as agrochemical active ingredients (for example, greater biological activity, an advantageous spectrum of activity, an increased safety profile (against non-target organisms above and below ground (such as fish, birds and bees), improved physico-chemical properties, or increased biodegradability). In particular, it has been surprisingly found that certain compounds of formula I may show an advantageous safety profile with respect to non-target arthropods, in particular pollinators such as honey bees, solitary bees, and bumble bees. Most particularly, *Apis mellifera*.

25

The compounds according to the invention can be used as pesticidal agents in unmodified form, but they are generally formulated into compositions in various ways using formulation adjuvants, such as carriers, solvents and surface-active substances. The formulations can be in various physical forms, e.g. in the form of dusting powders, gels, wettable powders, water-dispersible granules, water-dispersible tablets, effervescent pellets, emulsifiable concentrates, microemulsifiable concentrates, oil-in-water emulsions, oil-flowables, aqueous dispersions, oily dispersions, suspo-emulsions, capsule suspensions, emulsifiable granules, soluble liquids, water-soluble concentrates (with water or a water-miscible organic solvent as carrier), impregnated polymer films or in other forms known e.g. from the Manual on Development and Use of FAO and WHO Specifications for Pesticides, United Nations, First Edition, Second Revision (2010). Such formulations can either be used directly or diluted prior to use. The dilutions can be made, for example, with water, liquid fertilisers, micronutrients, biological organisms, oil or solvents.

35

The formulations can be prepared e.g. by mixing the active ingredient with the formulation adjuvants in order to obtain compositions in the form of finely divided solids, granules, solutions, dispersions or emulsions. The active ingredients can also be formulated with other adjuvants, such as finely divided solids, mineral oils, oils of vegetable or animal origin, modified oils of vegetable or animal origin,
5 organic solvents, water, surface-active substances or combinations thereof.

The active ingredients can also be contained in very fine microcapsules. Microcapsules contain the active ingredients in a porous carrier. This enables the active ingredients to be released into the environment in controlled amounts (e.g. slow-release). Microcapsules usually have a diameter of from
10 0.1 to 500 microns. They contain active ingredients in an amount of about from 25 to 95% by weight of the capsule weight. The active ingredients can be in the form of a monolithic solid, in the form of fine particles in solid or liquid dispersion or in the form of a suitable solution. The encapsulating membranes can comprise, for example, natural or synthetic rubbers, cellulose, styrene/butadiene copolymers, polyacrylonitrile, polyacrylate, polyesters, polyamides, polyureas, polyurethane or
15 chemically modified polymers and starch xanthates or other polymers that are known to the person skilled in the art. Alternatively, very fine microcapsules can be formed in which the active ingredient is contained in the form of finely divided particles in a solid matrix of base substance, but the microcapsules are not themselves encapsulated.

The formulation adjuvants that are suitable for the preparation of the compositions according to the invention are known *per se*. As liquid carriers there may be used: water, toluene, xylene, petroleum ether, vegetable oils, acetone, methyl ethyl ketone, cyclohexanone, acid anhydrides, acetonitrile, acetophenone, amyl acetate, 2-butanone, butylene carbonate, chlorobenzene, cyclohexane, cyclohexanol, alkyl esters of acetic acid, diacetone alcohol, 1,2-dichloropropane, diethanolamine, p-
25 diethylbenzene, diethylene glycol, diethylene glycol abietate, diethylene glycol butyl ether, diethylene glycol ethyl ether, diethylene glycol methyl ether, *N,N*-dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, dipropylene glycol, dipropylene glycol methyl ether, dipropylene glycol dibenzoate, diproxitol, alkylpyrrolidone, ethyl acetate, 2-ethylhexanol, ethylene carbonate, 1,1,1-trichloroethane, 2-heptanone, alpha-pinene, d-limonene, ethyl lactate, ethylene glycol, ethylene glycol butyl ether,
30 ethylene glycol methyl ether, gamma-butyrolactone, glycerol, glycerol acetate, glycerol diacetate, glycerol triacetate, hexadecane, hexylene glycol, isoamyl acetate, isobornyl acetate, isooctane, isophorone, isopropylbenzene, isopropyl myristate, lactic acid, laurylamine, mesityl oxide, methoxypropanol, methyl isoamyl ketone, methyl isobutyl ketone, methyl laurate, methyl octanoate, methyl oleate, methylene chloride, m-xylene, *n*-hexane, *n*-octylamine, octadecanoic acid, octylamine acetate,
35 oleic acid, oleylamine, o-xylene, phenol, polyethylene glycol, propionic acid, propyl lactate, propylene carbonate, propylene glycol, propylene glycol methyl ether, p-xylene, toluene, triethyl phosphate, triethylene glycol, xylenesulfonic acid, paraffin, mineral oil, trichloroethylene, perchloroethylene, ethyl acetate, amyl acetate, butyl acetate, propylene glycol methyl ether, diethylene glycol methyl ether, methanol, ethanol, isopropanol, and alcohols of higher molecular weight, such as amyl alcohol,

tetrahydrofurfuryl alcohol, hexanol, octanol, ethylene glycol, propylene glycol, glycerol, *N*-methyl-2-pyrrolidone and the like.

Suitable solid carriers are, for example, talc, titanium dioxide, pyrophyllite clay, silica, attapulgite clay, kieselguhr, limestone, calcium carbonate, bentonite, calcium montmorillonite, cottonseed husks, wheat flour, soybean flour, pumice, wood flour, ground walnut shells, lignin and similar substances.

A large number of surface-active substances can advantageously be used in both solid and liquid formulations, especially in those formulations which can be diluted with a carrier prior to use. Surface-active substances may be anionic, cationic, non-ionic or polymeric and they can be used as emulsifiers, wetting agents or suspending agents or for other purposes. Typical surface-active substances include, for example, salts of alkyl sulfates, such as diethanolammonium lauryl sulfate; salts of alkylarylsulfonates, such as calcium dodecylbenzenesulfonate; alkylphenol/alkylene oxide addition products, such as nonylphenol ethoxylate; alcohol/alkylene oxide addition products, such as tridecylalcohol ethoxylate; soaps, such as sodium stearate; salts of alkylnaphthalenesulfonates, such as sodium dibutylnaphthalenesulfonate; dialkyl esters of sulfosuccinate salts, such as sodium di(2-ethylhexyl)sulfosuccinate; sorbitol esters, such as sorbitol oleate; quaternary amines, such as lauryltrimethylammonium chloride, polyethylene glycol esters of fatty acids, such as polyethylene glycol stearate; block copolymers of ethylene oxide and propylene oxide; and salts of mono- and dialkylphosphate esters; and also further substances described e.g. in McCutcheon's Detergents and Emulsifiers Annual, MC Publishing Corp., Ridgewood New Jersey (1981).

Further adjuvants that can be used in pesticidal formulations include crystallisation inhibitors, viscosity modifiers, suspending agents, dyes, anti-oxidants, foaming agents, light absorbers, mixing auxiliaries, antifoams, complexing agents, neutralising or pH-modifying substances and buffers, corrosion inhibitors, fragrances, wetting agents, take-up enhancers, micronutrients, plasticisers, glidants, lubricants, dispersants, thickeners, antifreezes, microbicides, and liquid and solid fertilisers.

The compositions according to the invention can include an additive comprising an oil of vegetable or animal origin, a mineral oil, alkyl esters of such oils or mixtures of such oils and oil derivatives. The amount of oil additive in the composition according to the invention is generally from 0.01 to 10%, based on the mixture to be applied. For example, the oil additive can be added to a spray tank in the desired concentration after a spray mixture has been prepared. Preferred oil additives comprise mineral oils or an oil of vegetable origin, for example rapeseed oil, olive oil or sunflower oil, emulsified vegetable oil, alkyl esters of oils of vegetable origin, for example the methyl derivatives, or an oil of animal origin, such as fish oil or beef tallow. Preferred oil additives comprise alkyl esters of C₈-C₂₂ fatty acids, especially the methyl derivatives of C₁₂-C₁₈ fatty acids, for example the methyl esters of lauric acid, palmitic acid and oleic acid (methyl laurate, methyl palmitate and methyl oleate, respectively).

Many oil derivatives are known from the Compendium of Herbicide Adjuvants, 10th Edition, Southern Illinois University, 2010.

- 5 The inventive compositions generally comprise from 0.1 to 99% by weight, especially from 0.1 to 95% by weight, of compounds of the present invention and from 1 to 99.9% by weight of a formulation adjuvant which preferably includes from 0 to 25% by weight of a surface-active substance. Whereas commercial products may preferably be formulated as concentrates, the end user will normally employ dilute formulations.
- 10 The rates of application vary within wide limits and depend on the nature of the soil, the method of application, the crop plant, the pest to be controlled, the prevailing climatic conditions, and other factors governed by the method of application, the time of application and the target crop. As a general guideline compounds may be applied at a rate of from 1 to 2000 l/ha, especially from 10 to 1000 l/ha.
- 15 Preferred formulations can have the following compositions (weight%):
Emulsifiable concentrates:
active ingredient: 1 to 95%, preferably 60 to 90%
surface-active agent: 1 to 30%, preferably 5 to 20%
liquid carrier: 1 to 80%, preferably 1 to 35%
- 20 Dusts:
active ingredient: 0.1 to 10%, preferably 0.1 to 5%
solid carrier: 99.9 to 90%, preferably 99.9 to 99%
- 25 Suspension concentrates:
active ingredient: 5 to 75%, preferably 10 to 50%
water: 94 to 24%, preferably 88 to 30%
surface-active agent: 1 to 40%, preferably 2 to 30%
- 30 Wettable powders:
active ingredient: 0.5 to 90%, preferably 1 to 80%
surface-active agent: 0.5 to 20%, preferably 1 to 15%
solid carrier: 5 to 95%, preferably 15 to 90%
- 35 Granules:
active ingredient: 0.1 to 30%, preferably 0.1 to 15%
solid carrier: 99.5 to 70%, preferably 97 to 85%

The following Examples further illustrate, but do not limit, the invention.

<u>Wettable powders</u>	a)	b)	c)
active ingredients	25%	50%	75%
sodium lignosulfonate	5%	5%	-
sodium lauryl sulfate	3%	-	5%
sodium diisobutylphenylsulfonate	-	6%	10%
phenol polyethylene glycol ether (7-8 mol of ethylene oxide)	-	2%	-
highly dispersed silicic acid	5%	10%	10%
Kaolin	62%	27%	-

The combination is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording wettable powders that can be diluted with water to give suspensions of the desired concentration.

5

<u>Powders for dry seed treatment</u>	a)	b)	c)
active ingredients	25%	50%	75%
light mineral oil	5%	5%	5%
highly dispersed silicic acid	5%	5%	-
Kaolin	65%	40%	-
Talcum	-		20%

The combination is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording powders that can be used directly for seed treatment.

<u>Emulsifiable concentrate</u>	
active ingredients	10%
octylphenol polyethylene glycol ether (4-5 mol of ethylene oxide)	3%
calcium dodecylbenzenesulfonate	3%
castor oil polyglycol ether (35 mol of ethylene oxide)	4%
Cyclohexanone	30%
xylene mixture	50%

Emulsions of any required dilution, which can be used in plant protection, can be obtained from this concentrate by dilution with water.

10

<u>Dusts</u>	a)	b)	c)
Active ingredients	5%	6%	4%
Talcum	95%	-	-
Kaolin	-	94%	-
mineral filler	-	-	96%

Ready-for-use dusts are obtained by mixing the combination with the carrier and grinding the mixture in a suitable mill. Such powders can also be used for dry dressings for seed.

<u>Extruder granules</u>	
Active ingredients	15%
sodium lignosulfonate	2%
carboxymethylcellulose	1%
Kaolin	82%

The combination is mixed and ground with the adjuvants, and the mixture is moistened with water. The mixture is extruded and then dried in a stream of air.

<u>Coated granules</u>	
Active ingredients	8%
polyethylene glycol (mol. wt. 200)	3%
Kaolin	89%

The finely ground combination is uniformly applied, in a mixer, to the kaolin moistened with polyethylene glycol. Non-dusty coated granules are obtained in this manner.

10 Suspension concentrate

active ingredients	40%
propylene glycol	10%
nonylphenol polyethylene glycol ether (15 mol of ethylene oxide)	6%
Sodium lignosulfonate	10%
carboxymethylcellulose	1%
silicone oil (in the form of a 75% emulsion in water)	1%
Water	32%

The finely ground combination is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired dilution can be obtained by dilution with water. Using such dilutions, living plants as well as plant propagation material can be treated and protected against infestation by microorganisms, by spraying, pouring or immersion.

15

Flowable concentrate for seed treatment

active ingredients	40%
--------------------	-----

propylene glycol	5%
copolymer butanol PO/EO	2%
Tristyrenephenole with 10-20 moles EO	2%
1,2-benzisothiazolin-3-one (in the form of a 20% solution in water)	0.5%
monoazo-pigment calcium salt	5%
Silicone oil (in the form of a 75% emulsion in water)	0.2%
Water	45.3%

The finely ground combination is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired dilution can be obtained by dilution with water. Using such dilutions, living plants as well as plant propagation material can be treated and protected against infestation by microorganisms, by spraying, pouring or immersion.

5

Slow Release Capsule Suspension

28 parts of the combination are mixed with 2 parts of an aromatic solvent and 7 parts of toluene diisocyanate/polymethylene-polyphenylisocyanate-mixture (8:1). This mixture is emulsified in a mixture of 1.2 parts of polyvinylalcohol, 0.05 parts of a defoamer and 51.6 parts of water until the desired particle size is achieved. To this emulsion a mixture of 2.8 parts 1,6-diaminohexane in 5.3 parts of water is added. The mixture is agitated until the polymerization reaction is completed. The obtained capsule suspension is stabilized by adding 0.25 parts of a thickener and 3 parts of a dispersing agent. The capsule suspension formulation contains 28% of the active ingredients. The medium capsule diameter is 8-15 microns. The resulting formulation is applied to seeds as an aqueous suspension in an apparatus suitable for that purpose.

15

Formulation types include an emulsion concentrate (EC), a suspension concentrate (SC), a suspo-emulsion (SE), a capsule suspension (CS), a water dispersible granule (WG), an emulsifiable granule (EG), an emulsion, water in oil (EO), an emulsion, oil in water (EW), a micro-emulsion (ME), an oil dispersion (OD), an oil miscible flowable (OF), an oil miscible liquid (OL), a soluble concentrate (SL), an ultra-low volume suspension (SU), an ultra-low volume liquid (UL), a technical concentrate (TK), a dispersible concentrate (DC), a wettable powder (WP), a soluble granule (SG) or any technically feasible formulation in combination with agriculturally acceptable adjuvants.

20

Preparatory Examples:

25

"Mp" means melting point in °C. Free radicals represent methyl groups. ¹H NMR measurements were recorded on a Bruker 400MHz spectrometer, chemical shifts are given in ppm relevant to a TMS standard. Spectra measured in deuterated solvents as indicated. Either one of the LC-MS methods below was used to characterize the compounds. The characteristic LC-MS values obtained for each compound were the retention time ("Rt", recorded in minutes) and the measured molecular ion (M+H)⁺.

30

LC-MS and GC-MS Methods:

LC-MS Method 1:

Spectra were recorded on a Mass Spectrometer from Waters (SQD, SQDII Single quadrupole mass spectrometer) equipped with an electrospray source (Polarity: positive and negative ions, Capillary: 3.00 kV, Cone range: 30 V, Extractor: 2.00 V, Source Temperature: 150°C, Desolvation Temperature: 350°C, Cone Gas Flow: 50 l/h, Desolvation Gas Flow: 650 l/h, Mass range: 100 to 900 Da) and an Acquity UPLC from Waters: Binary pump, heated column compartment, diode-array detector and ELSD detector. Column: Waters UPLC HSS T3, 1.8 µm, 30 x 2.1 mm, Temp: 60 °C, DAD Wavelength range (nm): 210 to 500, Solvent Gradient: A = water + 5% MeOH + 0.05% HCOOH, B= Acetonitrile + 0.05% HCOOH, gradient: 10-100% B in 1.2 min; Flow (ml/min) 0.85

LC-MS Method 2:

Spectra were recorded on a ACQUITY Mass Spectrometer from Waters Corporations (SQD or SQDII Single quadrupole mass spectrometer) equipped with an electrospray source (Polarity: positive or negative ions, Capillary: 3.0 kV, Cone: 30V, Extractor: 3.00 V, Source Temperature: 150°C, Desolvation Temperature: 400°C, Cone Gas Flow: 60 L/hr, Desolvation Gas Flow: 700 L/hr, Mass range: 140 to 800 Da) and an ACQUITY UPLC from Waters Corporations with solvent degasser, binary pump, heated column compartment and diode-array detector. Column: Waters UPLC HSS T3, 1.8 µm, 30 x 2.1 mm, Temp: 60 °C, DAD Wavelength range (nm): 210 to 400, Solvent Gradient: A = Water/Methanol 9:1 + 0.1% formic acid, B= Acetonitrile + 0.1% formic acid, gradient: 0-100% B in 2.5 min; Flow (ml/min) 0.75.

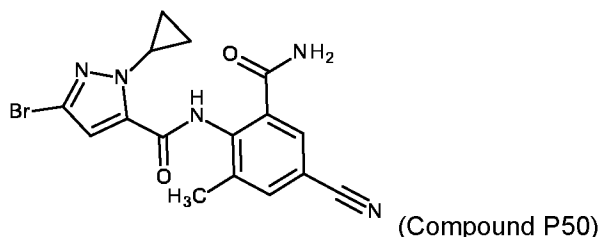
MS Method 3:

Spectra were recorded on a Mass Spectrometer from Agilent (Single quad mass spectrometer) equipped with Multimode- Electron Spray and APCI (Polarity: positive and negative ions), Capillary: 4.00KV, Corona Current 4.0µA, Charging Voltage, 2.00kV, Nitrogen Gas Flow: 12.0L/min, Nebulizer Pressure: 35 psig, Mass range: 100 to 1000 m/z), dry gas temperature 250°C, Vaporizer temperature 200°C

LC-MS Method 4:

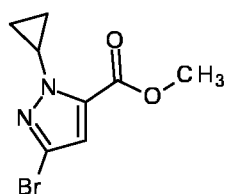
Spectra were recorded on a Mass Spectrometer from Waters (SQDII Single quadrupole mass spectrometer) equipped with an electrospray source (Polarity: positive and negative ions, Capillary: 3.20 kV, Cone range: 30 V, Extractor: 3.00 V, Source Temperature: 150 °C, Desolvation Temperature: 400 °C, Cone Gas Flow: 50 L/h, Desolvation Gas Flow: 1000 L/h, Mass range: 100 to 1000 Da) and an Acquity UPLC from Waters: Binary pump, heated column compartment, Photo diode-array detector . Column: Waters Sunfire C18, 3.5 µm, 50 x 2.1 mm and Column: Waters uplc BEH 1.7µm, 30 x 2.1 mm, Temp: Ambient, DAD Wavelength range (nm): 200 to 400, Solvent Gradient: A= 10mM Ammonium Formate in water, B = Acetonitrile, gradient (T/%B) - 0/2,0.2/2,2.2/45,3.8/95,4.4/95,4.5/2,5/2. In 5 min and gradient (T/%B) - 0/2,0.2/2,1.5/45,2.4/95,3.2/95,3.3/2,3.5/2. In 3.5 min Flow (mL/min) 0.6.

Example 1: Synthesis of 5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P50)



5

Step 1: Preparation of methyl 5-bromo-2-cyclopropyl-pyrazole-3-carboxylate



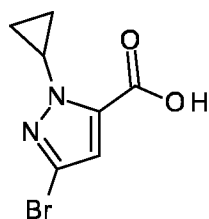
To a mixture of methyl 3-bromo-1H-pyrazole-5-carboxylate CAS 2246373-43-1 (600 mg, 2.92 mmol), cyclopropylboronic acid (628 mg, 7.31 mmol) and sodium carbonate (775 mg, 7.3167 mmol) in 1,2-dichloroethane (11.7 mL) at 70°C was added a heated suspension of 2,2'-Bipyridine (481 mg, 2.926 mmol) and copper (II) Acetate (531 mg, 2.9267 mmol) in 1,2-dichloroethane (11.7mL). The reaction mixture was then stirred vigorously under air (O₂) for 1h30 at 70°C and then at 70°C overnight with an opened condenser. The reaction mixture was cooled to room temperature, filtered through a pad of celite, and the solid was rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by column chromatography (CyHex/EtOAc) to afford methyl 5-bromo-2-cyclopropyl-pyrazole-3-carboxylate (311 mg, 1.26 mmol, 43%)

LCMS (Method 1): 247 [M+H], Rt: 0.97min

¹H NMR (400 MHz, CDCl₃) δ ppm 6.80 (1 H, s), 4.24-4.30 (1 H, m), 3.91 (3 H, s), 1.25-1.30 (2 H, m), 1.02-1.08 (2 H, m).

20

Step 2: Preparation of 5-bromo-2-cyclopropyl-pyrazole-3-carboxylic acid



To a solution of methyl 5-bromo-2-cyclopropyl-pyrazole-3-carboxylate (376 mg, 1.5343 mmol) in Ethanol (6 mL), lithium hydroxide (0.183 mg, 7.67 mmol) was added and the resulting mixture was stirred at room temperature for 1h30. The mixture was diluted with water and extracted with ethyl

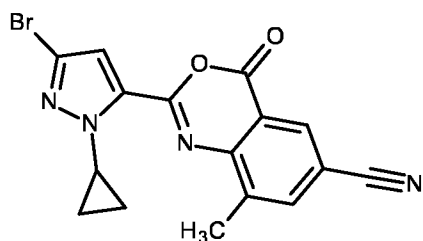
25

acetate. The aqueous layer was acidified with HCl 1M until pH 2/3 and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered and concentrated to give 5-bromo-2-cyclopropyl-pyrazole-3-carboxylic acid as crude (321mg, 1.38 mmol, 90%).

LCMS (Method 1): 233 [M+H], Rt: 0.76min

- 5 NMR crude: ¹H NMR (400 MHz, DMSO) δ ppm 13.37 - 14.00 (m, 1 H) 6.87 - 6.95 (m, 1 H) 4.27 - 4.39 (m, 1 H) 0.95 - 1.17 (m, 4 H)

Step 3: Preparation of 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile



10

2-amino-5-cyano-3-methylbenzoic acid CAS: 871239-18-8 (0.075 g, 0.409 mmol) and 5-bromo-2-cyclopropyl-pyrazole-3-carboxylic acid (0.09 g, 0.389 mmol) were suspended in Acetonitrile (3.1mL). Pyridine (0.161 mL, 1.98mmol) was added and resulting solution was cooled down to 0°C.

- 15 Methanesulfonyl chloride (0.094 mL, 1.207 mmol) was added slowly to the previous mixture, ice bath was removed and reaction was stirred at room temperature for 40 min. Then it was diluted with water and extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to get 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile as crude (0.122g, 0.328 mmol, 84%)

LCMS (Method 1): 373 [M+H], Rt: 1.13 min

- 20 ¹H NMR (400 MHz, CDCl₃) δ ppm 8.39 - 8.42 (m, 1 H) 7.93 (dd, J=1.8, 1.1 Hz, 1 H) 7.14 (s, 1 H) 4.44 (dt, J=7.4, 3.5 Hz, 1 H) 2.64 (s, 3 H) 1.36 - 1.46 (m, 2 H) 1.14 - 1.23 (m, 2 H)

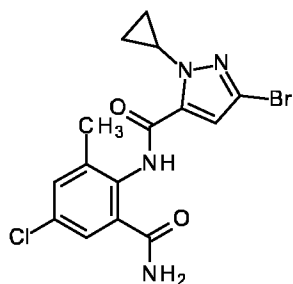
Step 4: Synthesis of 5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P50)

- 25 To a solution of 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile (120 mg, 0.323 mmol) in ethyl acetate (1.6 mL), was added ammonium acetate (0.206 g, 2.58 mmol). The reaction mixture was stirred at 60 °C. After 1 hour, water and ethyl acetate were added to the mixture, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were combined, dried over MgSO₄, filtered and concentrated under vacuum. The crude was purified by
- 30 Reversed phase chromatography with a gradient Water/ACN to afford 5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (0.029 g, 0.074 mmol, 23%)

LCMS (Method 1): 388 [M+H], Rt: 0.83 min

¹H NMR (400 MHz, DMSO) δ ppm 10.35 (br s, 1 H) 7.84 - 8.00 (m, 3 H) 7.59 (br s, 1 H) 7.04 (br s, 1 H) 4.23 - 4.36 (m, 1 H) 2.29 (s, 3 H) 1.07 - 1.14 (m, 2 H) 0.93 - 1.03 (m, 2 H)

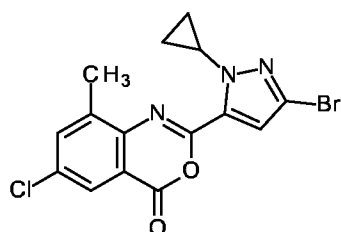
Example 2: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P39)



(Compound P39)

5

Step 1: Preparation of 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-6-chloro-8-methyl-3,1-benzoxazin-4-one



The desired product was prepared as described for example 1 step 3 using 2-amino-5-chloro-3-methylbenzoic acid CAS 20776-67-4 (265 mg, 1.38 mmol) to afford 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-6-chloro-8-methyl-3,1-benzoxazin-4-one (519 mg, 0.981 mmol, 98%)

LCMS (Method 1): 382 [M+H], Rt: 1.27min

NMR: ¹H NMR (400 MHz, DMSO) δ ppm 7.89 - 8.00 (m, 2 H) 7.10 - 7.20 (m, 1 H) 4.37 - 4.52 (m, 1 H) 2.52 - 2.59 (m, 3 H) 1.08 - 1.28 (m, 4 H)

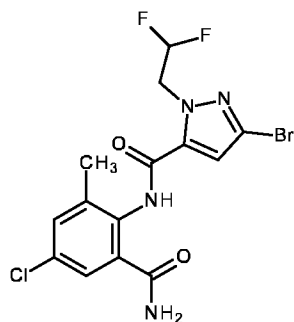
Step 2: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P39)

To a solution of 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-6-chloro-8-methyl-3,1-benzoxazin-4-one (519 mg, 1.364 mmol) in ethyl acetate (7 mL), was added ammonium carbonate (1.31g, 13.64 mmol). The resulting mixture was stirred at 77 °C for 1h30. After cooling down at room temperature, water and ethyl acetate were added to the mixture, and the product was extracted. The combined organic layers were combined, dried over MgSO₄, filtered and concentrated under vacuum. The crude obtained was triturated in Et₂O and filtered off to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (333 mg, 0.837 mmol, 61%)

LCMS (Method 1): 397 [M+H], Rt: 0.90min

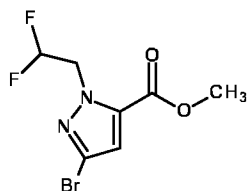
NMR solid: ¹H NMR (400 MHz, DMSO) δ ppm 9.65 - 10.21 (m, 1 H) 7.74 - 7.90 (m, 1 H) 7.39 - 7.57 (m, 3 H) 6.96 - 7.08 (m, 1 H) 4.23 - 4.39 (m, 1 H) 2.16 - 2.28 (m, 3 H) 0.83 - 1.11 (m, 4 H)

Example 3: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P40)



(Compound P40)

5 Step 1: Preparation of methyl 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylate

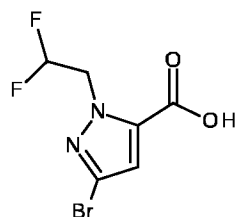


To a solution of methyl 3-bromo-1H-pyrazole-5-carboxylate CAS 2246373-43-1 (200 mg, 0.975 mmol) and dipotassium carbonate (471 mg 3.414 mmol) in N,N-dimethylformamide (3 mL) at 35°C, was added a solution of 1,1-difluoro-2-iodomethane CAS: 598-39-0 (0.257 mL, 2.926 mmol) dropwise. The reaction mixture was stirred at 35°C for 5h then was diluted with ether and washed with brine and NH₄Cl solution. The organic layer was dried over MgSO₄, filtered and concentrated. The crude was purified by chromatography over silica gel to afford methyl 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylate (173 mg, 0.643 mmol, 66%)

LCMS (Method 1): 269-271 [M+H], Rt: 0.98 min

¹H NMR (400 MHz, DMSO) δ ppm 7.08 - 7.19 (m, 1 H) 6.21 - 6.59 (m, 1 H) 4.87 - 5.05 (m, 2 H) 3.77 - 3.89 (m, 3 H)

Step 2: Preparation of 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid



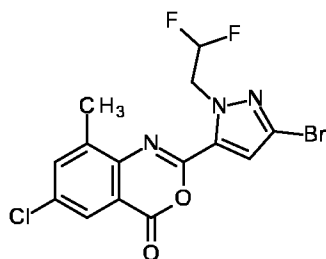
To a solution of methyl 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylate (163 mg, 0.605 mmol,) in ethanol (2.4 mL), lithium hydroxide (72 mg, 3.029 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The mixture was diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with HCl 1M until pH 2/3 and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and concentrated to afford 5-bromo-2-(2,2-

5 difluoroethyl)pyrazole-3-carboxylic acid (150mg, 0.588 mmol, 97%)

LCMS (Method 1): 255-256 [M+H], Rt: 0.77 min

¹H NMR (400 MHz, DMSO-d₆): δ 14.01 (brs, 1H), 7.04 (s, 1H), 6.38 (tt, J = 3.6 Hz, 54.8 Hz, 1H), 4.97 (dt, J = 4.0 Hz, 14.8 Hz, 2H)

5 Step 3: Preparation of 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



10 To an ice-cooled solution of 2-amino-5-chloro-3-methylbenzoic acid CAS 20776-67-4 (0.112 mg 0.58819 mmol) and 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid (150 mg, 0.58819 mmol) in acetonitrile (2.25 mL) and pyridine (0.19 mL, 2.3528 mmol), methanesulfonyl chloride (0.114 mL, 1.4705 mmol) was added dropwise. After 30 minutes the ice-bath was removed and the reaction mixture was stirred at room temperature for 30 min. The mixture was concentrated, Water was added and the reaction mixture was extracted with Ethyl acetate. The combined organic layers were dried over MgSO₄, filtered and concentrated to give 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one as crude mixture (222 mg, 0.548 mmol, 93%)

15 LCMS (Method 1): 406 [M+H], Rt: 1.26 min

¹H NMR (400 MHz, DMSO) δ ppm 7.97 - 8.01 (m, 1 H) 7.96 (dd, J=2.5, 0.7 Hz, 1 H) 7.32 (s, 1 H) 6.40 - 6.73 (m, 1 H) 5.24 (td, J=13.9, 4.2 Hz, 2 H) 2.53 (s, 3 H)

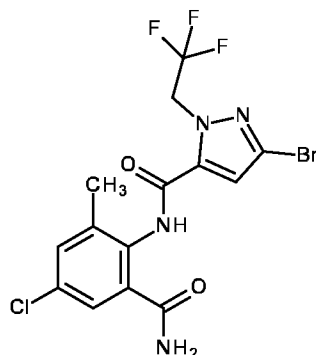
20 Step 4: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P40)

25 To a solution of 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (222 mg, 0.548 mmol) in ethyl acetate (2.7 mL), was added ammonium carbonate (527 mg, 5.487 mmol) and the resulting mixture was stirred at 77°C for 1 hour. At room temperature, water and ethyl acetate were added to the mixture, and the product was extracted. The combined organic layers were combined, dried over MgSO₄, filtered and concentrated under vacuum. The crude was purified by Combiflash chromatography over silica gel with a gradient cyclohexane/ethyl acetate to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (170 mg, 0.403 mmol, 73%)

30 LCMS (Method 1): 421 [M+H], Rt: 0.96min

¹H NMR (400 MHz, DMSO) δ ppm 10.14 - 10.26 (m, 1 H) 7.76 - 7.89 (m, 1 H) 7.51 - 7.57 (m, 1 H) 7.40 - 7.51 (m, 2 H) 7.14 - 7.24 (m, 1 H) 6.17 - 6.52 (m, 1 H) 4.85 - 5.05 (m, 2 H) 2.18 - 2.25 (m, 3 H) 4.85 - 5.05 (m, 2 H)

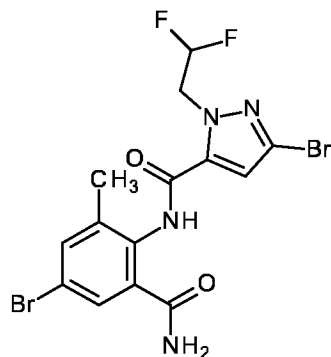
Example 4: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2,2-trifluoroethyl)pyrazole-3-carboxamide (compound P24)



(Compound P24)

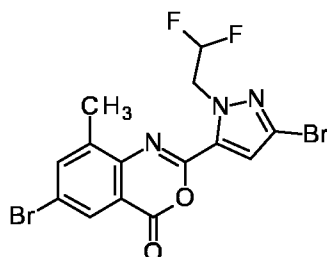
- 5 The desired product was prepared as described for Example 3 using 2,2,2-trifluoroethyl trifluoromethanesulfonate CAS: 6226-25-1 instead of 1,1-difluoro-2-iodomethane CAS: 598-39-0 for the Step 1 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2,2-trifluoroethyl)pyrazole-3-carboxamide.
- LCMS (Method 1): 439 [M+H], Rt: 0.95 min
- 10 ¹H NMR (400 MHz, DMSO) δ ppm 10.23 - 10.34 (m, 1 H) 7.76 - 7.92 (m, 1 H) 7.53 (s, 1 H) 7.46 (br d, J=2.2 Hz, 2 H) 7.23 - 7.33 (m, 1 H) 5.49 (q, J=8.7 Hz, 2 H) 2.20 (s, 3 H)

Example 5: Preparation of 5-bromo-N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (compound P22)



(Compound P22)

Step 1: Preparation of 6-bromo-2-[5-bromo-2-(2,2-difluoroethyl) pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one:



A 25 mL two-necked round-bottom flask was charged with 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid (300 mg, 1.18 mmol) (example 3, step 2) in acetonitrile (15 mL) was added 2-amino-5-bromo-3-methyl-benzoic acid (0.271 g, 1.18 mmol), pyridine (0.279 g, 3.53 mmol) and methanesulfonyl chloride (0.539 g, 4.71 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 6-bromo-2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (0.400 g, 0.534 mmol) as yellow solid. Crude product was used as such for next step.

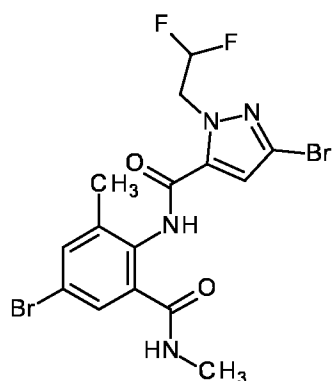
Step 2: Preparation of 5-bromo-N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound 22)

A 25 mL two-necked round-bottom flask was equipped with nitrogen balloon was charged with 6-bromo-2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.445 mmol) in acetonitrile (10.0 mL) and added ammonia (2000 mmol/L, 2.23 mL, 4.45 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by combi flash column chromatography (0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to afford 5-bromo-N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (100 mg, 0.215 mmol, 48.2%) as off-white solid.

MS (method 3): m/z = 465.07 [(M+2) – H]

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.20 (s, 1H), 7.84 (s, 1H), 7.66 (s, 1H), 7.56 (d, J = 1.6 Hz, 1H), 7.49 (s, 1H), 7.19 (s, 1H), 6.34 (tt, J = 3.2 Hz, 54.8 Hz, 1H), 4.96 (dt, J = 3.2 Hz, 14.4 Hz, 2H), 2.21 (s, 3H).

Example 6: Preparation of 5-bromo-N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (compound P21)



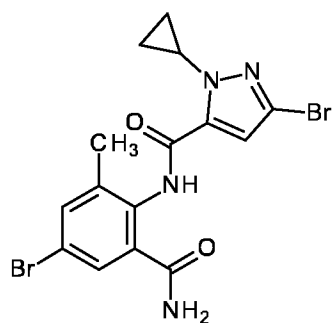
(Compound P21)

A 25 mL 2-neck round-bottom flask was equipped with nitrogen balloon was charged with 6-bromo-2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.445 mmol) (example 5 step 1) in acetonitrile (15.0 mL) and added methanamine (2000 mmol/L, 2.23 mL, 4.45 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by combi flash column chromatography (0 to 10% MeOH/DCM). Pure fractions were combined and evaporated under reduced pressure to afford 5-bromo-N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (130 mg, 0.271 mmol, 60.8%) as an off-white solid.

MS (method 3): $m/z = m/z$ 481.01 [(M+2) + H]⁺

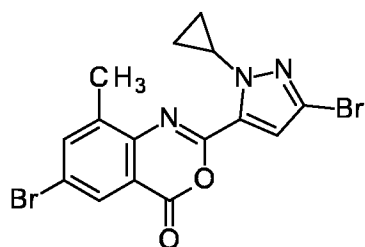
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.20 (s, 1H), 8.34 (d, J = 4.8 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.19 (s, 1H), 6.34 (tt, J = 4.0 Hz, 55.2 Hz, 1H), 4.96 (dt, J = 3.6 Hz, 14.4 Hz, 2H), 2.68 (d, J = 4.4 Hz, 3H), 2.23 (s, 3H).

Example 7: Preparation of 5-bromo-N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (compound P27)



(Compound P27)

Step 1: Preparation of 6-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one:



A 25 mL two-necked round-bottom flask was charged with 5-bromo-2-cyclopropyl-pyrazole-3-carboxylic acid (400 mg, 1.73 mmol) (example 1, step 2) in acetonitrile (20.0 mL) was added 2-amino-5-bromo-3-methyl-benzoic acid (0.398 g, 1.73 mmol), pyridine (0.411 g, 5.19 mmol) and methane sulfonyl chloride (0.793 g, 6.93 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 6-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (0.420 g, 0.988 mmol) as yellow solid. Crude product was used as such for next step.

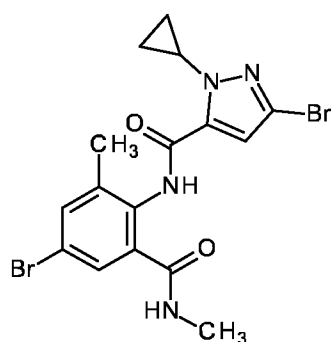
Step 2: Preparation of 5-bromo-N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P27)

A 25 mL two-necked round-bottom flask was equipped with a nitrogen balloon was charged with 6-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.471 mmol) in acetonitrile (10.0 mL) and added ammonia (2000 mmol/L, 2.35 mL, 4.71 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by combi flash column chromatography (0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to afford 5-bromo-N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (0.120 g, 0.271 mmol, 57.7%) as an off-white solid.

MS (method 3): $m/z = 443.02 [(M+2) + H]^+$

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.07 (s, 1H), 7.84 (s, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.50 (s, 1H), 7.02 (s, 1H), 4.33 – 4.27 (m, 1H), 2.23 (s, 3H), 1.11 – 1.07 (m, 2H), 0.99 – 0.96 (m, 2H).

Example 8: Preparation of 5-bromo-N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (compound P26)



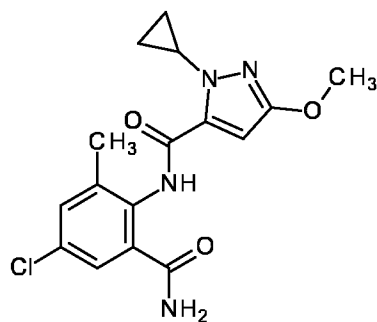
(Compound P26)

A 25 mL two-necked round-bottom flask equipped with a nitrogen balloon was charged with 6-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.471 mmol) in acetonitrile (10.0 mL) and added methanamine (2.35 mL, 4.71 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by combi flash column chromatography (0 to 10% MeOH/DCM). Pure fractions were combined and evaporated under reduced pressure to afford 5-bromo-N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (110 mg, 0.241 mmol, 51.3%) as off-white solid.

MS (method 3): $m/z = 455.0$ $[M+2H]^+$.

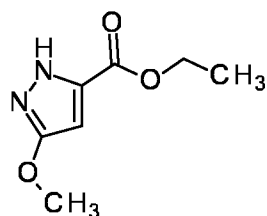
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.06 (s, 1H), 8.35 (d, $J = 4.8$ Hz, 1H), 7.66 (d, $J = 1.6$ Hz, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.00 (s, 1H), 4.29 – 4.23 (m, 1H), 2.68 (d, $J = 4.4$ Hz, 3H), 2.23 (s, 3H), 1.10 – 1.06 (m, 2H), 0.99 – 0.95 (m, 2H).

Example 9: Preparation of 5-bromo-N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (compound P55)



(Compound P55)

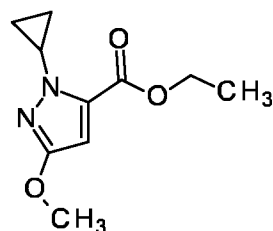
Step 1: Preparation of ethyl 3-methoxy-1H-pyrazole-5-carboxylate



A 100 mL two-necked round bottom flask was charged with ethyl 3-hydroxy-1H-pyrazole-5-carboxylate (3.00 g, 19.2 mmol) in N, N-dimethylformamide (30.0 mL) was added dipotassium carbonate (3.98 g, 28.8 mmol) and iodomethane (2.73 g, 19.2 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100.0 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The resulting crude residue was purified by combi flash column chromatography. Pure fractions were combined and evaporated under reduced pressure to afford ethyl 3-methoxy-1H-pyrazole-5-carboxylate (0.880 g, 4.91 mmol, 25.6%) as white solid.

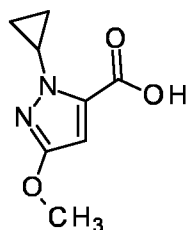
¹H NMR (400 MHz, CDCl₃): 10.56 (bs, H), 6.22 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 1.83 (t, *J* = 7.2 Hz, 3H).

Step 2: Preparation of ethyl 2-cyclopropyl-5-methoxy-pyrazole-3-carboxylate



A 100 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 3-methoxy-1H-pyrazole-5-carboxylate (2.60 g, 15.3 mmol) in 1,2-dichloroethane (40.0 mL) was added cyclopropylboronic acid (1.31 g, 15.3 mmol), disodium carbonate (1.62 g, 15.3 mmol), 2-(2-pyridyl)pyridine (2.39 g, 15.3 mmol), copper diacetate (2.78 g, 15.3 mmol) the resulting reaction mixture was stirred at 70° C for 16 h under oxygen balloon. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was poured in ice water extracted with EtOAc (2 x 200 mL) The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The resulting crude residue was purified by combi flash column chromatography using (0 to 100%) EtOAc in hexanes. Pure fractions were combined and evaporated under reduced pressure to afford ethyl 2-cyclopropyl-5-methoxy-pyrazole-3-carboxylate (1.85 g, 8.36 mmol, 54.7%) as colorless gum.

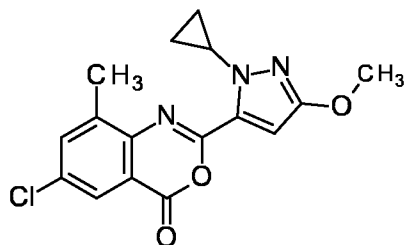
¹H NMR (400 MHz, DMSO-*d*₆): δ 6.28 (s, 1H), 4.32 – 4.24 (m, 2H), 4.17 – 4.11 (m, 1H), 3.75 (s, 1H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.05 – 1.03 (m, 2H), 0.97 – 0.93 (m, 2H).

Step 3: Preparation of 2-cyclopropyl-5-methoxy-pyrazole-3-carboxylic acid

A 50 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 2-cyclopropyl-5-methoxy-pyrazole-3-carboxylate (1.80 g, 8.13 mmol) in MeOH (5 mL) was added LiOH (1.63 g, 40.7 mmol) and H₂O (1.00 mL) at room temperature. The resulting reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was concentrated and diluted with water (100.0 mL), acidify the aqueous layer with Saturated citric acid solution and formed solids were filtered and washed with water, dried under vacuum to afford 2-cyclopropyl-5-methoxy-pyrazole-3-carboxylic acid (1.25 g, 6.52 mmol, 80.1%) as white solid.

MS (method 3): m/z = 183.2 [M+H]⁺

¹H NMR (400 MHz, DMSO-*d*₆): δ 6.09 (s, 1H), 4.49 – 4.38 (m, 1H), 3.71 (s, 1H), 1.03 – 1.04 (m, 2H), 0.88 – 0.85 (m, 2H).

Step 4: Preparation of 6-chloro-2-(2-cyclopropyl-5-methoxy-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one

A 25 two-necked round bottom flask was charged with 2-cyclopropyl-5-methoxy-pyrazole-3-carboxylic acid (95.0%, 300 mg, 1.56 mmol) in acetonitrile: THF (1:1) (10 mL) were added 2-amino-5-chloro-3-methyl-benzoic acid (348 mg, 1.88 mmol), pyridine (371 mg, 4.69 mmol) and methane sulfonyl chloride (717 mg, 6.26 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 6-chloro-2-(2-cyclopropyl-5-methoxy-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (450 mg, 1.22 mmol) as a yellow solid. Crude product was used as such for next step.

¹H NMR (400 MHz, CDCl₃): δ 8.05 – 8.04 (m, 1H), 7.65 – 7.64 (m, 1H), 6.45 (s, 1H), 4.35 – 4.31 (m, 1H), 3.89 (s, 3H), 2.56 (s, 3H), 1.30 – 1.28 (m, 2H), 1.08 – 1.06 (m, 2H).

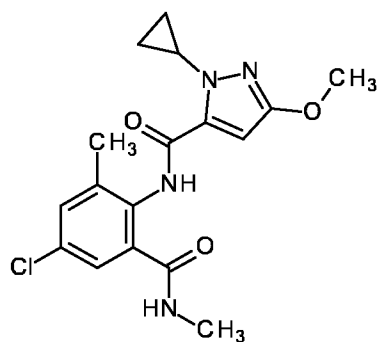
Step 5: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-5-methoxy-pyrazole-3-carboxamide (Compound P55)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 6-chloro-2-(2-cyclopropyl-5-methoxy-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (90.0%, 200 mg, 0.543 mmol) in Acetonitrile: THF (1:1) (10.0 mL) and added 2 M Ammonia in Ethanol (3.0 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-5-methoxy-pyrazole-3-carboxamide (70.0 mg, 0.191 mmol, 35.1%) as an off white solid.

MS (method 3): *m/z* = 349.1 [(M+1)+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆): δ 9.95 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.35 (s, 1H), 4.21 – 4.18 (m, 1H), 3.77 (s, 3H), 2.23 (s, 1H), 1.04 – 1.02 (m, 2H), 0.89 – 0.87 (m, 2H).

Example 10: Preparation of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-5-methoxy-pyrazole-3-carboxamide (compound P56)



(Compound P56)

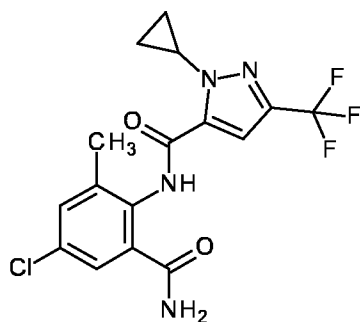
A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 6-chloro-2-(2-cyclopropyl-5-methoxy-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.543 mmol) (example 9, step 4) in Acetonitrile: THF (1:1) (10.0 mL) and added methanamine (2.00 mol/L, 1.36 mL, 2.71 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by Reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under

reduced pressure to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-5-methoxy-pyrazole-3-carboxamide (120 mg, 0.314 mmol, 57.9%) as an off white solid.

MS (method 3): $m/z = 363.1 [(M+1)+H]^+$.

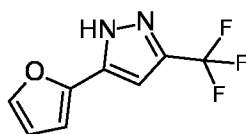
^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.91 (s, 1H), 8.31 (d, $J = 4.4$ Hz, 1H), 7.51 (d, $J = 2$ Hz, 1H), 7.39 (d, $J = 2.4$ Hz, 1H), 6.33 (s, 1H), 4.17–4.14 (m, 1H), 3.77 (s, 3H), 2.69 (d, $J = 4.8$ Hz, 3H), 2.32 (s, 3H), 1.03–1.01 (m, 2H), 0.88–0.86 (m, 2H).

Example 11: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (compound P29)



(Compound P29)

Step 1: Preparation of 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole

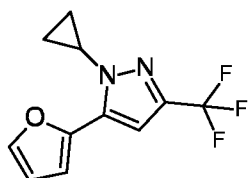


A 50 mL two-necked round bottom flask equipped with nitrogen balloon was charged with 4,4,4-trifluoro-1-(2-furyl) butane-1,3-dione (5.00 g, 24.3 mmol) in acetic acid (20.0 mL) and added hydrazine hydrate (2.35 mL, 48.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 80 °C for 5 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (50.0 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude residue. The resulting crude residue was purified by combi flash column chromatography. Pure fractions were combined and evaporated under reduced pressure to afford 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole (4.00 g, 19.8 mmol, 81.6%) as off-white solid.

MS (method 3): $m/z = 201.1 [M-H]^-$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.84 (dd, $J = 0.4$ Hz, 1.2 Hz, 1H), 6.99 (s, 1H), 6.96 (dd, $J = 0.4$ Hz, 2.8 Hz, 1H), 6.66 (q, $J = 1.6$ Hz, 1H).

Step 2: Preparation of 1-cyclopropyl-5-(2-furyl)-3-(trifluoromethyl) pyrazole:

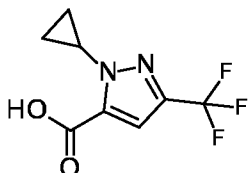


A 250 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole (6.00 g, 29.7 mmol) in 1,2 Dichloroethane (80.0 mL) was added cyclopropylboronic acid (2.55 g, 29.7 mmol), disodium; carbonate (3.15 g, 29.7 mmol), copper diacetate (5.40 g, 29.7 mmol) the resulting reaction mixture was stirred at 70° C for 16 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was poured in ice water extracted with EtOAc (2 x 200 mL) The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The resulting crude residue was purified by combi flash column chromatography using (0 to 100%) EtOAc in hexanes. Pure fractions were combined and evaporated under reduced pressure to afford 1-cyclopropyl-5-(2-furyl)-3-(trifluoromethyl) pyrazole (3.80 g, 15.7 mmol, 52.9%) as colorless gum.

MS (Method 3): m/z = 243.1 [M+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.91 (d, *J* = 1.2 Hz, 1H), 7.13 (d, *J* = 3.6 Hz, 1H), 7.01 (s, 1H), 6.73 (dd, *J* = 1.6 Hz, 3.6 Hz, 1H), 3.91 – 3.88 (m, 1H), 1.17 – 1.14 (m, 4H).

Step 3: Preparation of 2-cyclopropyl-5-(trifluoromethyl) pyrazole-3-carboxylic acid

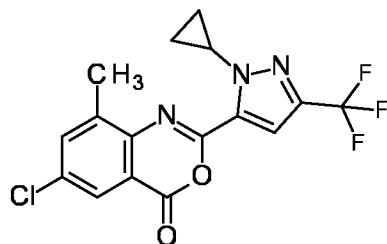


A 500 mL two-necked round bottom flask was charged with 1-cyclopropyl-5-(2-furyl)-3-(trifluoromethyl) pyrazole (3.80 g, 15.7 mmol) in acetone (200 mL) were added aqueous solution of potassium; permanganate (12.4 g, 78.4 mmol) and potassium; dihydrogen phosphate (10.7 g, 78.4 mmol) at -5 °C. The resulting reaction mixture was stirred at -5 °C to room temperature for 5 h. The reaction mixture was monitored by TLC (60% ethyl acetate/hexane) and it showed no starting material. The reaction mixture was filtered and filtrate pH was adjusted to 2 with 1 N HCl diluted with water (200 mL), extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by combi flash column chromatography (0 to 10% MeOH/DCM). Pure fractions were combined and concentrated under reduced pressure to afford 2-cyclopropyl-5-(trifluoromethyl) pyrazole-3-carboxylic acid (1.10 g, 5.00 mmol, 31.8%) as light-brown solid.

MS (Method 3): m/z = 219.1 [M+H]⁺;

¹H NMR (400 MHz, DMSO-*d*₆): δ 13.92 (brs, 1H), 7.27 (s, 1H), 4.48 – 4.42 (m, 1H), 1.19 – 1.15 (m, 4H)

Step 4: Synthesis of 6-chloro-2-[2-cyclopropyl-5-(trifluoromethyl) pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one

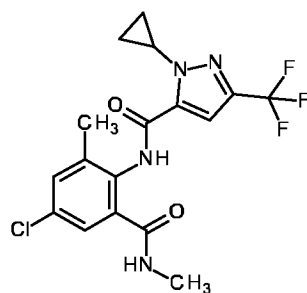


- 5 A 25 mL two-necked round bottom flask was charged with 2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxylic acid (100 mg, 0.454 mmol) in acetonitrile (10.0 mL) was added 2-amino-5-chloro-3-methylbenzoic acid (84.3 mg, 0.454 mmol), pyridine (108 mg, 1.36 mmol) and methane sulfonyl chloride (454 mg, 3.97 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 6-chloro-2-[2-cyclopropyl-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (110 mg, 0.298 mmol) as yellow solid. Crude product was used as such for next step.
- 15 MS (Method 3): m/z = 369.8 [M+H]⁺.

Step 5: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl) pyrazole-3-carboxamide (Compound P 29)

- 20 A 25 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with 6-chloro-2-[2-cyclopropyl-5-(trifluoromethyl) pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.541 mmol) in acetonitrile (10.0 mL) and added ammonia (2.70 mL, 5.41 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 5 h. The progress of the reaction was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by flash column chromatography (0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl) pyrazole-3-carboxamide (180 mg, 0.465 mmol, 86.0%) as off-white solid.
- 25
- 30 MS (Method 3): m/z = 387.15 [M + H]⁺.
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.18 (s, 1H), 7.84 (s, 1H), 7.54 – 7.45 (m, 3H), 7.35 (s, 1H), 4.43 – 4.37 (m, 1H), 2.25 (s, 3H), 1.17 – 1.13 (m, 2H), 1.12 – 0.99 (m, 2H).

Example 12: Preparation of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (compound P28)



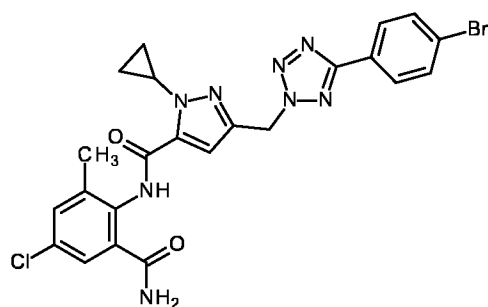
(Compound P28)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 6-chloro-2-[2-cyclopropyl-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.406 mmol) in acetonitrile (10 mL) was added methanamine (0.0126 g, 0.406 mmol) at 0 °C . The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl) phenyl]-2-cyclopropyl-5-(trifluoromethyl) pyrazole-3-carboxamide (90 mg, 0.225 mmol, 55.4%) as off-white solid.

MS (Method 3): m/z = 401.19 [M + H]⁺

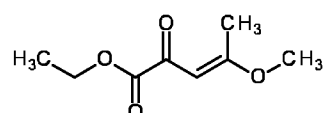
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.17 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.34 (s, 1H), 4.39 – 4.35 (m, 1H), 2.69 (d, J = 4.4 Hz, 3H), 2.25 (s, 3H), 1.19 – 1.17 (m, 2H), 1.15 – 1.14 (m, 2H)

Example 13: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (compound P18)



(Compound P18)

Step 1: Preparation of ethyl (E)-4-methoxy-2-oxo-pent-3-enoate

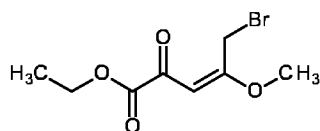


A 1L two-necked round bottom flask equipped with a nitrogen balloon was charged with ethyl 2-chloro-2-oxo-acetate (30.0 g, 220 mmol) in Dichloromethane (200 mL) were added 2-methoxyprop-1-ene (19.0 g, 264 mmol) and pyridine (24.3 g, 308 mmol) in Dichloromethane (100 mL), at 0 °C in 30 min. The reaction mixture was stirred at 0 °C to room temperature for 16 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. Reaction mixture was diluted with Dichloromethane (500 mL) washed with 10% hydrochloric acid (200 mL), washed with water (200 mL) brine solution (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude product. The resulting crude residue was purified by combi flash column chromatography using (0 to 100%) EtOAc in hexanes. Pure fractions were combined and evaporated under reduced pressure to afford ethyl (E)-4-methoxy-2-oxo-pent-3-enoate (30.0 g, 174 mmol, 79.3%) colour less gel.

MS (Method 3): m/z = 173.1 [M+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆): δ 6.12 (s, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.27 (t, 3H).

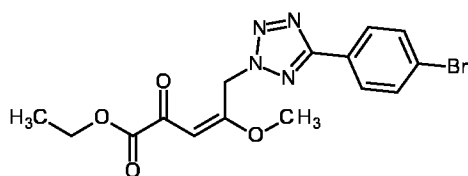
Step 2 : Preparation of ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate



A 500 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with ethyl (E)-4-methoxy-2-oxo-pent-3-enoate (10.0 g, 58.1 mmol) in Dichloromethane (50 mL) was added drop wise solution of molecular bromine (3.00 mL, 58.2 mmol) in Dichloromethane (100 mL) at 0 °C. The reaction mixture stirred at 0 °C for 1 h, followed by addition of a solution of pyridine (5.00 mL, 61.9 mmol) in dichloromethane (50 mL) at 0 °C. Then the reaction mixture was stirred at 0 °C for 1 h. The progress of the reaction was monitored by TLC (20% EtOAc/hexanes) and it showed no starting material. Reaction mixture was diluted with Dichloromethane (200 mL) and added water (200 mL), 2N Hydrochloric acid (10 mL). The reaction mixture was stirred for 5 min, organic layer was separated. Aqueous layer was extracted with Dichloromethane (200 mL). The combined organic layers were washed with water (200 ml), brine solution (200 ml), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude reaction mixture. The crude reaction mixture was purified by combi flash column chromatography (0 to 100% EtOAc in hexanes). Pure fractions were combined and evaporated under reduced pressure to afford ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate (4.00 g, 15.9 mmol, 27.4%) as red colour gel.

¹H NMR (400 MHz, DMSO-*d*₆): δ 6.25 (s, 1H), 4.51 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 1.28 (t, J = 6.8 Hz, 3H).

Step 3 : Preparation of ethyl (E)-5-[5-(4-bromophenyl) tetrazol-2-yl]-4-methoxy-2-oxo-pent-3-enoate

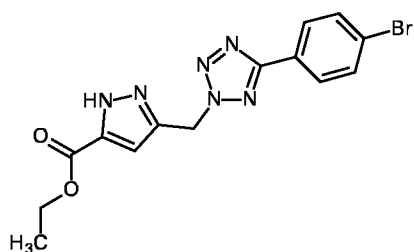


A 100 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate (5.00 g, 19.9 mmol) in acetonitrile (20.00 mL) was added dipotassium; carbonate (5.50 g, 39.8 mmol) and 5-(4-bromophenyl)-2H-tetrazole (4.48 g, 19.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by combi flash column chromatography (0 to 100% EtOAc in hexanes). Pure fractions were combined and evaporated under reduced pressure to afford ethyl (E)-5-[5-(4-bromophenyl) tetrazol-2-yl]-4-methoxy-2-oxo-pent-3-enoate (3.50 g, 8.86 mmol, 44.5%) as off white solid.

MS (method 3): m/z = 397.0 [M+2H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.99 (dd, *J* = 2.0 Hz, 6.8 Hz, 2H), 7.77 (dd, *J* = 2.0 Hz, 6.8 Hz, 2H), 6.44 (s, 1H), 6.14 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

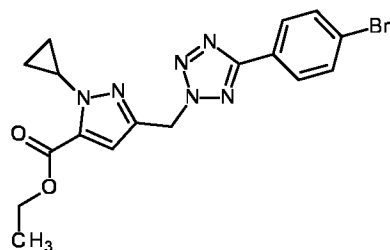
Step 4: Preparation of ethyl 3-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-1H-pyrazole-5-carboxylate



A 100 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with ethyl (E)-5-[5-(4-bromophenyl) tetrazol-2-yl]-4-methoxy-2-oxo-pent-3-enoate ((3.50 g, 8.86 mmol) in acetic acid (10.0 mL) was added hydrazine; hydrate (1.01 g, 20.2 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 2 h. The progress of the reaction was monitored by TLC (20% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude product ethyl 3-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-1H-pyrazole-5-carboxylate (3.00 g, 7.95 mmol, 89.8%) as light brown solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 1H), 6.05 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

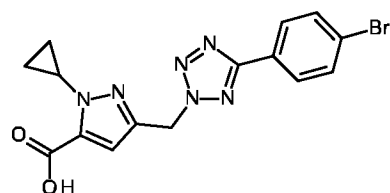
Step 5: Preparation of ethyl 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-cyclopropyl-pyrazole-3-carboxylate



A 250 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with ethyl 3-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate (4.00 g, 10.6 mmol) in 1,2-dichloroethane (30 mL) were added disodium; carbonate (1.35 g, 12.7 mmol), cyclopropylboronic acid (1.09 g, 12.7 mmol), copper; diacetate (1.35 g, 7.42 mmol) and 2-(2-pyridyl)pyridine (1.16 g, 7.42 mmol) at room temperature. The reaction mixture was stirred at 80°C for 5 h under oxygen balloon. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by combi flash column chromatography (0 to 100% EtOAc in hexanes). Pure fractions were combined and evaporated under reduced pressure to afford ethyl 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-cyclopropyl-pyrazole-3-carboxylate (2.40 g, 5.75 mmol, 54.2%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.99 (dd, J = 2.0 Hz, 6.8 Hz, 2H), 7.77 (dd, J = 2.0 Hz, 6.8 Hz, 2H), 6.44 (s, 1H), 6.14 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H).

Step 6: Preparation of 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-cyclopropyl-pyrazole-3-carboxylic acid



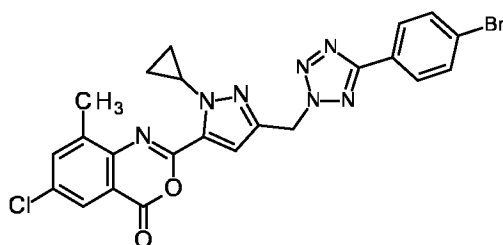
A 100 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-cyclopropyl-pyrazole-3-carboxylate (2.00 g, 4.79 mmol) in Methanol (5.0 mL) were added Tetrahydrofuran (2.0 mL), lithium; hydroxide; hydrate (1.01 g, 24.0 mmol) in water (2.0 mL) at 0 °C. The reaction mixture was stirred for at room temperature 1 h. The progress of the reaction was monitored by TLC (10% MeOH/DCM) and it showed no starting material. Most of the solvent was evaporated under reduced pressure and acidified with saturated citric acid solution at 0 °C. The aqueous mixture was extracted with 10% MeOH/DCM (2 x 100 mL). The combined organic layers washed with brine (100 mL), dried over Na₂SO₄ and concentrated under

reduced pressure to afford 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-cyclopropyl-pyrazole-3-carboxylic acid (1.86 g, 4.78 mmol, 99.7%) as an off-white solid.

MS (Method 3): $m/z = 389.0 [(M+2) - H]$

1H NMR (400 MHz, DMSO- d_6): δ 7.98 (d, $J = 8.8$ Hz, 2H), 7.76 (d, $J = 8.8$ Hz, 2H), 6.66 (s, 1H), 5.89 (s, 2H), 4.58 – 4.72 (m, 1H), 1.07 – 1.05 (m, 2H), 0.94 – 0.92 (m, 2H).

Step 7: Preparation of 2-[5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



- 10 A 25 mL two-necked round bottom flask was charged with 5-[[5-(4-bromophenyl) tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazole-3-carboxylic acid (300 mg, 0.771 mmol) in acetonitrile (10 mL) were added 2-amino-5-chloro-3-methyl-benzoic acid (172 mg, 0.925 mmol), pyridine (183 mg, 2.31 mmol) and methane sulfonyl chloride (353 mg, 3.08 mmol) at 0 °C . The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (30% Ethyl
- 15 acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 2-[5-[[5-(4-bromophenyl) tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (300 mg, 0.445 mmol) as yellow solid. Crude product was used as such for next step.
- 20 MS (Method 3): $m/z = 540.0 [(M+2) +H]^+$.

Step 8: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P18)

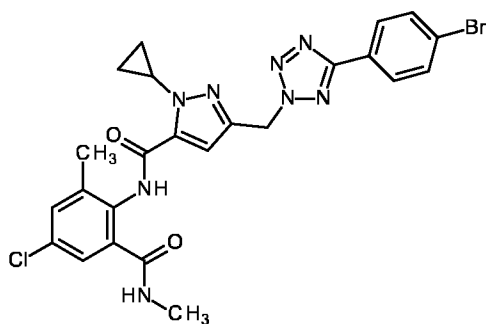
- 25 A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 2-[5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.278 mmol) in Acetonitrile (10.00 mL) and added 2M ammonia in ethanol (10.00 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined
- 30 organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by Reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-chloro-6-

methyl-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (100 mg, 0.180 mmol, 64.6%) as an off white solid.

MS (Method 3): $m/z = 555.1$ $[M+H]^+$

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.04 (s, 1H), 8.02 – 7.99 (m, 2H), 7.81 – 7.76 (m, 3H), 7.51 – 7.41 (m, 3H), 6.96 (s, 1H), 5.99 (s, 2H), 4.36 – 4.31 (m, 1H), 2.20 (s, 3H), 1.10 – 1.08 (m, 2H), 0.98 – 0.96 (m, 2H)

Example 14: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (compound P19)



(Compound P19)

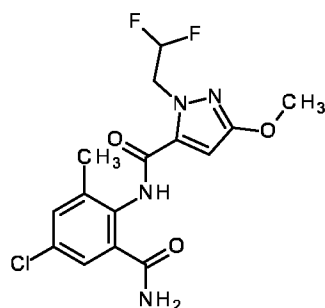
A 25 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with 2-[5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.278 mmol) (Example 13, step 7) in acetonitrile (10.00 mL) and added 2M Methylamine in ethanol (2.00 mL) at 0°C. The resulting reaction mixture was stirred at room temperature for 2 h.

The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (50.0 mg, 0.0877 mmol, 31.5%) as an off white solid.

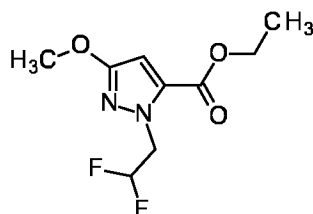
MS (Method 3): $m/z = 571.2$ $[M+2H]^+$

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.01 (s, 1H), 8.29 (d, $J = 4.8$ Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 2.4$ Hz, 1H), 6.95 (s, 1H), 5.99 (s, 2H), 4.31 – 4.28 (m, 1H), 2.66 (d, $J = 4.8$ Hz, 3H), 2.21 (s, 3H), 1.10 – 1.06 (m, 2H), 0.98 – 0.93 (m, 2H).

Example 15: Preparation of 5-bromo-N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (compound P53)



(Compound P53)

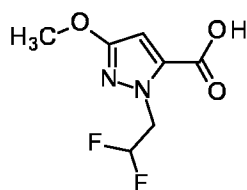
Step 1: Preparation of 2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxylic acid:

- 5 A 100 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 3-methoxy-1H-pyrazole-5-carboxylate (95.0%, 4.00 g, 22.3 mmol) (Example 9, step 1) in DMF (30.0 mL) was added 1,1-difluoro-2-iodo-ethane (5.14 g, 26.8 mmol) and dipotassium; carbonate (9.26 g, 67.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting
- 10 material. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with H₂O (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by chromatography (combi flash, 0 to 100% EtOAc/ hexane). Pure fractions were combined and evaporated under reduced pressure to afford ethyl 2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-
- 15 carboxylate (2.90 g, 11.8 mmol, 52.7%) as an off-white solid.

MS (Method 3): $m/z = 183.2 [(M+1) +H]^+$.

¹H NMR (400 MHz, DMSO-*d*₆): δ 6.23 (s, 1H), 6.49 – 6.19 (m, 1H), 4.50 – 4.23 (m, 2H), 4.28 – 4.23 (m, 2H), 3.93 (s, 3H), 1.28 (t, 7.2 Hz, 3H).

20 Step 2: Preparation of 2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxylic acid

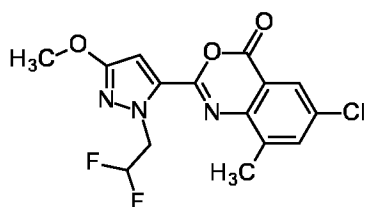


- A 100 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxylate (2.90 g, 11.8 mmol) in MeOH (20 mL) was added LiOH (2.35 g, 58.8 mmol) and H₂O (1.00 mL) at room temperature. The resulting reaction
- 25 mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC

(50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was concentrated and diluted with water (100.0 mL), acidify the aqueous layer with Saturated citric acid solution and formed solids were filtered and washed with water, dried under vacuum to afford 2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxylic acid (2.35 g, 10.8 mmol, 92.1%) as white solid.

¹H NMR (400 MHz, DMSO-*d*₆): 6.45 – 6.15 (m, 1H), 6.34 (s, 1H), 4.85 – 4.77 (m, 2H), 3.80 (s, 3H)

Step 3 : Preparation of 6-chloro-2-[2-(2,2-difluoroethyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



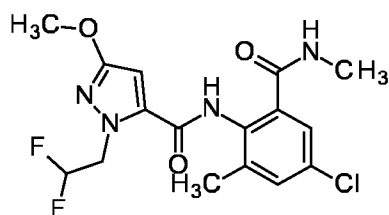
A 25 mL two-necked round bottom flask was charged with 2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxylic acid (95.0%, 300 mg, 1.38 mmol) in acetonitrile: THF (1:1) (10 mL) were added 2-amino-5-chloro-3-methyl-benzoic acid (308 mg, 1.66 mmol), pyridine (328 mg, 4.15 mmol) and methanesulfonyl chloride (633 mg, 5.53 mmol) at 0 °C . The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 6-chloro-2-[2-(2,2-difluoroethyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (600 mg, 1.27 mmol) as a yellow solid. Crude product was used as such for next step.

Step 4: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxamide (Compound P53)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 6-chloro-2-[2-(2,2-difluoroethyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (80.0%, 300 mg, 0.675 mmol) in Acetonitrile: THF (1:1) (10.0 mL) and added 2 M Ammonia in Ethanol (2.00 mol/L, 1.69 mL, 3.37 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxamide (152 mg, 0.387 mmol, 57.4%) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.05 (bs, 1H), 7.80 (bs, 1H), 7.51 (d, *J* = 2 Hz, 1H), 7.48 (s, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.53 (s, 1H), 6.41 – 6.11 (m, 1H), 4.83 – 4.75 (m, 2H), 3.82 (s, 3H), 2.20 (s, 3H).

5 **Example 16: Preparation of 5 N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxamide (Compound P54)**

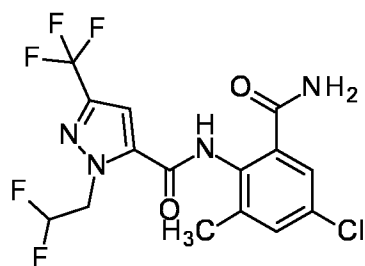


(Compound P54)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 6-chloro-2-[2-(2,2-difluoroethyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (80.0%, 300 mg, 0.675 mmol) in Acetonitrile: THF (1:1) (10.0 mL) and added methanamine (2.00 mol/L, 1.69 mL, 3.37 mmol) at 0°C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-methoxy-pyrazole-3-carboxamide (225 mg, 0.553 mmol, 81.9%) as an off white solid.

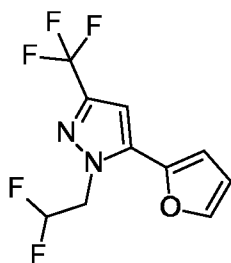
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.00 (bs, 1H), 8.31 (d, *J* = 4.4 Hz, 1H), 7.51 (d, *J* = 2 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 6.52 (s, 1H), 6.40 – 6.10 (m, 1H), 4.82 – 4.74 (m, 2H), 3.83 (s, 3H), 2.67 (d, *J* = 4.4 Hz, 3H), 2.21 (s, 1H).

Example 17: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (compound P20)



(Compound P20)

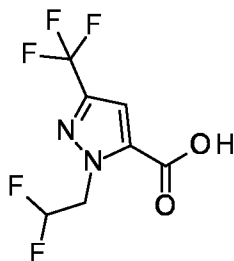
Step 1: Preparation of 1-(2,2-difluoroethyl)-5-(2-furyl)-3-(trifluoromethyl) pyrazole



A 250 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole (6.00 g, 29.7 mmol) (Example 11, step 1) in acetonitrile (50.0 mL) were added dipotassium; carbonate (12.3 g, 89.1 mmol) and 1,1-difluoro-2-iodo-ethane (11.4 g, 59.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by chromatography (0 to 100% EtOAc/ hexane). Pure fractions were combined and evaporated under reduced pressure to afford 1-(2,2-difluoroethyl)-5-(2-furyl)-3-(trifluoromethyl) pyrazole (3.60 g, 13.5 mmol, 45.6%) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.92 (dd, J = 0.4 Hz, 1.6 Hz, 1H), 7.18 (s, 1H), 7.08 (dd, J = 0.4 Hz, 3.2 Hz, 1H), 6.72 (q, 1.6 Hz, 1H), 6.48 (tt, J = 3.6 Hz, 54.4 Hz, 1H), 4.95 (dt, J = 3.6 Hz, 14.8 Hz, 2H).

Step 2: Preparation of 2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazole-3-carboxylic acid



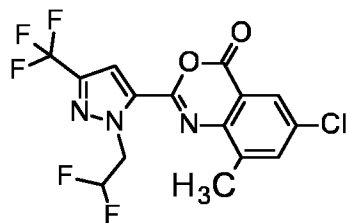
A 250 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with 1-(2,2-difluoroethyl)-5-(2-furyl)-3-(trifluoromethyl) pyrazole (3.60 g, 13.5 mmol) in acetone (50 mL) were added aqueous solution of potassium; dihydrogen phosphate (9.20 g, 67.6 mmol) and potassium; permanganate (10.7 g, 67.6 mmol) at -5 °C. The resulting reaction mixture was stirred at -5 °C to room temperature for 5 h. The progress of the reaction was monitored by TLC (60% ethyl acetate/hexane) and it showed no starting material. The reaction mixture was filtered and filtrate pH was adjusted to 2 with 1 N HCl diluted with water (100 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by combi flash column chromatography (0 to 10% MeOH/DCM). Pure fractions were combined and evaporated under

reduced pressure to afford 2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazole-3-carboxylic acid (2.20 g, 9.01 mmol, 66.6%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 14.13 (brs, 1H), 7.38 (s, 1H), 6.45 (tt, *J* = 3.6 Hz, 54.8 Hz, 1H), 5.09 (dt, *J* = 3.6 Hz, 14.4 Hz, 2H).

5

Step 3: Preparation of 6-chloro-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



A 25 mL two-necked round bottom flask was charged with 2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazole-3-carboxylic acid (300 mg, 1.23 mmol) in acetonitrile (15 mL) were added 2-amino-5-chloro-3-methyl-benzoic acid (0.228 g, 1.23 mmol), pyridine (0.292 g, 3.69 mmol) and methane sulfonyl chloride (0.563 g, 4.92 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 6-chloro-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (0.350 g, 0.889 mmol) as yellow solid. Crude product was used as such for next step.

MS (Method 3): *m/z* = 394.0 [M+H]⁺.

20

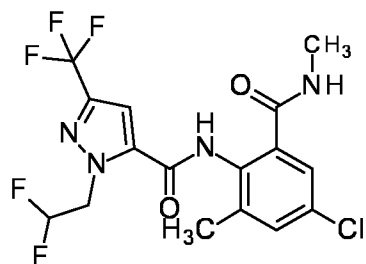
Step 4: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazole-3-carboxamide (Compound P20)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 6-chloro-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.381 mmol) in acetonitrile (10.0 mL) and added ammonia (2000 mmol/L, 3.81 mL, 7.62 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazole-3-carboxamide (80 mg, 0.195 mmol, 51.1%) as light brown solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.32 (s, 1H), 7.84 (s, 1H), 7.54 – 7.45 (m, 4H), 6.41 (tt, *J* = 3.6 Hz, 54.8 Hz, 1H), 5.09 (dt, *J* = 3.6 Hz, 14.4 Hz, 2H), 2.23 (s, 3H).

35

Example 18: Preparation of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P17)



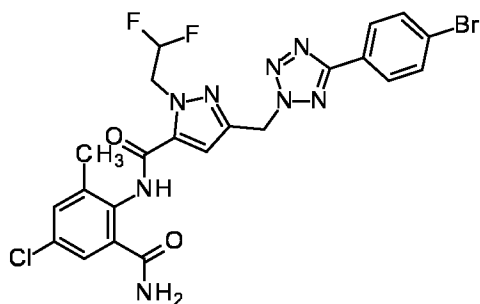
(Compound P17)

- 5 A 25 mL two-necked round bottom flask equipped with nitrogen balloon was charged with 6-chloro-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.381 mmol) (Example 17, step 3) in acetonitrile (10.0 mL) and added methanamine (2000 mmol/L, 1.91 mL, 3.81 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford N-[4-chloro-2-methyl-6-(methyl carbamoyl) phenyl]-2-(2,2-difluoroethyl)-5-(trifluoromethyl) pyrazole-3-carboxamide (85 mg, 0.200 mmol, 52.5%) as off-white solid.

MS (Method 3): *m/z* 425.21 [M + H]⁺.

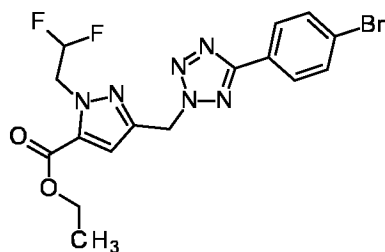
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.32 (s, 1H), 8.35 (d, *J* = 4.8 Hz, 1H), 7.53 (t, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 6.40 (tt, *J* = 3.6 Hz, 54.8 Hz, 1H), 5.08 (dt, *J* = 3.6 Hz, 14.4 Hz, 2H), 2.67 (d, *J* = 4.8 Hz, 1H), 2.23 (s, 3H).

Example 19: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P51)



(Compound P51)

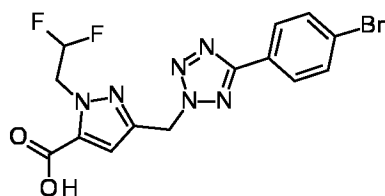
- 25 **Step 1: Preparation of ethyl 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-(2,2-difluoroethyl) pyrazole-3-carboxylate**



A 100 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 3-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-1H-pyrazole-5-carboxylate (1.50 g, 3.98 mmol) (Example 13, step 4) in Acetonitrile (10.0 mL) were added dipotassium;carbonate (1.10 g, 7.95 mmol) and 1,1-difluoro-2-iodo-ethane (1.53 g, 7.95 mmol) at room temperature. The reaction mixture was stirred at 60 °C 12 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude residue. The crude residue was purified by chromatography (0 to 100% EtOAc/ hexane). Pure fractions were combined and evaporated under reduced pressure to afford ethyl 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-(2,2-difluoroethyl) pyrazole-3-carboxylate (1.20 g, 2.72 mmol, 68.4%) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.98 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.03 (s, 1H), 6.53 – 6.24 (m, 1H), 5.75 (s, 2H), 5.00 – 4.92 (m, 2H), 4.30 (q, , J = 7.2 Hz, 2H), 1.29 (t, , J = 7.2 Hz, 3H).

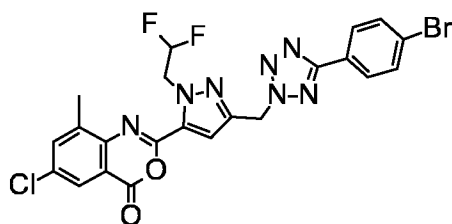
Step 2: Preparation of 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-(2,2-difluoroethyl) pyrazole-3-carboxylic acid



A 100 mL two-necked round bottom flask was equipped with nitrogen balloon was charged with ethyl 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-(2,2-difluoroethyl) pyrazole-3-carboxylate (2.80 g, 6.35 mmol) in Methanol (10.0 mL) were added Tetrahydrofuran (5.00 mL), lithium;hydroxide;hydrate (1.33 g, 31.7 mmol) and water (3.00 mL) at 0°C . The reaction mixture was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. Most of the solvent was evaporated under reduced pressure and adjust Ph 2.0 to 3.0 with saturated citric acid solution at 0 °C. Aqueous layer was extracted with 10% MeOH/DCM (2 x 100 mL). The combined organic layers washed with brine (100 mL), dried over Na₂SO₄ and evaporated under reduced pressure to afford crude product. The crude product was purified by reverse-phase column chromatography (0 to 100% Acetonitrile/ water). Pure fractions were combined and evaporated under reduced pressure to afford 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-(2,2-difluoroethyl) pyrazole-3-carboxylic acid (2.40 g, 5.81 mmol, 91.5%) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.02 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 6.52 – 6.20 (m, 1H), 6.02 (s, 2H), 5.02 – 4.94 (m, 2H).

Step 3: Preparation of 2-[5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



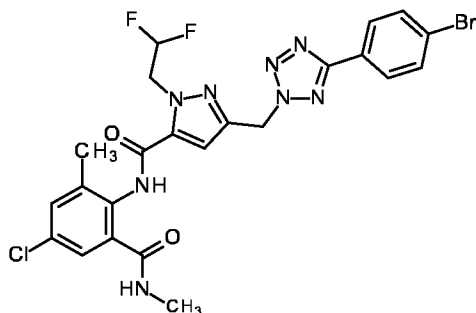
A 25 mL two-necked round bottom flask was charged with 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid (300 mg, 0.726 mmol) in acetonitrile (10 mL) were added 2-amino-5-chloro-3-methyl-benzoic acid (162 mg, 0.871 mmol), pyridine (172 mg, 2.18 mmol) and methanesulfonyl chloride (333 mg, 2.90 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 2-[5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (300 mg, 0.445 mmol) as yellow solid. Crude product was used as such for next step.

Step 4: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P51)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 2-[5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.267 mmol) in Acetonitrile 5.00 mL) and added 2M ammonia in ethanol (2.00 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (50.0 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (33.0 mg, 0.0569 mmol, 21.4%) as an off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.18 (s, 1H), 8.02 – 8.00 (m, 2H), 7.79 – 7.77 (m, 3H), 7.49 – 7.41 (m, 3H), 7.12 (s, 1H), 6.48– 6.18 (m, 1H), 6.07 (s, 2H), 5.00 – 4.92 (m, 2H), 2.20 (s, 3H).

Example 20: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P52)



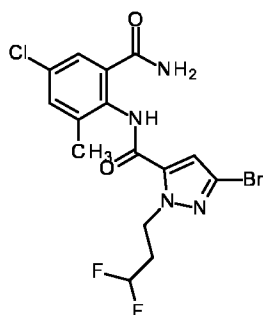
(Compound P52)

A 25 mL two-necked round bottom flask equipped with a nitrogen balloon was charged with 2-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-2-(2,2-difluoroethyl) pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.267 mmol) in Acetonitrile (5.00 mL) was added 2M methylamine in ethanol (3.00 mL) at 0°C. The resulting reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC (50% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100.0 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The crude product was purified by reversed-phase column chromatography (0 to 100% Acetonitrile/water). Pure fractions were combined and evaporated under reduced pressure to afford 5-[[5-(4-bromophenyl) tetrazol-2-yl] methyl]-N-[4-chloro-2-methyl-6-(methyl carbamoyl) phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (50.0 mg, 0.0842 mmol, 31.6%) as an off white solid.

MS (Method 3): m/z = 595.1 [M+2H]⁺.

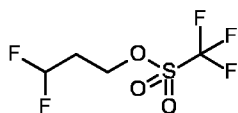
¹H NMR (400 MHz, DMSO-*d*₆): δ 10.19 (s, 1H), 8.33 (d, *J* = 4.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.13 (s, 1H), 6.47 – 6.17 (m, 1H), 6.08 (s, 2H), 4.98 – 4.90 (m, 2H), 2.64 (d, *J* = 4.8 Hz, 3H), 2.19 (s, 3H).

Example 21: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3,3-difluoropropyl)pyrazole-3-carboxamide (Compound P1)



(Compound P1)

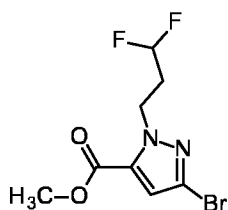
Step 1: Preparation of 3,3-difluoropropyl trifluoromethanesulfonate



To a solution of 3,3-difluoropropan-1-ol CAS 461-52-9 (0.500 g, 5.05 mmol) in DCM (15.1 mL) and 2,6-Lutidine (1.2 mL, 10.6 mmol) was added, dropwise at 0°C, Triflic anhydride (0.953 mL, 5.55 mmol). The purple solution was stirred at 0°C for 1h. The reaction mixture was poured into a mix of diethyl ether and water. The aqueous phase was extracted twice with diethyl ether. Then the combined organic layer was washed twice with citric acid (10%), then with brine, dried over Na2SO4, filtered and concentrated to afford 3,3-difluoropropyl trifluoromethanesulfonate (520 mg, 2.28 mmol, 45% yield) as a brownish liquid. 1H NMR (400 MHz, CDCl3): δ ppm 5.85 - 6.16 (m, 1 H) 4.70 (t, J=5.99 Hz, 2 H) 2.40 (ttd, J=16.03, 16.03, 6.13, 6.13, 4.36 Hz, 2 H).

19F NMR (377 MHz, CDCl3) δ ppm -74.54 (s, -CF3) -118.53 (s, -CHF2)

Step 2: Preparation of methyl 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylate



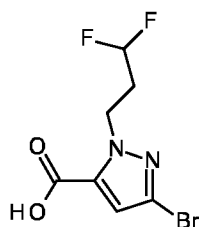
To a white suspension of methyl 5-bromo-1H-pyrazole-3-carboxylate (0.400 g, 1.93 mmol) and cesium carbonate (1.26 g, 3.86 mmol) in acetonitrile (11.6 mL) was added dropwise 3,3-difluoropropyl trifluoromethanesulfonate (0.529 g, 2.32 mmol). The reaction mixture was stirred at 50°C for 1h, then diluted with ethyl acetate and quenched with sat. aq. NaHCO3. The aqueous layer was extracted with ethyl acetate, then the organic layer was washed with brine, dried over Na2SO4, filtered and concentrated under vacuum. The crude was purified by Combiflash chromatography using a cyclohexane/ethyl acetate gradient to afford methyl 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylate (330 mg, 1.17 mmol, 60% yield) as a colourless liquid.

MS (method 1): 285 [M+H], Rt: 0.94 min

1H NMR (400 MHz, CDCl3) δ ppm 6.82 (s, 1 H) 5.76 - 6.10 (m, 1 H) 4.72 (t, J=7.08 Hz, 2 H) 3.89 (s, 3 H) 2.34 - 2.48 (m, 2 H).

19F NMR (377 MHz, CDCl3) δ ppm -117.25 (s, -CHF2).

Step 3: Preparation of 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylic acid

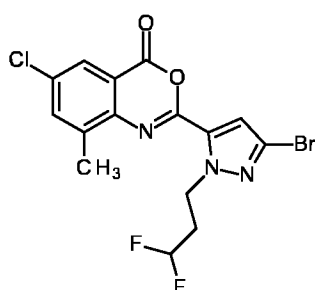


The desired product was prepared as described for example 1 step 2, using methyl 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylate to afford 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylic acid (290 mg, 98% yield) as a white solid.

LCMS (Method 1): 271 [M+H], Rt: 0.75min

- 5 ¹H NMR (400 MHz, DMSO) δ ppm 13.83 (br s, 1 H) 6.94 (s, 1 H) 5.98 - 6.30 (m, 1 H) 4.65 (t, J=6.90 Hz, 2 H) 2.36 (ttd, J=17.82, 17.82, 6.88, 6.88, 4.36 Hz, 2 H).
¹⁹F NMR (377 MHz, DMSO) δ ppm -116.35 (s, -CHF₂).

Step 4: Preparation of 2-[5-bromo-2-(3,3-difluoropropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



The desired product was prepared as described for example 1 step 3 using 2-amino-5-chloro-3-methylbenzoic acid CAS 20776-67-4 (201 mg, 1.06 mmol) and 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylic acid (285 mg, 1.06 mmol) to afford 2-[5-bromo-2-(3,3-difluoropropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (280 mg, 0.669 mmol, 63%).

LCMS (Method 1): 420 [M+H], Rt: 1.21min.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.05 (d, J=1.82 Hz, 1 H) 7.67 (dd, J=2.36, 0.91 Hz, 1 H) 7.09 (s, 1 H) 5.83 - 6.15 (m, 1 H) 4.97 - 5.07 (m, 2 H) 2.49 - 2.58 (m, 5 H)
¹⁹F NMR (377 MHz, CDCl₃) δ ppm -117.12 (s, -CHF₂).

Step 5: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3,3-difluoropropyl)pyrazole-3-carboxamide (Compound P1)

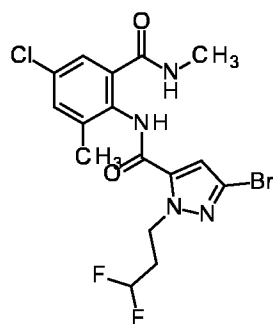
To a suspension of 2-[5-bromo-2-(3,3-difluoropropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (200mg, 0.382 mmol) in ethyl acetate (5.73 mL) was added ammonium carbonate (371 mg, 3.82 mmol). The reaction was stirred at 70°C for 8h. Then the mixture was cooled to rt, diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The solid was triturated with a solution of pentane/diethyl ether with some drops of dichloromethane. The liquid was removed via pipette and the solid was triturated twice again. The remaining clean solid was fully dried under vacuum to afford the desired compound 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3,3-difluoropropyl)pyrazole-3-carboxamide (Compound P1) (132 mg, 79% yield) as a brown solid.

LCMS (Method 1): 437 [M+H], Rt: 0.92min.

¹H NMR (400 MHz, DMSO) δ ppm 10.12 (s, 1 H) 7.82 (br s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.41 - 7.48 (m, 2 H) 7.11 (s, 1 H) 5.96 - 6.30 (m, 1 H) 4.62 (t, J=7.08 Hz, 2 H) 2.26 - 2.42 (m, 2 H) 2.22 (s, 3 H).

¹⁹F NMR (377 MHz, DMSO) δ ppm -116.13 (s, -CHF₂).

5 **Example 22: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(3,3-difluoropropyl)pyrazole-3-carboxamide (Compound P3)**



(Compound P3)

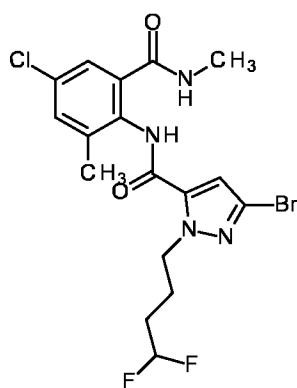
To a brown suspension of 2-[5-bromo-2-(3,3-difluoropropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (150 mg, 0.287 mmol), preparation described in Example 21 step 4, in ethyl acetate
10 (3.44 mL) was added methylamine (2M in THF, 0.43 mL, 0.86 mmol). The reaction mixture was stirred at 60°C for 1h. The solution was cooled to rt, then diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The resulting brown solid was triturated with a solution of pentane/diethylether (2:1) with some drops of dichloromethane. The liquid was removed via pipette
15 and triturated twice again. The remaining clean solid was fully dried under vacuum to afford the desired compound 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(3,3-difluoropropyl)pyrazole-3-carboxamide (Compound P3) (118 mg, 91.5% yield) as a beige solid.

LCMS (Method 1): 451 [M+H], Rt: 0.96min.

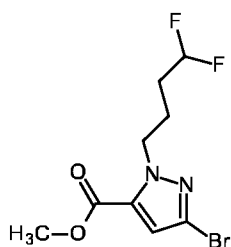
¹H NMR (400 MHz, DMSO) δ ppm 10.11 (s, 1 H) 8.28 - 8.37 (m, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.39 (d, J=2.54 Hz, 1 H) 7.11 (s, 1 H) 5.96 - 6.28 (m, 1 H) 4.61 (t, J=6.90 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H)
20 2.29 - 2.40 (m, 2 H) 2.23 (s, 3 H).

¹⁹F NMR (377 MHz, DMSO) δ ppm -116.12 (s, -CHF₂).

25 **Example 23: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P4)**



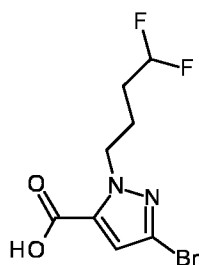
(Compound P4)

Step 1: Preparation of methyl 5-bromo-2-(4,4-difluorobutyl)pyrazole-3-carboxylate

The desired product was prepared as described for example 21 step 2, using methyl 5-bromo-1H-pyrazole-3-carboxylate CAS 1328893-17-9 (500mg, 2.41 mmol) and 4-bromo-1,1-difluorobutane CAS 1457946-33-6 (572 mg, 3.14 mmol) to afford methyl 5-bromo-2-(4,4-difluorobutyl)pyrazole-3-carboxylate (480 mg, 67% yield) as a colorless liquid.

LCMS (Method 1): 299 [M+H], Rt: 0.88min.

¹H NMR (400 MHz, CDCl₃) δ ppm 6.82 (s, 1 H) 5.66 - 5.99 (m, 1 H) 4.58 (t, J=7.08 Hz, 2 H) 3.88 (s, 3 H) 1.97 - 2.06 (m, 2 H) 1.78 - 1.93 (m, 2 H).

Step 2: Preparation of 5-bromo-2-(4,4-difluorobutyl)pyrazole-3-carboxylic acid

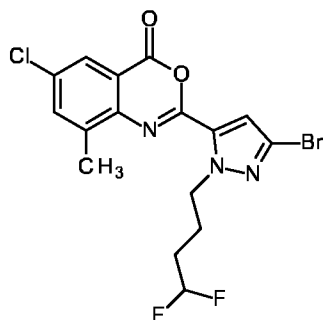
The desired product was prepared as described for example 1 step 2, using methyl 5-bromo-2-(4,4-difluorobutyl)pyrazole-3-carboxylate (460 mg, 1.55 mmol) to afford 5-bromo-2-(4,4-difluorobutyl)pyrazole-3-carboxylic acid (430 mg, 98% yield) as a white solid.

LCMS (Method 1): 284 [M+H], Rt: 0.83min

¹H NMR (400 MHz, DMSO) δ ppm 13.46 - 13.93 (br, 1 H) 6.94 (s, 1 H) 5.90 - 6.26 (m, 1 H) 4.52 (t, J=6.90 Hz, 2 H) 1.72 - 1.90 (m, 4 H).

¹⁹F NMR (377 MHz, DMSO) δ ppm -115.68 (s, -CHF₂).

Step 3: Preparation of 2-[5-bromo-2-(4,4-difluorobutyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



The desired product was prepared as described for example 1 step 3 using 2-amino-5-chloro-3-methylbenzoic acid CAS 20776-67-4 (288 mg, 1.52 mmol) and 5-bromo-2-(4,4-difluorobutyl)pyrazole-3-carboxylic acid (430 mg, 1.52 mmol) to afford 2-[5-bromo-2-(4,4-difluorobutyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (500 mg, 1.16 mmol, 76%).

LCMS (Method 1): 434 [M+H], Rt: 1.24min.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.06 (d, J=1.82 Hz, 1 H) 7.64 - 7.70 (m, 1 H) 7.09 (s, 1 H) 5.69 - 6.03 (m, 1 H) 4.84 (t, J=7.08 Hz, 2 H) 2.57 (s, 3 H) 2.11 - 2.19 (m, 2 H) 1.89 - 2.01 (m, 2 H).

¹⁹F NMR (377 MHz, DMSO) δ ppm -116.25 (s, -CHF₂).

Step 4: Preparation of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P4)

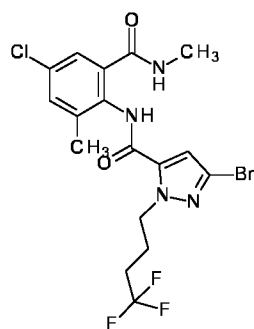
The desired product was prepared as described for example 22 using 2-[5-bromo-2-(4,4-difluorobutyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (200 mg, 0.37 mmol) to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P4) (148 mg, 0.319 mmol, 86%) as a beige solid.

LCMS (Method 1): 465 [M+H], Rt: 0.99min.

¹H NMR (400 MHz, DMSO) δ ppm 10.09 (s, 1 H) 8.32 (br d, J=4.72 Hz, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.08 (s, 1 H) 5.90 - 6.23 (m, 1 H) 4.48 (t, J=6.72 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H) 2.22 (s, 3 H) 1.72 - 1.92 (m, 4 H).

¹⁹F NMR (377 MHz, DMSO) δ ppm -115.60 (s, -CHF₂).

Example 24: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4,4-trifluorobutyl)pyrazole-3-carboxamide (Compound P5)



(Compound P5)

The desired product was prepared as described for example 23 (step 1 to 4) using 1,1,1-trifluoro-4-iodobutane CAS 461-17-6 to afford of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4,4-trifluorobutyl)pyrazole-3-carboxamide (Compound P5) as a beige solid.

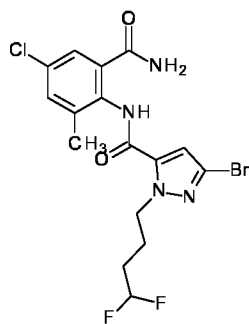
5 LCMS (Method 1): 483 [M+H], Rt: 1.04min.

^1H NMR (400 MHz, DMSO) δ ppm 10.10 (s, 1 H) 8.28 - 8.37 (m, 1 H) 7.52 (d, $J=1.82$ Hz, 1 H) 7.39 (d, $J=2.18$ Hz, 1 H) 7.09 (s, 1 H) 4.51 (t, $J=7.08$ Hz, 2 H) 2.67 (d, $J=4.72$ Hz, 3 H) 2.18 - 2.29 (m, 5 H) 1.94 - 2.02 (m, 2 H).

^{19}F NMR (377 MHz, DMSO) δ ppm -64.89 (s, -CF₃).

10

Example 25: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P6)



(Compound P6)

The desired product was prepared as described for example 21 step 5 using 2-[5-bromo-2-(4,4-difluorobutyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one, preparation described in example 23 step 3, (200 mg, 0.462 mmol) to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P6) (122 mg, 0.271 mmol, 59%) as a brown solid.

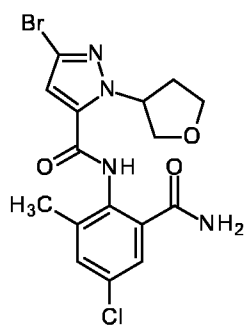
LCMS (Method 1): 451 [M+H], Rt: 0.94min.

^1H NMR (400 MHz, DMSO) δ ppm 10.11 (s, 1 H) 7.82 (br s, 1 H) 7.52 (d, $J=2.18$ Hz, 1 H) 7.41 - 7.47 (m, 2 H) 7.09 (s, 1 H) 5.91 - 6.24 (m, 1 H) 4.49 (t, $J=6.90$ Hz, 2 H) 2.22 (s, 3 H) 1.72 - 1.92 (m, 4 H).

^{19}F NMR (377 MHz, DMSO) δ ppm -115.59 (s, -CHF₂).

20

Example 26: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P7)



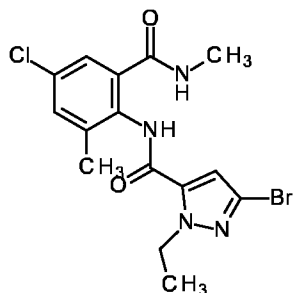
(Compound P7)

The desired product was prepared as described for example 21 using 3-Bromooxolane CAS 59253-21-3 to afford of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorobutyl)pyrazole-3-carboxamide (Compound P7) as a beige solid.

5 LCMS (Method 1): 429 [M+H], Rt: 0.86min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.10 (1 H, br. s), 7.80 (1 H, br. s), 7.52 (1 H, d, J=2.18 Hz), 7.47 (1 H, br. s), 7.43 (1 H, d, J=2.54 Hz), 7.08 (1 H, s), 5.66-5.73 (1 H, m), 3.93-3.99 (2 H, m), 3.77-3.83 (2 H, m), 2.27-2.39 (2 H, m), 2.23 (3 H, s).

10 **Example 27: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-ethyl-pyrazole-3-carboxamide (Compound P8)**



(Compound P8)

The desired product was prepared as described for example 23 using iodoethane CAS 75-03-6 to afford of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-ethyl-pyrazole-3-carboxamide (Compound P8) as a beige solid.

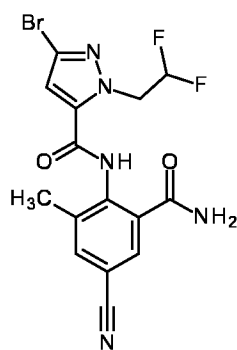
15 (Compound P8) as a beige solid.

LCMS (Method 1): 399 [M+H], Rt: 0.93min.

¹H NMR (400 MHz, DMSO) δ ppm 10.06 (s, 1 H) 8.31 (br d, J=4.72 Hz, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.05 (s, 1 H) 4.44 (q, J=7.02 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H) 2.23 (s, 3 H) 1.31 (t, J=7.27 Hz, 3 H).

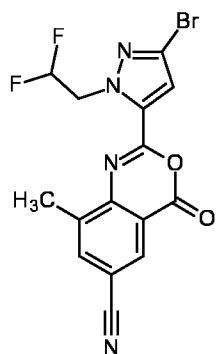
20

Example 28: Synthesis of 5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P9)



(Compound P9)

Step 1: Preparation of 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile



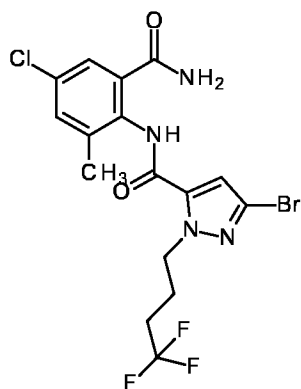
- 5 The desired product was prepared as described for example 1 step 3 using 2-amino-5-cyano-3-methylbenzoic acid CAS: 871239-18-8 (41.4 mg, 0.235 mmol) and 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, preparation described in example 3 step 2, (50 mg, 0.196 mmol) to afford 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile.
- 10 LCMS (Method 1): 397 [M+H], Rt: 1.06min.
¹H NMR (400 MHz, CDCl₃) δ ppm 2.62 (s, 3 H) 5.25 (td, J=1.00 Hz, 2 H) 6.24 (tt, J=1.00 Hz, 1 H) 7.21 (s, 1 H) 7.94 (s, 1 H) 8.39 (s, 1 H)

Step 2: synthesis of 5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P9)

- 15 The desired product was prepared as described for example 5 step 2 using 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile (63 mg, 0.159 mmol) to afford 5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (34mg, 52% yield) as a solid.
- 20 LCMS (Method 1): 414 [M+H], Rt: 0.83min.
¹H NMR (400 MHz, CDCl₃) δ ppm 10.48 (s, 1 H) 7.95 (br s, 2 H) 7.86 (s, 1 H) 7.59 (s, 1 H) 7.22 (s, 1 H) 6.36 (tt, J=1.00 Hz, 1 H) 4.97 (td, J=1.00 Hz, 2 H) 2.26 - 2.30 (m, 3 H)

Example 29: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4,4-trifluorobutyl)pyrazole-3-carboxamide (Compound P10)

- 25



(Compound P10)

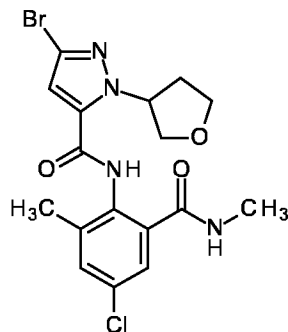
The desired product was prepared as described for example 21 using 1,1,1-trifluoro-4-iodobutane CAS 461-17-6 to afford 5-bromo-N-(2-carbamoyl-4-cyano-6-methylphenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P10) (140 mg, 84% yield) as a beige solid.

5 LCMS (Method 1): 469 [M+H], Rt: 0.99min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.12 (s, 1 H) 7.82 (br s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.40 - 7.48 (m, 2 H) 7.09 (s, 1 H) 4.51 (t, J=7.08 Hz, 2 H) 2.19 - 2.30 (m, 5 H) 1.94 - 2.02 (m, 2 H).

¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -64.84 (s, -CF₃).

10 **Example 30: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydrofuran-3-yl-pyrazole-3-carboxamide (Compound P11)**



(Compound P11)

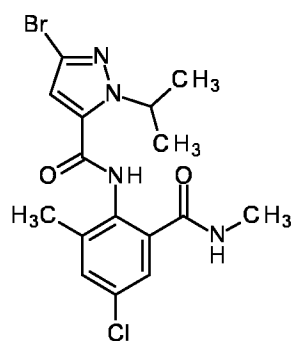
The desired product was prepared as described for example 23 using 3-Bromooxolane CAS 59253-21-3 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydrofuran-3-yl-pyrazole-3-carboxamide (Compound P11) (161 mg, 0.365 mmol, 85% yield) as a beige solid.

15 LCMS (Method 1): 443 [M+H], Rt: 0.91min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.10 (1 H, br. s), 8.31 (1 H, br. q, J=4.72 Hz), 7.51 (1 H, d, J=1.82 Hz), 7.39 (1 H, d, J=2.18 Hz), 7.07 (1 H, s), 5.64-5.71 (1 H, m), 3.93-3.99 (2 H, m), 3.77-3.83 (2 H, m), 2.68 (3 H, d, J=4.36 Hz), 2.27-2.40 (2 H, m), 2.23 (3 H, s).

20

Example 31: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydrofuran-3-yl-pyrazole-3-carboxamide (Compound P12)



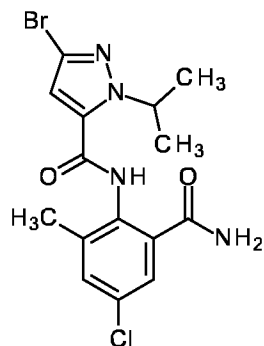
(Compound P12)

The desired product was prepared as described for example 23 using 2-Bromopropane CAS 75-26-3 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-isopropyl-pyrazole-3-carboxamide (Compound P12) (142 mg, 0.344 mmol, 83% yield) as a beige solid.

LCMS (Method 1): 415 [M+H], Rt: 0.99min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.06 (1 H, br. s), 8.30 (1 H, br. q, J=4.72 Hz), 7.51 (1 H, d, J=2.18 Hz), 7.38 (1 H, d, J=2.54 Hz), 6.99 (1 H, s), 5.27-5.38 (1 H, m), 2.67 (3 H, d, J=4.36 Hz), 2.23 (3 H, s), 1.38 (6 H, d, J=6.54 Hz).

Example 32: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-isopropyl-pyrazole-3-carboxamide (Compound P13)



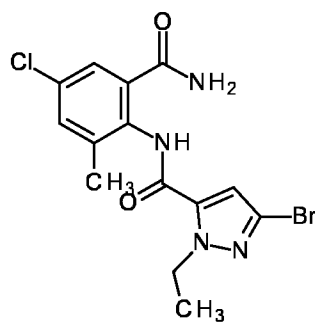
(Compound P13)

The desired product was prepared as described for example 21 using 2-Bromopropane CAS 75-26-3 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-isopropyl-pyrazole-3-carboxamide (Compound P13) as a beige solid.

LCMS (Method 1): 401 [M+H], Rt: 0.94min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.80 (1 H, br. s), 7.52 (1 H, d, J=2.18 Hz), 7.47 (1 H, br. s), 7.44 (1 H, d, J=2.54 Hz), 7.00 (1 H, s), 5.28-5.39 (1 H, m), 2.23 (3 H, s), 1.38 (6 H, d, J=6.54 Hz).

Example 33: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-ethyl-pyrazole-3-carboxamide (Compound P14)



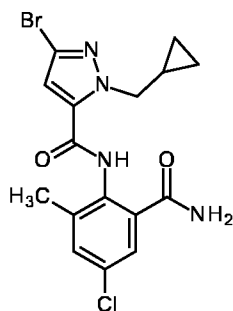
(Compound P14)

The desired product was prepared as described for example 21 using iodoethane CAS 75-03-6 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-ethyl-pyrazole-3-carboxamide (Compound P14) (175 mg, 0.454 mmol, 93% yield) as a beige solid.

5 LCMS (Method 1): 387 [M+H], Rt: 0.88min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.06 (s, 1 H) 7.80 (br s, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.45 - 7.49 (m, 1 H) 7.42 - 7.45 (m, 1 H) 7.06 (s, 1 H) 4.45 (q, J=7.27 Hz, 2 H) 2.22 (s, 3 H) 1.31 (t, J=7.27 Hz, 3 H).

10 **Example 34: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(cyclopropylmethyl)pyrazole-3-carboxamide (Compound P15)**



(Compound P15)

The desired product was prepared as described for example 21 using 1-(Bromomethyl)cyclopropane CAS 7051-34-5 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-

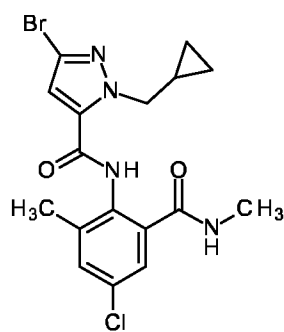
15 (cyclopropylmethyl)pyrazole-3-carboxamide (Compound P15) as a brown solid.

LCMS (Method 1): 413 [M+H], Rt: 0.94min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.01 - 10.17 (m, 1 H) 7.74 - 7.88 (m, 1 H) 7.46 - 7.49 (m, 1 H) 7.41 - 7.55 (m, 2 H) 7.07 - 7.12 (m, 1 H) 4.28 - 4.36 (m, 2 H) 2.19 - 2.26 (m, 3 H) 1.22 - 1.33 (m, 1 H) 0.31 - 0.51 (m, 4 H)

20

Example 35: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclopropylmethyl)pyrazole-3-carboxamide (Compound P16)



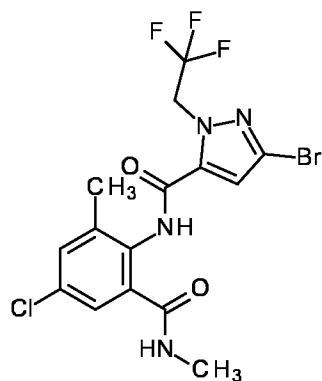
(Compound P16)

The desired product was prepared as described for example 23 using 1-(Bromomethyl)cyclopropane CAS 7051-34-5 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclopropylmethyl)pyrazole-3-carboxamide (Compound P16) as a white solid.

5 LCMS (Method 1): 427 [M+H], Rt: 1.00min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.32 (1 H, br. q, J=4.72 Hz), 7.51 (1 H, d, J=2.18 Hz), 7.40 (1 H, br. s), 7.38 (1 H, d, J=2.18 Hz), 7.07 (1 H, s), 4.30 (2 H, d, J=7.27 Hz), 2.66 (3 H, d, J=4.72 Hz), 2.22 (3 H, s), 1.21-1.31 (1 H, m), 0.42-0.47 (2 H, m), 0.31-0.35 (2 H, m).

10 **Example 36: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2,2-trifluoroethyl)pyrazole-3-carboxamide (Compound P23)**



(Compound P23)

The desired product was prepared as described for example 23 using 2,2,2-trifluoroethyl trifluoromethanesulfonate CAS 6226-25-1 to afford 5-bromo-N-[4-chloro-2-methyl-6-

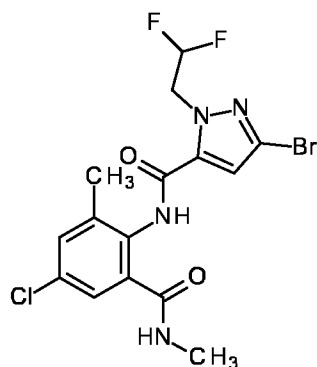
15 (methylcarbamoyl)phenyl]-2-(2,2,2-trifluoroethyl)pyrazole-3-carboxamide (Compound P23) as a white solid.

LCMS (Method 1): 455 [M+H], Rt: 1.02min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.13 - 10.31 (m, 1 H) 8.21 - 8.40 (m, 1 H) 7.46 - 7.58 (m, 1 H) 7.35 - 7.45 (m, 1 H) 7.19 - 7.34 (m, 1 H) 5.39 - 5.56 (m, 2 H) 2.64 - 2.69 (m, 3 H) 2.18 - 2.22 (m, 3 H)

20

Example 37: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P25)



(Compound P25)

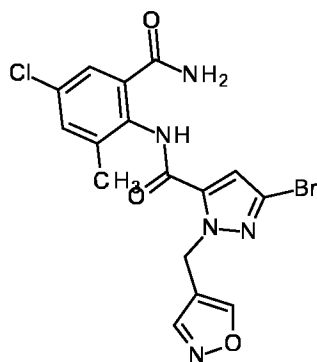
The desired product was prepared as described for example 22 using 2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one, preparation described in example 3 step 3 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P25) as a white solid.

LCMS (Method 1): 437 [M+H], Rt: 0.94min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.13 - 10.25 (m, 1 H) 8.23 - 8.39 (m, 1 H) 7.51 - 7.54 (m, 1 H) 7.39 - 7.42 (m, 1 H) 7.15 - 7.21 (m, 1 H) 6.35 (m, 1 H) 4.95 (m, 2 H) 2.68 (m, 3 H) 2.23 (s, 3 H)

¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -122.67 (s, CHF₂)

Example 38: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(isoxazol-4-ylmethyl)pyrazole-3-carboxamide (Compound P30)



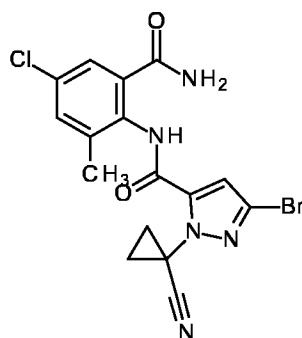
(Compound P30)

The desired product was prepared as described for example 21 using 4-(bromomethyl)-1,2-oxazole CAS 6455-40-9 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(isoxazol-4-ylmethyl)pyrazole-3-carboxamide (Compound P30) as a brown solid.

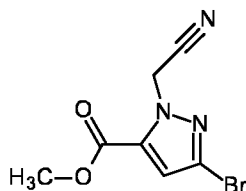
LCMS (Method 1): 440 [M+H], Rt: 0.86min.

¹H NMR (400 MHz, DMSO) δ ppm 10.17 (s, 1 H) 8.96 (s, 1 H) 8.58 (s, 1 H) 7.86 (br s, 1 H) 7.53 (d, J=2.18 Hz, 1 H) 7.47 - 7.51 (m, 1 H) 7.44 - 7.47 (m, 1 H) 7.13 (s, 1 H) 5.58 (s, 2 H) 2.22 (s, 3 H).

Example 39: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1-cyanocyclopropyl)pyrazole-3-carboxamide (Compound P31)



Step 1: Preparation of methyl 5-bromo-2-(cyanomethyl)pyrazole-3-carboxylate

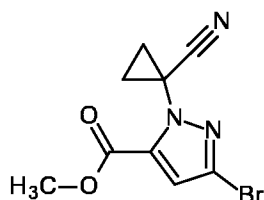


To a suspension of methyl 5-bromo-1H-pyrazole-3-carboxylate, CAS 1328893-17-9 (1.10 g, 5.31 mmol) and potassium carbonate (1.11g, 7.97 mmol) in acetonitrile (32 mL) was added dropwise chloroacetonitrile CAS 107-14-2 (0.407 mL, 6.37 mmol). The mixture was stirred at 70°C for 1h. Then ethyl acetate was added, followed by sat. aq. NaHCO₃. The aq. phase was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound (0.98 g, 4.0 mmol, 76% yield) as a white solid.

LCMS (Method 1): 244 [M+H], Rt: 0.80 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 6.91 (s, 1 H) 5.48 (s, 2 H) 3.95 (s, 3 H).

Step 2: Preparation of methyl 5-bromo-2-(1-cyanocyclopropyl)pyrazole-3-carboxylate

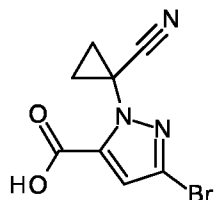


To a colorless solution of methyl 5-bromo-2-(cyanomethyl)pyrazole-3-carboxylate (400 mg, 1.64 mmol) and 1,2-dibromoethane CAS 106-93-4 (0.202 mL, 2.29 mmol) in DMF (6.56 mL) was added in 3 portions every 15 min at rt, sodium hydride (60% in oil, 0.164 g, 4.10 mmol). The yellowish solution was stirred at rt for 1h. The crude was slowly quenched with water and diluted with ethyl acetate. It was extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was purified by chromatography using a CH/EA gradient to afford the desired compound (65 mg, 0.24 mmol, 15% yield) as a white solid.

LCMS (Method 1): 270 [M+H], Rt: 0.87 min.

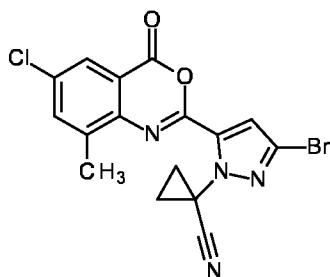
¹H NMR (400 MHz, CDCl₃) δ ppm 6.89 (s, 1 H) 3.96 (s, 3 H) 1.90 - 1.96 (m, 2 H) 1.83 - 1.89 (m, 2 H).

Step 3: Preparation of 5-bromo-2-(1-cyanocyclopropyl)pyrazole-3-carboxylic acid



The desired product was prepared as described for example 3 step 2 using 4 methyl 5-bromo-2-(1-cyanocyclopropyl)pyrazole-3-carboxylate (65 mg, 0.24 mmol) to afford 5-bromo-2-(1-cyanocyclopropyl)pyrazole-3-carboxylic acid (60 mg, 0.23 mmol, 97% yield) as a white solid. LCMS (Method 1): 256 [M-H], Rt: 0.66 min.

Step 4: Preparation of 1-[3-bromo-5-(6-chloro-8-methyl-4-oxo-3,1-benzoxazin-2-yl)pyrazol-1-yl]cyclopropanecarbonitrile



The desired product was prepared as described for example 3 step 3 using 5-bromo-2-(1-cyanocyclopropyl)pyrazole-3-carboxylic acid (60 mg, 0.23 mmol) to afford 1-[3-bromo-5-(6-chloro-8-methyl-4-oxo-3,1-benzoxazin-2-yl)pyrazol-1-yl]cyclopropanecarbonitrile (110 mg, 0.217 mmol, 93% yield) as a beige solid.

LCMS (Method 1): 405 [M-H], Rt: 1.15 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (d, J=2.91 Hz, 1 H) 7.70 (dd, J=2.54, 0.73 Hz, 1 H) 7.15 (s, 1 H) 2.72 (s, 3 H) 1.94 - 2.06 (m, 4 H).

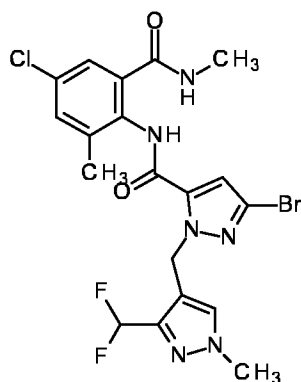
Step 5: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1-cyanocyclopropyl)pyrazole-3-carboxamide (Compound P31)

The desired compound was prepared as described for example 2 step 2 using 1-[3-bromo-5-(6-chloro-8-methyl-4-oxo-3,1-benzoxazin-2-yl)pyrazol-1-yl]cyclopropanecarbonitrile (85 mg, 0.21 mmol) to afford the desired compound (50 mg, 0.12 mmol, 56% yield) as an orange gum.

LCMS (Method 1): 424 [M-H], Rt: 0.83 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 - 7.56 (m, 2 H) 6.95 - 6.96 (m, 1 H) 5.88 - 6.07 (m, 1 H) 5.45 - 5.85 (m, 2 H) 2.16 (s, 3 H) 1.88 - 2.01 (m, 2 H) 1.57 - 1.70 (m, 2 H).

Example 40: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[[3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl]pyrazole-3-carboxamide (Compound P32)



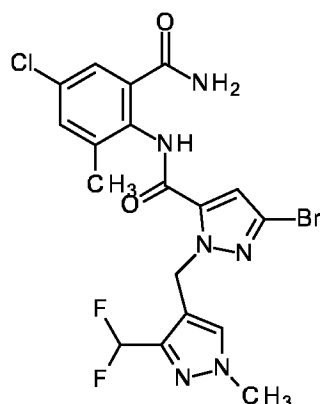
(Compound P32)

The desired product was prepared as described for example 23 using 4-(bromomethyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole CAS 1089212-38-3 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[[3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl]pyrazole-3-carboxamide (Compound P32) as a beige solid.

LCMS (Method 1): 517 [M+H], Rt: 0.94min.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.29 - 2.31 (m, 3 H) 2.96 - 2.99 (m, 3 H) 3.86 - 3.89 (m, 3 H) 5.72 - 5.75 (m, 2 H) 6.12 - 6.18 (m, 1 H) 6.66 - 6.96 (m, 2 H) 7.31 - 7.33 (m, 1 H) 7.39 - 7.42 (m, 1 H) 7.42 - 7.45 (m, 1 H) 9.93 - 10.02 (m, 1 H)

Example 41: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-[[3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl]pyrazole-3-carboxamide (Compound P33)



(Compound P33)

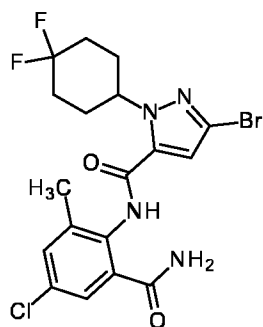
The desired product was prepared as described for example 21 using 4-(bromomethyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole CAS 1089212-38-3 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-[[3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl]pyrazole-3-carboxamide (Compound P33) as a beige solid.

LCMS (Method 1): 503 [M+H], Rt: 0.90min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.12 (s, 1 H) 7.84 (s, 1 H) 7.68 (s, 1 H) 7.53 (d, J=2.18 Hz, 1 H) 7.42 - 7.49 (m, 2 H) 6.86 - 7.16 (m, 2 H) 5.63 (s, 2 H) 3.82 (s, 3 H) 2.20 (s, 3 H).

^{19}F NMR (377 MHz, DMSO- d_6) δ ppm -111.18 (-CHF₂).

Example 42: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorocyclohexyl)pyrazole-3-carboxamide (Compound P34)



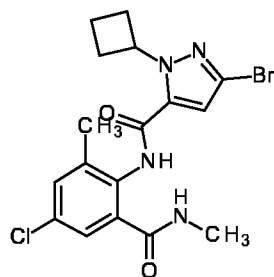
(Compound P34)

The desired product was prepared as described for example 21 using 4-bromo-1,1-difluorocyclohexane CAS 1196156-51-0 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorocyclohexyl)pyrazole-3-carboxamide (Compound P34) as a beige solid.

LCMS (Method 1): 477 [M+H], Rt: 1.02min.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.09 - 10.15 (m, 1 H) 7.74 - 7.85 (m, 1 H) 7.39 - 7.54 (m, 2 H) 7.45 - 7.49 (m, 1 H) 7.00 - 7.07 (m, 1 H) 5.06 - 5.18 (m, 1 H) 2.21 - 2.25 (m, 3 H) 1.89 - 2.19 (m, 9 H)

Example 43: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclobutylpyrazole-3-carboxamide (Compound P35)



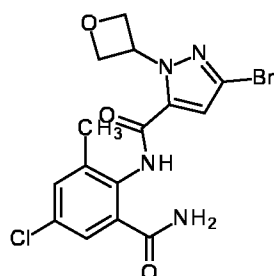
(Compound P35)

The desired product was prepared as described for example 23 using bromocyclobutane CAS 4399-47-7 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclobutylpyrazole-3-carboxamide as a solid.

LCMS (Method 1): 425 [M+H], Rt: 1.04min.

^1H NMR (400 MHz, CDCl₃) δ ppm 9.87 - 10.00 (m, 1 H) 7.28 - 7.39 (m, 2 H) 6.79 - 6.85 (m, 1 H) 6.11 - 6.23 (m, 1 H) 5.56 - 5.68 (m, 1 H) 2.92 - 3.00 (m, 3 H) 2.62 - 2.77 (m, 2 H) 2.35 - 2.49 (m, 2 H) 2.25 - 2.33 (m, 2 H) 1.72 - 1.94 (m, 2 H)

Example 44: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(oxetan-3-yl)pyrazole-3-carboxamide (Compound P36)



(Compound P36)

The desired product was prepared as described for example 21 using 3-bromooxetane

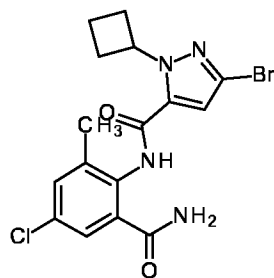
CAS 39267-79-3 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(oxetan-3-yl)pyrazole-3-carboxamide (Compound P36).

5 LCMS (Method 1): 415 [M+H], Rt: 0.77min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.30 - 10.45 (m, 1 H) 7.91 - 8.04 (m, 1 H) 7.58 - 7.71 (m, 1 H) 7.42 - 7.58 (m, 2 H) 6.96 - 7.05 (m, 1 H) 5.66 - 5.85 (m, 1 H) 4.89 - 5.11 (m, 4 H) 2.14 - 2.30 (m, 3 H)

Example 45: Synthesis of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclobutylpyrazole-3-carboxamide (Compound P37)

10



(Compound P37)

The desired product was prepared as described for example 21 using bromocyclobutane

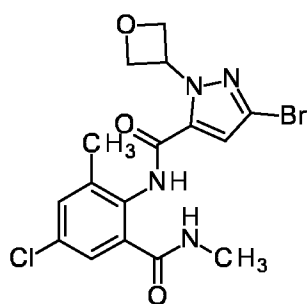
CAS 4399-47-7 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclobutylpyrazole-3-carboxamide (Compound P37) as a solid.

15 LCMS (Method 1): 413 [M+H], Rt: 0.97min.

¹H NMR (400 MHz, CDCl₃) δ ppm 9.82 - 9.91 (m, 1 H) 7.36 - 7.46 (m, 2 H) 6.76 - 6.82 (m, 1 H) 5.93 - 6.15 (m, 1 H) 5.55 - 5.70 (m, 2 H) 2.62 - 2.76 (m, 2 H) 2.36 - 2.47 (m, 2 H) 2.27 - 2.35 (m, 3 H) 1.70 - 1.93 (m, 2 H)

Example 46: Synthesis of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(oxetan-3-yl)pyrazole-3-carboxamide (Compound P38)

20



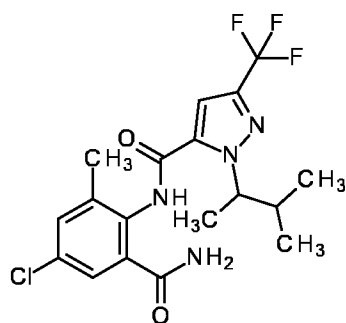
(Compound P38)

The desired product was prepared as described for example 21 using 3-bromooxetane CAS 39267-79-3 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(oxetan-3-yl)pyrazole-3-carboxamide (Compound P38).

5 LCMS (Method 1): 429 [M+H], Rt: 0.81min.

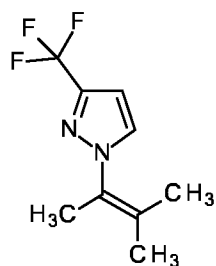
¹H NMR (400 MHz, CDCl₃) δ ppm 9.58 - 9.67 (m, 1 H) 7.30 - 7.37 (m, 2 H) 6.92 - 6.95 (m, 1 H) 6.23 - 6.32 (m, 1 H) 5.63 - 5.72 (m, 1 H) 5.22 - 5.29 (m, 2 H) 5.00 - 5.08 (m, 2 H) 2.87 - 2.92 (m, 3 H) 2.28 - 2.34 (m, 3 H)

10 **Example 47: Synthesis of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P41)**



(Compound P41)

Step 1: Preparation of 1-(1,2-dimethylprop-1-enyl)-3-(trifluoromethyl)pyrazole



15 Under argon, a 250mL flask was charged with copper iodide (5.60g, 29.4 mmol), potassium carbonate (8.13g, 58.8 mmol) and 3-(trifluoromethyl)-1H-pyrazole, CAS 99 20154-03-4, (4.0g, 29.4 mmol). Toluene (150mL) was added followed by N,N'-dimethylethane-1,2-diamine (6.39 mL, 58.8 mmol) and 2-bromo-3-methyl-but-2-ene, cas 3017-70-7, (5.13 mL, 44.1 mmol). The mixture was stirred overnight at 100°C. The suspension was cooled down to rt, then filtered twice over celite. The filtrate was

20 evaporated and the crude was purified by chromatography using a cyclohexane/ethyl acetate gradient to afford the desired compound

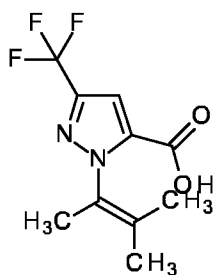
LCMS (Method 1): 205 [M+H], Rt: 1.04min.

^1H NMR (400 MHz, CDCl_3) δ ppm 7.36 - 7.44 (m, 1 H) 6.53 - 6.59 (m, 1 H) 2.09 - 2.14 (m, 3 H) 1.85 - 1.88 (m, 3 H) 1.52 - 1.55 (m, 3 H)

^{19}F NMR (376 MHz, CDCl_3) δ ppm -61.84 (s, CF_3)

5

Step 2: Preparation of 2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid



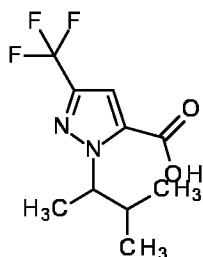
To a solution of 1-(1,2-dimethylprop-1-enyl)-3-(trifluoromethyl)pyrazole (1.43g, 7.0 mmol) in THF (30 mL) was slowly added at -65°C a solution of LDA (2M in THF/ethyl benzene, 4.2 mL, 8.40 mmol). The mixture was stirred at -65°C for 4h. CO_2 was bubbled through the solution over 20min, then the mixture was stirred overnight at rt. The solvent was partially removed under vacuum, then water and few NaOH was added. Then the aqueous layer was extracted with TBME. The aqueous layer was acidified with HCl (1M) and extracted with ethyl acetate. The organic layer was dried over MgSO_4 , filtered and evaporated to afford the desired crude product (1.6g, 93% yield). No further purification was done.

LCMS (Method 1): 249 [M+H], Rt: 0.92min.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 13.16 - 14.46 (br.s, 1 H) 7.30 (s, 1 H) 1.94 - 2.03 (m, 3 H) 1.74 - 1.86 (m, 3 H) 1.18 - 1.26 (m, 3 H)

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm -60.68 (s, CF_3)

Step 3: Preparation of 2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid



To a solution of 2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid (500mg, 2.01 mmol) in trifluoroethanol (8 mL) was added 1,1'-Bis(di-i-propylphosphino)ferrocene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (100g, 0.201 mmol). The suspension was purged with argon. Then it was stirred overnight at 50°C under hydrogen (50bars). Then, it was evaporated and the resulting black solid was treated with NaOH (0.5N, 50mL), extracted with TBME. The aqueous phase was acidified with HCl (1N) and extracted with TBME with few Me-THF. The resulting organic

25

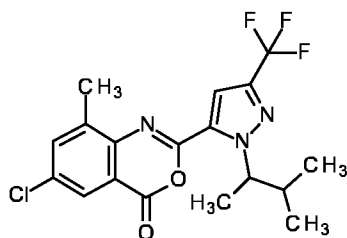
layer was dried over MgSO₄, filtered, and evaporated under vacuum to afford the desired compound (455 mg, 91% yield) as an orange solid.

LCMS (Method 1): 251 [M+H], Rt: 1.02min.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.17 - 7.20 (m, 1 H) 5.12 - 5.21 (m, 1 H) 2.19 - 2.27 (m, 1 H) 1.49 - 1.57 (m, 3 H) 0.96 - 1.05 (m, 3 H) 0.67 - 0.76 (m, 3 H)

¹⁹F NMR (376 MHz, CDCl₃) δ ppm -62.22 (s, CF₃)

Step 4: Preparation of 6-chloro-2-[2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



The desired product was prepared as described for example 1 step 3 using 2-amino-5-chloro-3-methylbenzoic acid CAS 20776-67-4 (326 mg, 1.76 mmol) and 2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid (440 mg, 1.76 mmol) to afford 6-chloro-2-[2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (530 mg, 1.32 mmol, 75%).

LCMS (Method 1): 400 [M+H], Rt: 1.37min.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.04 - 8.12 (m, 1 H) 7.65 - 7.73 (m, 1 H) 7.30 - 7.34 (m, 1 H) 5.61 - 5.71 (m, 1 H) 2.58 - 2.65 (m, 3 H) 2.32 - 2.43 (m, 1 H) 1.58 - 1.63 (m, 3 H) 1.04 - 1.10 (m, 3 H) 0.74 - 0.81 (m, 3 H)

Step 5: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P41)

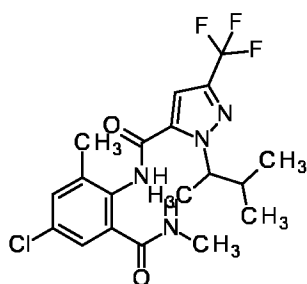
The desired product was prepared as described for example 21 step 5 using 6-chloro-2-[2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (280 mg, 0.70 mmol) to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P41) (243 mg, 0.583 mmol, 83% yield) as a white solid.

LCMS (Method 1): 417 [M+H], Rt: 1.10min.

¹H NMR (400 MHz, CDCl₃) δ ppm 9.87 - 9.97 (m, 1 H) 7.35 - 7.47 (m, 2 H) 7.01 - 7.08 (m, 1 H) 5.65 - 6.21 (m, 2 H) 5.08 - 5.22 (m, 1 H) 2.27 - 2.39 (m, 3 H) 2.16 - 2.27 (m, 1 H) 1.42 - 1.58 (m, 3 H) 0.94 - 1.03 (m, 3 H) 0.64 - 0.76 (m, 3 H)

¹⁹F NMR (376 MHz, CDCl₃) δ ppm -61.94 (s, CF₃)

Example 48: Synthesis of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P42)



(Compound P42)

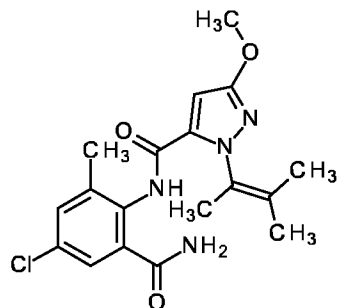
The desired product was prepared as described for example 22 using 6-chloro-2-[2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one, preparation described in example 47 step 4, (280 mg, 0.70 mmol) to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P42) (243 mg, 0.583 mmol, 83% yield) as a white solid.

LCMS (Method 1): 431 [M+H], Rt: 1.15 min.

^1H NMR (400 MHz, CDCl_3) δ ppm 9.88 - 10.00 (m, 1 H) 7.33 - 7.42 (m, 1 H) 7.03 - 7.17 (m, 1 H) 6.13 - 6.27 (m, 1 H) 5.08 - 5.21 (m, 1 H) 2.90 - 3.00 (m, 4 H) 2.26 - 2.35 (m, 4 H) 2.14 - 2.26 (m, 1 H) 1.46 - 1.58 (m, 4 H) 0.94 - 1.04 (m, 3 H) 0.63 - 0.77 (m, 3 H)

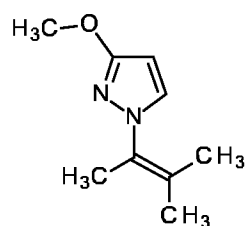
^{19}F NMR (376 MHz, CDCl_3) δ ppm -61.96 (m, 3 F)

Example 49: Synthesis of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide (Compound P43)



(Compound P43)

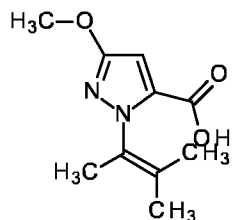
Step 1: Preparation of 1-(1,2-dimethylprop-1-enyl)-3-methoxy-pyrazole



The desired product was prepared as described in example 47 step 1 using 3-methoxy-1H-pyrazole CAS 215610-30-3 to afford 1-(1,2-dimethylprop-1-enyl)-3-methoxy-pyrazole as a colorless oil.

LCMS (Method 1): 167 [M+H], Rt: 0.89 min.

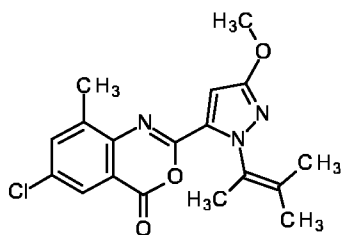
^1H NMR (400 MHz, CDCl_3) δ ppm 7.12 - 7.17 (m, 1 H) 5.67 - 5.72 (m, 1 H) 3.93 - 3.97 (m, 3 H) 2.04 - 2.09 (m, 3 H) 1.80 - 1.86 (m, 3 H) 1.57 - 1.63 (m, 3 H)

Step 2: Preparation of 2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxylic acid

The desired product was prepared as described in example 47 step 2 using 1-(1,2-dimethylprop-1-enyl)-3-methoxy-pyrazole to afford 2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxylic acid as a gum.

LCMS (Method 1): 211 [M+H], Rt: 0.89 min.

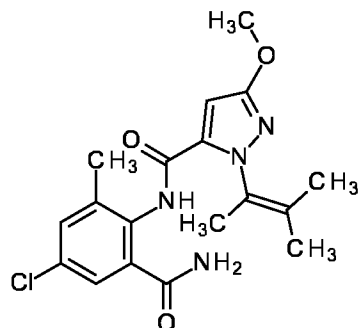
¹H NMR (400 MHz, acetone) δ ppm 6.21 - 6.27 (m, 1 H) 3.81 - 3.86 (m, 3 H) 1.93 - 1.99 (m, 3 H) 1.74 - 1.80 (m, 3 H) 1.32 (d, J=1.45 Hz, 3 H)

Step 3: Preparation of 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one

The desired product was prepared as described in example 47 step 4 using 2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxylic acid to afford 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one as beige solid.

LCMS (Method 1): 360 [M+H], Rt: 1.24 min.

¹H NMR (400 MHz, DMSO) δ ppm 7.98 - 8.09 (m, 1 H) 7.59 - 7.67 (m, 1 H) 6.47 - 6.52 (m, 1 H) 3.88 - 4.00 (m, 3 H) 2.46 - 2.53 (m, 3 H) 2.09 - 2.17 (m, 3 H) 1.85 - 1.90 (m, 3 H) 1.38 - 1.47 (m, 3 H)

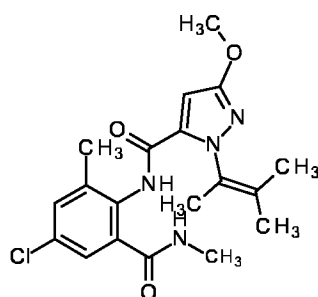
Step 4: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide

The desired product was prepared as described in example 47 step 5 using 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide (Compound P43) as a white solid.

5 LCMS (Method 1): 377 [M+H], Rt: 0.90 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 9.52 - 9.59 (m, 1 H) 7.34 - 7.39 (m, 2 H) 6.25 - 6.29 (m, 1 H) 5.63 - 6.20 (m, 2 H) 3.91 - 3.97 (m, 3 H) 2.25 - 2.28 (m, 3 H) 2.06 - 2.11 (m, 3 H) 1.81 - 1.84 (m, 3 H) 1.44 - 1.49 (m, 3 H)

10 **Example 50: Synthesis of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide (Compound P44)**



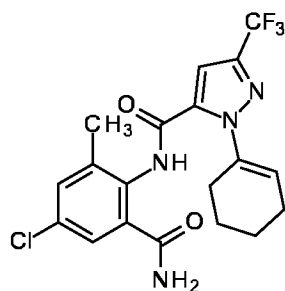
(Compound P44)

The desired product was prepared as described in example 22 using 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one, preparation of the starting material is described in example 49 step 3 (300 mg, 0.833 mmol) to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide (Compound P44) (112mg, 0.286 mmol, 34% yield) as a yellow solid.

LCMS (Method 1): 391 [M+H], Rt: 0.95 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 9.57 - 9.63 (m, 1 H) 7.25 - 7.27 (m, 1 H) 7.21 (d, J=2.54 Hz, 1 H) 6.36 - 6.44 (m, 1 H) 6.30 - 6.33 (m, 1 H) 3.91 - 3.95 (m, 3 H) 2.88 (d, J=4.72 Hz, 4 H) 2.19 - 2.25 (m, 3 H) 2.06 - 2.09 (m, 3 H) 1.80 - 1.85 (m, 3 H) 1.44 - 1.47 (m, 3 H)

Example 51: Synthesis of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P45)



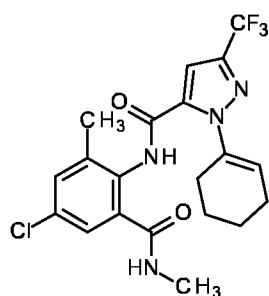
(Compound P45)

The desired product was prepared as described in example 49, using 3-(trifluoromethyl)-1H-pyrazole CAS 20154-03-4 and 1-bromocyclohexene CAS 2044-08-8, to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.20 - 10.33 (m, 1 H) 7.78 - 7.90 (m, 1 H) 7.47 - 7.51 (m, 1 H) 7.42 - 7.55 (m, 3 H) 5.88 - 5.97 (m, 1 H) 3.27 - 3.36 (m, 1 H) 2.35 - 2.44 (m, 2 H) 2.21 - 2.27 (m, 2 H) 2.12 - 2.20 (m, 2 H) 1.69 - 1.79 (m, 2 H) 1.53 - 1.66 (m, 2 H)

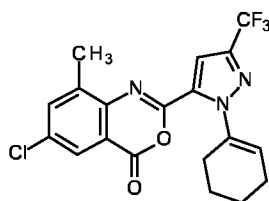
¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -60.73 (s, CF₃)

Example 52: Synthesis of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P46)



(Compound P46)

Step 1: Preparation of 6-chloro-2-[2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



The desired product was prepared as described in example 49 step 1 to 3, using 3-(trifluoromethyl)-1H-pyrazole CAS 20154-03-4 and 1-bromocyclohexene CAS 2044-08-8 in step 1, to afford 6-chloro-2-[2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one as an off-white solid.

LCMS (Method 1): 410 [M+H], Rt: 1.33 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.03 - 8.10 (m, 1 H) 7.63 - 7.71 (m, 1 H) 7.31 - 7.38 (m, 1 H) 5.96 - 6.05 (m, 1 H) 2.59 - 2.64 (m, 3 H) 2.50 - 2.58 (m, 2 H) 2.25 - 2.33 (m, 2 H) 1.91 - 1.98 (m, 2 H) 1.73 - 1.83 (m, 2 H) 1.53 - 1.61 (m, 2 H)

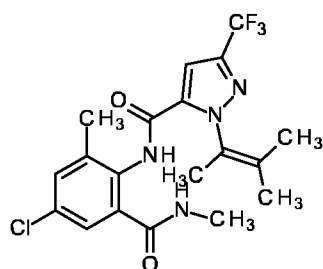
¹⁹F NMR (376 MHz, CDCl₃) δ ppm -62.38 (m, 3 F)

Step 2: Preparation of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P46)

The desired product was prepared as described in example 22, using 6-chloro-2-[2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (250mg, 0.610 mmol) to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide (251 mg, 93% yield) as a white solid.

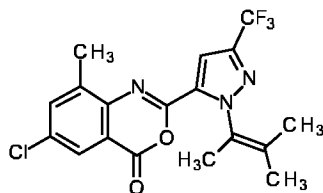
- 5 ^1H NMR (400 MHz, CDCl_3) δ ppm 9.91 - 10.00 (m, 1 H) 7.32 - 7.41 (m, 1 H) 7.09 - 7.18 (m, 1 H) 6.18 - 6.31 (m, 1 H) 5.92 - 6.10 (m, 1 H) 2.88 - 3.03 (m, 3 H) 2.42 - 2.55 (m, 2 H) 2.28 (s, 3 H) 2.20 - 2.26 (m, 2 H) 1.81 - 1.91 (m, 2 H) 1.66 - 1.76 (m, 2 H) 1.56 - 1.64 (m, 1 H)
- ^{19}F NMR (376 MHz, CDCl_3) δ ppm -62.15 (s, CF_3)

10 **Example 53: Preparation of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P47)**



(Compound P47)

Step 1: Preparation of 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



15

The desired product was prepared as described in example 47 step 4, using 2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid, preparation described in example 47 step 2, (430 mg, 1.56 mmol), preparation described in example 44 step 2, to afford 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (530 mg, 1.33 mmol, 85% yield) as a white solid.

20

LCMS (Method 1): 398 $[\text{M}+\text{H}]$, R_t : 1.29 min.

^1H NMR (400 MHz, CDCl_3) δ ppm 8.04 - 8.08 (m, 1 H) 7.64 - 7.69 (m, 1 H) 7.35 - 7.38 (m, 1 H) 2.49 - 2.55 (m, 3 H) 2.16 - 2.21 (m, 3 H) 1.90 - 1.94 (m, 3 H) 1.35 - 1.39 (m, 3 H)

^{19}F NMR (376 MHz, CDCl_3) δ ppm -62.33 (s, 3 F)

25

Step 2: Preparation of N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P47)

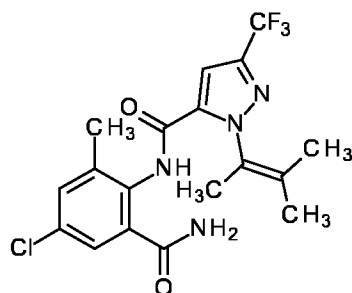
The desired product was prepared as described in example 22 using 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (150mg, 0.377 mmol), to afford N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P47) (114mg, 0.266 mmol, 70% yield) as a white solid.

LCMS (Method 1): 429 [M+H], Rt: 1.07 min.

^1H NMR (400 MHz, CDCl_3) δ ppm 9.86 - 9.97 (m, 1 H) 7.33 - 7.39 (m, 1 H) 7.26 - 7.28 (m, 1 H) 7.17 - 7.22 (m, 1 H) 6.17 - 6.24 (m, 1 H) 2.89 - 3.00 (m, 3 H) 2.22 - 2.31 (m, 3 H) 2.10 - 2.20 (m, 3 H) 1.83 - 1.91 (m, 3 H) 1.39 - 1.45 (m, 3 H)

^{19}F NMR (376 MHz, CDCl_3) δ ppm -62.09 (s, 3 F)

Example 54: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P48)



(Compound P48)

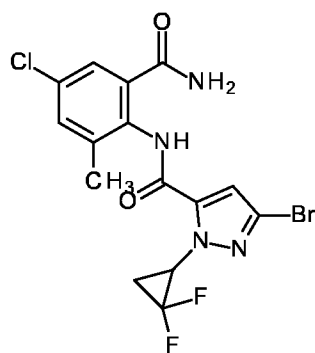
The desired product was prepared as described in example 1 step 4, using 6-chloro-2-[2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one, preparation described in example 53 step 1 (250 mg, 0.628 mmol) to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (185 mg, 0.446 mmol, 71% yield) as a white solid.

LCMS (Method 1): 415 [M+H], Rt: 1.02 min.

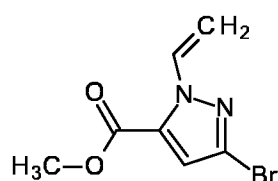
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.12 - 10.22 (m, 1 H) 7.74 - 7.88 (m, 1 H) 7.51 - 7.53 (m, 1 H) 7.47 - 7.50 (m, 1 H) 7.42 - 7.45 (m, 1 H) 7.36 - 7.41 (m, 1 H) 2.21 (s, 3 H) 2.00 - 2.03 (m, 3 H) 1.74 - 1.80 (m, 3 H) 1.26 - 1.34 (m, 3 H)

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm -60.64 (s, CF_3)

Example 55: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxamide (Compound P49)



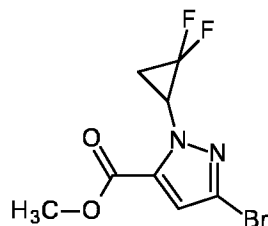
(Compound P49)

Step 1: Preparation of methyl 5-bromo-2-vinyl-pyrazole-3-carboxylate

To a solution of methyl 5-bromo-1H-pyrazole-3-carboxylate, CAS 1328893-17-9 (1.00g, 4.83 mmol) and vinylboronic acid dibutyl ester, CAS 6336-45-4 (1.3 mL, 5.79 mmol) in DCE (14.5 mL) and pyridine (1.97 mL) was added copper acetate (1.85g, 9.66 mmol). The green mixture was stirred at 70°C for 4h. The mixture was diluted with ethyl acetate and quenched with sat.aq. NaHCO₃. The aqueous layer was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na₂SO₄, filtered and evaporated. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound as white solid (0.370g, 1.60 mmol, 33% yield).

LCMS (Method 1): 231 [M+H], Rt: 0.95 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.92 (dd, *J*=15.26, 8.72 Hz, 1 H) 6.89 (s, 1 H) 5.91 (dd, *J*=15.26, 0.73 Hz, 1 H) 5.01 (d, *J*=8.72 Hz, 1 H) 3.90 (s, 3 H).

Step 2: Preparation of methyl 5-bromo-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxylate

A solution of methyl 5-bromo-2-vinyl-pyrazole-3-carboxylate (60 mg, 0.26 mmol) and NaI (0.16 g, 1.0 mmol) in ACN (2.1 mL) was stirred at 80°C and Trimethyl(trifluoromethyl)silane CAS 480635 (0.19 mL, 1.3 mmol) was added dropwise. The mixture was stirred at 80°C for 3h. The reaction mixture was diluted with EA and quenched with water. The aq. layer was extracted with EA and the combined org. layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude was purified by

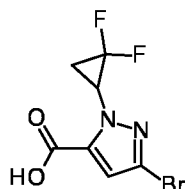
flash chromatography using a CH/EA gradient to afford the desired compound as a white solid (42 mg, 0.15 mmol, 58% yield).

LCMS (Method 1): 281 [M+H], Rt: 0.95 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 6.88 (s, 1 H) 4.36 (dddd, J=10.35, 8.36, 6.18, 2.00 Hz, 1 H) 3.93 (s, 3 H) 2.47 (ddt, J=13.81, 9.81, 5.81, 5.81 Hz, 1 H) 2.05 - 2.17 (m, 1 H).

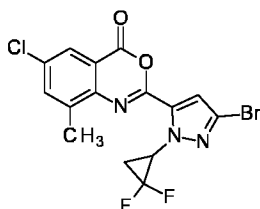
¹⁹F NMR (377 MHz, CDCl₃) δ ppm -132.04 (d, J=163.41 Hz, 1 F) -144.08 (d, J=163.59 Hz, 1 F).

Step 3: Preparation of 5-bromo-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxylic acid



- 10 The desired product was prepared as described for example 1 step 2, using methyl 5-bromo-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxylate (80 mg, 0.28 mmol) to afford 5-bromo-2-(3,3-difluoropropyl)pyrazole-3-carboxylic acid (70 mg, 0.26 mmol, 92% yield) as a beige solid.
LCMS (Method 1): 265 [M+H], Rt: 0.75 min.

- 15 Step 4: Preparation of 2-[5-bromo-2-(2,2-difluorocyclopropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



- The desired product was prepared as described for example 1 step 3 using 2-amino-5-chloro-3-methylbenzoic acid CAS 20776-67-4 (50 mg, 0.26 mmol) and 5-bromo-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxylic acid (70 mg, 0.26 mmol) to afford 2-[5-bromo-2-(2,2-difluorocyclopropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (68 mg, 0.16 mmol, 62%).
LCMS (Method 1): 418 [M+H], Rt: 1.23min.
¹H NMR (400 MHz, CDCl₃) δ ppm 8.06 (d, J=2.54 Hz, 1 H) 7.64 - 7.69 (m, 1 H) 7.12 (s, 1 H) 4.68 (dddd, J=10.17, 8.08, 5.90, 2.00 Hz, 1 H) 2.60 - 2.69 (m, 1 H) 2.58 (s, 3 H) 2.15 - 2.24 (m, 1 H).
25 ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -129.89 (d, J=162.49 Hz, 1 F) -144.47 (d, J=162.50 Hz, 1 F).

Step 5: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxamide (Compound P49)

- The desired product was prepared as described for example 1 step 4 using 2-[5-bromo-2-(2,2-difluorocyclopropyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (85 mg, 0.16 mmol) to afford

5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxamide (55 mg, 0.13 mmol, 78% yield) as a brown solid.

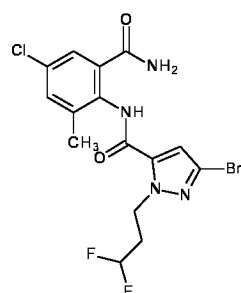
LCMS (Method 1): 435 [M+H], Rt: 0.91min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (s, 1 H) 7.82 (br s, 1 H) 7.53 (d, J=2.18 Hz, 1 H) 7.47 -

5 7.50 (m, 1 H) 7.44 - 7.47 (m, 1 H) 7.18 (s, 1 H) 4.64 (br d, J=8.36 Hz, 1 H) 2.29 - 2.40 (m, 2 H) 2.22 (s, 3 H).

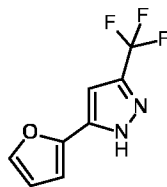
¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -131.01 (d, J=159.75 Hz, 1 F) -142.28 (d, J=159.74 Hz, 1 F).

Example 56: Preparation of N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P57)



(Compound P57)

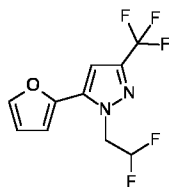
Step 1: Preparation of 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole



To a solution of hydrazine hydrate (2.35 mL, 48.51 mmol) in acetic acid (20 mL) was added 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (5g, 24.26 mmol) at 0°C. The reaction mixture was stirred at 80°C for 5h. The reaction was concentrated under vacuum and the residue was dissolved in water (200mL), extracted with EA (2 * 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated. The crude was purified by reverse phase chromatography to afford 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole (4g, 19.78 mmol, 81% yield) as an off white solid.

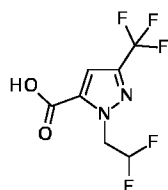
MS (method 3): M+H+=203

Step 2: Preparation of 1-(2,2-difluoroethyl)-5-(2-furyl)-3-(trifluoromethyl)pyrazole



To a solution of 5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazole (200mg, 0.989 mmol) in DMF (20mL) was added dipotassium carbonate (2.05g, 14.8mmol) and 1,1-difluoro-2-iodo-ethane (1.90g, 9.89 mmol) at 0°C. The reaction mixture was stirred at rt for 12h. Then water (30 mL) was added and extracted with
 5 EA (2*50mL). The combined organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude was purified several times by flash chromatography using a CH/EA gradient to afford 1-(2,2-difluoroethyl)-5-(2-furyl)-3-(trifluoromethyl)pyrazole (130mg, 0.488 mmol, 49% yield) as an off-white solid.

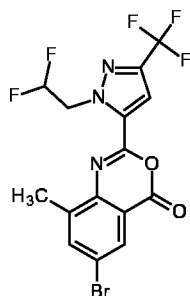
Step 3: Preparation of 2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid



To a solution of 1-(2,2-difluoroethyl)-5-(2-furyl)-3-(trifluoromethyl)pyrazole (3.60g, 13.5 mmol) in acetone (50 mL) was added an aqueous solution of Potassium dihydrogen phosphate (9.20g, 67.62 mmol) and potassium permanganate (10.69g, 67.62 mmol) at -5°C. The reaction mixture was stirred at the same temperature for 5h. The suspension was filtered, and the filtrate pH was adjusted to 2 by
 15 adding aq. HCl (1N), then it was diluted with water (100 mL), extracted with EA (2*200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography using a DCM/MeOH gradient to afford 2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid (2.20g, 9.01 mmol, 66.6% yield) as an off-white solid.

20 MS (method 3): M+H+=203

Step 4: Preparation of 6-bromo-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



The desired product was prepared as described for example 1 step 3 using 2-Amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 (153 mg, 0.645 mmol) and 2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxylic acid (150 mg, 0.61 mmol) to afford 6-bromo-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (255 mg, 0.58 mmol, 95%).

LCMS (Method 1): 440 [M+H], Rt: 1.21min.

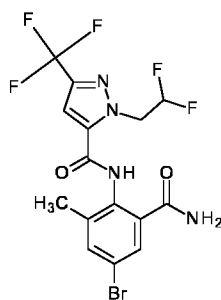
Step 5: Preparation of N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P57)

The desired product was prepared as described for example 22 using 6-bromo-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (125 mg, 0.285 mmol) to afford N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P57) (119 mg, 0.253 mmol, 89%).

LCMS (Method 1): 471 [M+H], Rt: 1.01min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.24 - 10.40 (m, 1 H) 8.25 - 8.40 (m, 1 H) 7.48 - 7.72 (m, 3 H) 6.40 (tt, J=1.00 Hz, 1 H) 5.08 (td, J=1.00 Hz, 2 H) 2.68 (d, J=1.00 Hz, 4 H) 2.23 (s, 3 H)

Example 57: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P58)



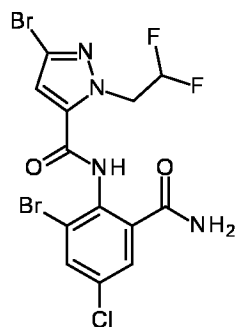
(Compound P58)

The desired product was prepared as described for example 1 step 4 using 6-bromo-2-[2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one, preparation described in example 56 step 4, (125 mg, 0.285 mmol) to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (74 mg, 0.162 mmol, 57%).

LCMS (Method 1): 457 [M+H], Rt: 0.97min.

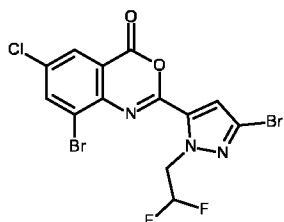
¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.32 (s, 1 H) 7.84 (s, 1 H) 7.64 - 7.71 (m, 1 H) 7.46 - 7.62 (m, 3 H) 6.41 (tt, J=1.00 Hz, 1 H) 5.09 (td, J=1.00 Hz, 2 H) 2.23 (s, 3 H)

5 **Example 58: Preparation of 5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P59)**



(Compound P59)

Step 1: Preparation of 8-bromo-2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-3,1-benzoxazin-4-one



10

The desired product was prepared as described for example 1 step 3 using 5-bromo-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, preparation described in example 3 step 2 (150 mg, 0.588 mmol), and 2-Amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 (159mg, 0.62 mmol) to afford 8-bromo-2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-3,1-benzoxazin-4-one (220 mg, 80% yield) as a yellow solid.

15

LCMS (Method 1): 470 [M+H], Rt: 1.19 min.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.10 - 8.23 (m, 2 H) 7.17 - 7.22 (m, 1 H) 6.17 - 6.49 (m, 1 H) 5.28 - 5.38 (m, 2 H)

20 **Step 2: Preparation of 5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P59)**

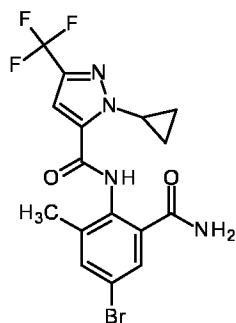
The desired product was prepared as described for example 1 step 4 using 8-bromo-2-[5-bromo-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-3,1-benzoxazin-4-one (100 mg, 0.213 mmol) to afford 5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P59) (51 mg, 0.105 mmol, 49%).

25

LCMS (Method 1): 487 [M+H], Rt: 0.91min.

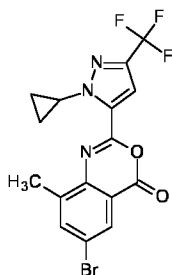
¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.34 - 10.49 (m, 1 H) 7.19 - 8.06 (m, 5 H) 6.33 (m, 1 H) 4.93 (m, 2 H)

Example 59: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P60)



(Compound P60)

Step 1: Preparation of 6-bromo-2-[2-cyclopropyl-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one

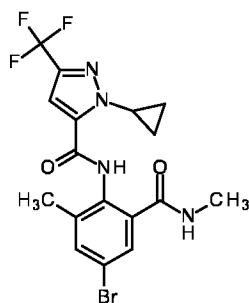


- 10 The desired product was prepared as described in example 1 step 3 using 2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxylic acid, preparation described in example 11 step 3 (150 mg, 0.68 mmol) and 2-amino-5-bromo-3-methyl-benzoic acid CAS 206548-13-2 (165 mg, 0.715 mmol) to afford 6-bromo-2-[2-cyclopropyl-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (275 mg, 0.66 mmol, 97% yield).
- 15 LCMS (Method 1): 416 [M+H], Rt: 1.30min.

Step 2: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P60)

- The desired product was prepared as described in example 1 step 4 using 6-bromo-2-[2-cyclopropyl-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (160 mg, 0.386 mmol) to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (compound P60) (112 mg, 0.259 mmol, 67% yield)
- 20 LCMS (Method 1): 433 [M+H], Rt: 0.98min.
- ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.11 - 10.25 (m, 1 H) 7.79 - 7.92 (m, 1 H) 7.29 - 7.71 (m, 4 H)
- 25 4.31 - 4.52 (m, 1 H) 2.21 - 2.31 (m, 3 H) 0.94 - 1.23 (m, 4 H)

Example 60: Preparation of N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P61)



(Compound P61)

The desired product was prepared as described for example 23 using 6-bromo-2-[2-cyclopropyl-5-(trifluoromethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one, preparation described in example 59 step 1, to afford N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide (Compound P61).

LCMS (Method 1): 445 [M+H], Rt: 1.03min.

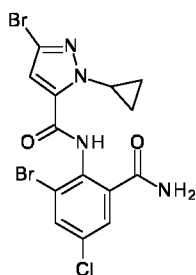
¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.99 - 10.26 (m, 1 H) 8.22 - 8.43 (m, 1 H) 7.61 - 7.72 (m, 1 H)

7.47 - 7.58 (m, 1 H) 7.27 - 7.39 (m, 1 H) 4.29 - 4.46 (m, 1 H) 2.65 - 2.73 (m, 3 H) 2.19 - 2.30 (m, 3 H)

0.97 - 1.23 (m, 4 H)

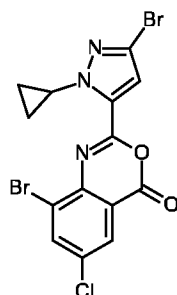
¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -60.56 (s, CF₃)

Example 61: Preparation of 5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P62)



(Compound P62)

Step 1: Preparation of 8-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-6-chloro-3,1-benzoxazin-4-one



The desired product was prepared as described for example 7 step 1 using 5-bromo-2-cyclopropyl-pyrazole-3-carboxylic acid (90 mg, 0.389 mmol) (example 1, step 2) and 2-Amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 (102 mg, 0.397 mmol) to afford 8-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-6-chloro-3,1-benzoxazin-4-one (135 mg, 0.303 mmol, 78% yield).

5 LCMS (Method 1): 446 [M+H], Rt: 1.29min.

^1H NMR (400 MHz, CDCl_3) δ ppm 8.19 - 8.22 (m, 1 H) 8.08 - 8.12 (m, 1 H) 7.09 - 7.12 (m, 1 H) 4.61 - 4.70 (m, 1 H) 1.34 - 1.41 (m, 2 H) 1.19 - 1.27 (m, 2 H)

^{19}F NMR (376 MHz, CDCl_3) δ ppm -49.98 (s, CF_3)

10 **Step 2: Preparation of 5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P62)**

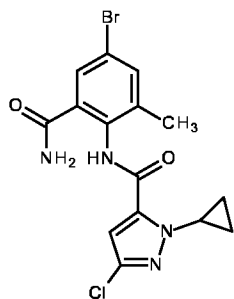
The desired product was prepared as described for example 1 step 4 using 8-bromo-2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-6-chloro-3,1-benzoxazin-4-one (120 mg, 0.269 mmol) to afford 5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P62) (75 mg, 0.162 mmol, 60% yield).

15 LCMS (Method 1): 463 [M+H], Rt: 0.91min.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.22 - 10.29 (m, 1 H) 7.98 - 8.04 (m, 1 H) 7.81 - 7.87 (m, 1 H) 7.62 - 7.66 (m, 1 H) 7.52 - 7.62 (m, 1 H) 6.99 - 7.09 (m, 1 H) 4.24 - 4.36 (m, 1 H) 1.07 - 1.14 (m, 2 H) 0.94 - 1.03 (m, 2 H)

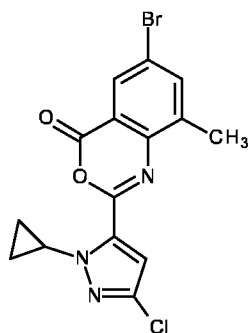
20

Example 62: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P68)



(Compound P68)

Step 1: Preparation of 6-bromo-2-(5-chloro-2-cyclopropyl-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one



25

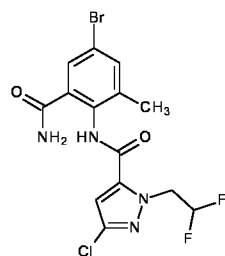
5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid (0.250 mmol) was dissolved in acetonitrile (0.5 mL). Then, a solution of 2-amino-5-bromo-3-methyl-benzoic acid CAS 206548-13-2 (0.250 mmol) in acetonitrile (1 mL) and pyridine (0.0817 mL) was added followed by methanesulonyl chloride (0.05mL). The mixture was stirred at rt for 2h. Solvent was evaporated. Ethyl ester (2mL) was added followed by water (2mL). The bi-phasic suspension was stirred vigorously for 2min. The phases were separated. The extraction was repeated 3 times. The combined organic layers were combined and dried under a nitrogen flow. The crude desired material was used as such in the following step.

Step 2: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P68)

6-bromo-2-(5-chloro-2-cyclopropyl-pyrazol-3-yl)-8-methyl-3,1-benzoxazin-4-one (0.250 mmol) was dissolved in ethyl acetate (1.5 mL) and diammonium carbonate (240 mg, 2.5 mmol) was added to the solution. The reaction was stirred at 80°C for 2h. Solvent was evaporated. Ethyl ester (2 mL) and water (2 mL) were added. The bi-phasic suspension was stirred vigorously for 2min. The phases were separated. The extraction was repeated 3 times. The combined organic layers were combined and dried under a nitrogen flow. The crude was purified by prep HPLC to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P68).

LCMS (Method 2): 397 [M+H], Rt: 0.69min.

Example 63: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P69)

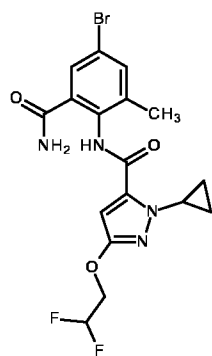


(Compound P69)

The desired compound was prepared as described for example 62 (step 1 and 2) using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid CAS 1006486-42-5, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P69).

LCMS (Method 2): 403.99 [M+H], Rt: 1.08min.

Example 64: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P70)

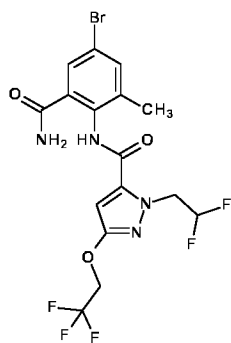


(Compound P70)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxylic acid to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P70)

LCMS (Method 2): 443 [M+H], Rt: 0.72min.

Example 65: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P71)

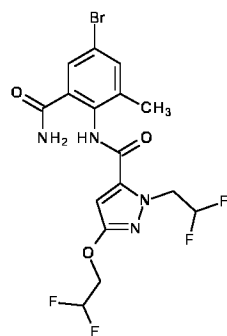


(Compound P71)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid in step 1, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P71)

LCMS (Method 2): 485 [M+H], Rt: 0.80min.

Example 66: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P72)

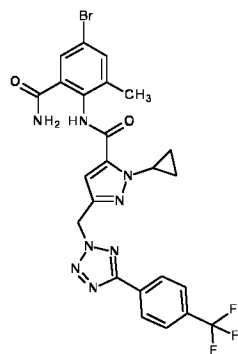


(Compound P72)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P72).

LCMS (Method 2): 467 [M+H], Rt: 0.73min.

Example 67: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P73)

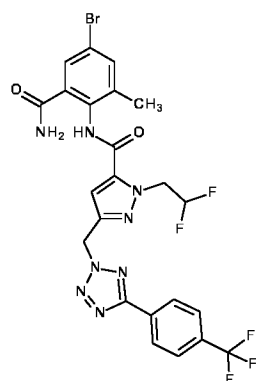


(Compound P73)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P73).

LCMS (Method 2): 589 [M+H], Rt: 0.97min.

Example 68: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P74)

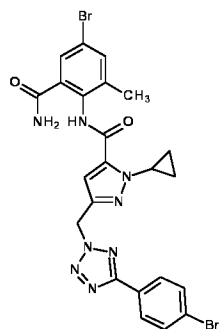


(Compound P74)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P74).

LCMS (Method 2): 613 [M+H], Rt: 0.95 min.

Example 69: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P75)

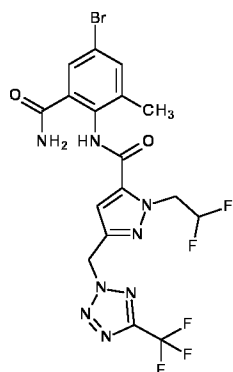


(Compound P75)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P75).

LCMS (Method 2): 599 [M+H], Rt: 0.95 min.

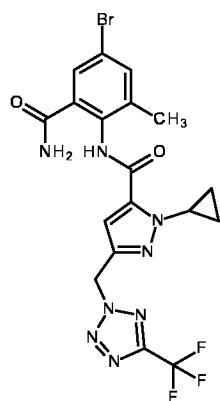
Example 70: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P76)



(Compound P76)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P76). LCMS (Method 2): 537 [M+H], Rt: 0.78 min.

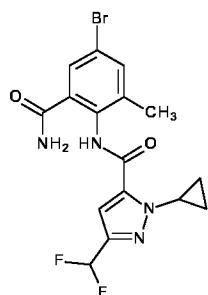
Example 71: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P77)



(Compound P77)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P77). LCMS (Method 2): 513 [M+H], Rt: 0.82 min.

Example 72: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-(difluoromethyl)pyrazol-3-carboxamide (Compound P78)

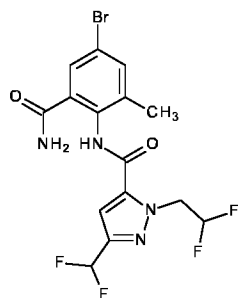


(Compound P78)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P78).

LCMS (Method 2): 413 [M+H], Rt: 0.69 min.

Example 73: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P79)

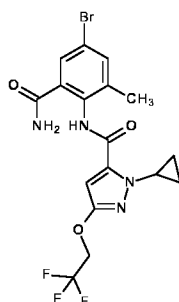


(Compound P79)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid in step 1, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P79).

LCMS (Method 2): 437 [M+H], Rt: 0.69 min.

Example 74: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P80)



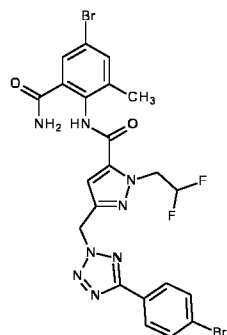
(Compound P80)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to

afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P80).

LCMS (Method 2): 461 [M+H], Rt: 0.81 min.

5 **Example 75: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P81)**

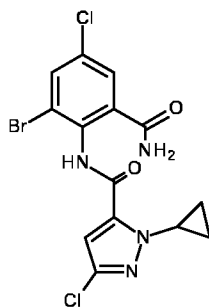


(Compound P81)

The desired compound was prepared as described for example 62 using 2-amino-5-bromo-3-methylbenzoic acid CAS 206548-13-2 and 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P81).

LCMS (Method 2): 623 [M+H], Rt: 0.94 min.

15 **Example 76: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-chloro-2-cyclopropylpyrazole-3-carboxamide (Compound P82)**

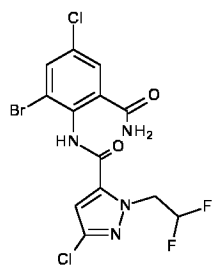


(Compound P82)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 and 5-chloro-2-cyclopropylpyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-chloro-2-cyclopropylpyrazole-3-carboxamide (Compound P82).

LCMS (Method 2): 416 [M+H], Rt: 0.68 min.

25 **Example 77: Preparation of N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P83)**

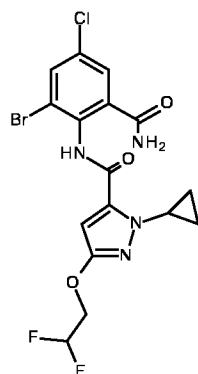


(Compound P83)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 and 5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid CAS 1006486-42-5, to afford N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P83).

LCMS (Method 2): 440 [M+H], Rt: 0.68 min.

Example 78: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P84)

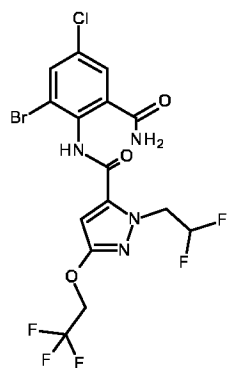


(Compound P84)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P84)

LCMS (Method 2): 463 [M+H], Rt: 0.71min.

Example 79: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P85)



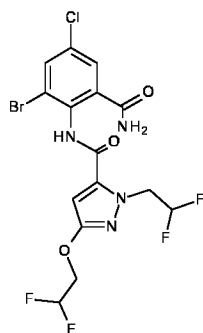
(Compound P85)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 and 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-

5 trifluoroethoxy)pyrazole-3-carboxamide (Compound P85)

LCMS (Method 2): 504 [M+H], Rt: 0.79min.

Example 80: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P86)

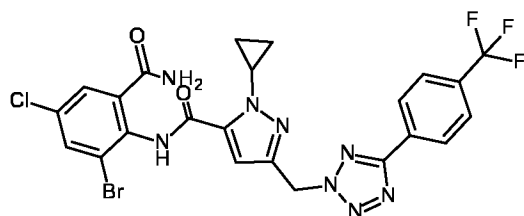


(Compound P86)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chlorobenzoic acid CAS 41198-02-1 and 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P86).

15 LCMS (Method 2): 486 [M+H], Rt: 0.71 min.

Example 81: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P87)

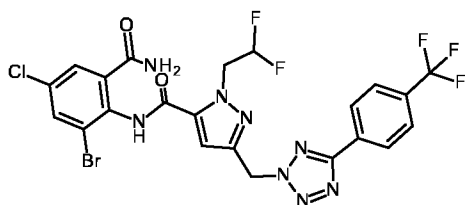


(Compound P87)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P87).

5 LCMS (Method 2): 609 [M+H], Rt: 1.02 min.

Example 82: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P88)

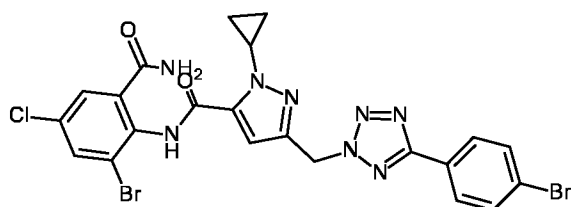


(Compound P88)

10 The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P88).

15 LCMS (Method 2): 633 [M+H], Rt: 0.95 min.

Example 83: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P89)



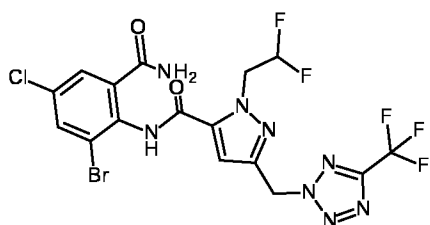
(Compound P89)

20 The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P89).

LCMS (Method 2): 599 [M+H], Rt: 0.95 min.

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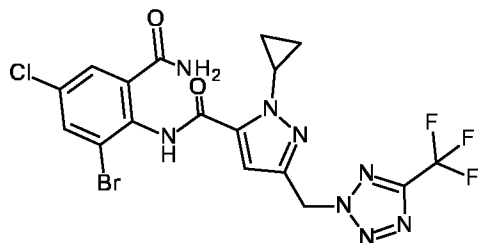
Example 84: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P90)



(Compound P90)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P90).
LCMS (Method 2): 557 [M+H], Rt: 0.82 min.

Example 85: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P91)

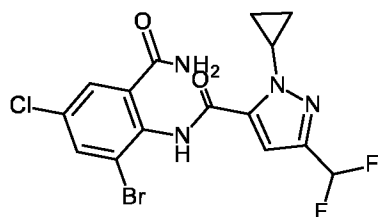


(Compound P91)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P91).

LCMS (Method 2): 533 [M+H], Rt: 0.80 min.

Example 86: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P92)

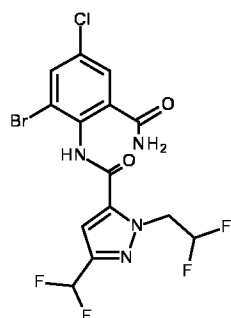


(Compound P92)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P92).

LCMS (Method 2): 433 [M+H], Rt: 0.68 min.

Example 87: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P93)

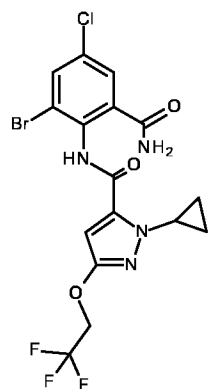


(Compound P93)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P93).

LCMS (Method 2): 456 [M+H], Rt: 0.67 min.

Example 88: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P94)

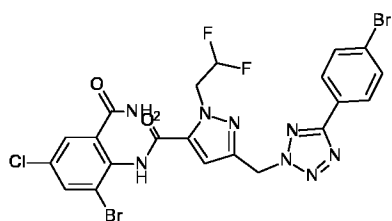


(Compound P94)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P94).

LCMS (Method 2): 480 [M+H], Rt: 0.79 min.

Example 89: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P95)

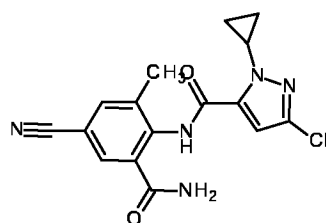


(Compound P95)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P95).

LCMS (Method 2): 643 [M+H], Rt: 0.94 min

Example 90: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P96)

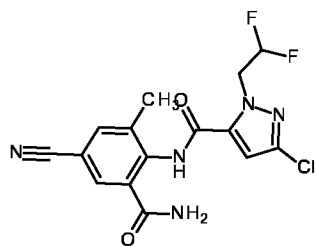


(Compound P96)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P96).

LCMS (Method 2): 344 [M+H], Rt: 0.58 min.

Example 91: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P97)

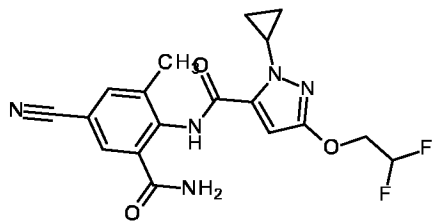


(Compound P97)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid CAS 1006486-42-5, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P97).

LCMS (Method 2): 368 [M+H], Rt: 0.57 min.

Example 92: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P98)



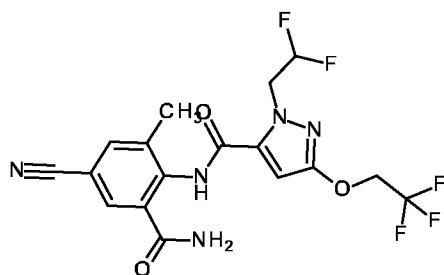
(Compound P98)

- 5 The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P98)

LCMS (Method 2): 390 [M+H], Rt: 0.62 min.

10

Example 93: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P99)

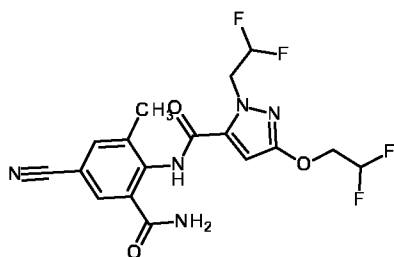


(Compound P99)

- 15 The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P99)

LCMS (Method 2): 432 [M+H], Rt: 0.70 min.

- 20 **Example 94: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P100)**

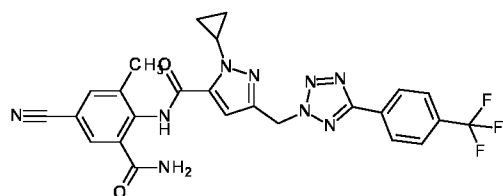


(Compound P100)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P100)).

5 LCMS (Method 2): 390 [M+H], Rt: 0.62 min.

Example 95: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P101)



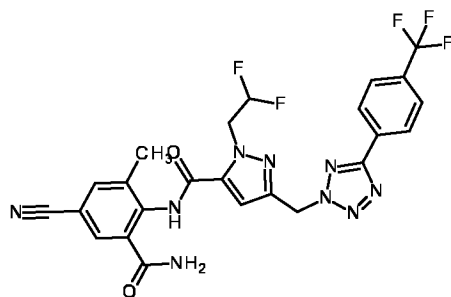
(Compound P101)

10 The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P101).

LCMS (Method 2): 536 [M+H], Rt: 0.94 min.

15

Example 96: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P102)



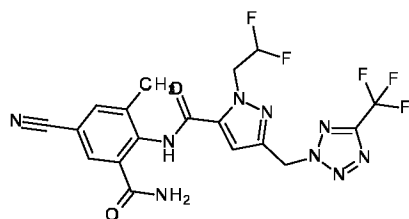
(Compound P102)

20 The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P102).

LCMS (Method 2): 560 [M+H], Rt: 0.91 min.

25

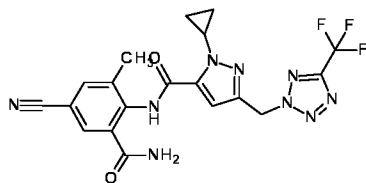
Example 97: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P103)



(Compound P103)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)phenyl]tetrazol-2-yl]methylpyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P103) LCMS (Method 2): 484 [M+H], Rt: 0.71 min.

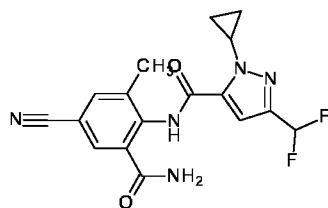
Example 98: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P104)



(Compound P104)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P104). LCMS (Method 2): 460 [M+H], Rt: 0.78 min.

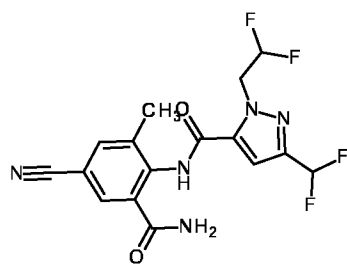
Example 99: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P105)



(Compound P105)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P105). LCMS (Method 2): 360 [M+H], Rt: 0.58 min.

Example 100: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P106)

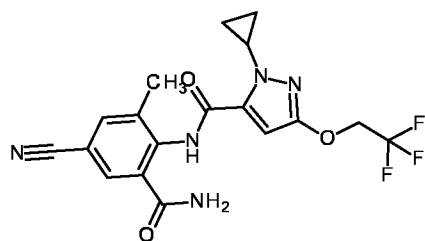


(Compound P106)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P106).

LCMS (Method 2): 384 [M+H], Rt: 0.57 min.

Example 101: Preparation of N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P107)

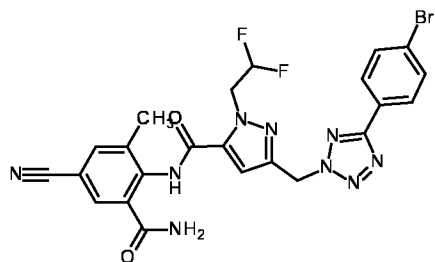


(Compound P107)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P107).

LCMS (Method 2): 407 [M+H], Rt: 0.71 min.

Example 102: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P108)

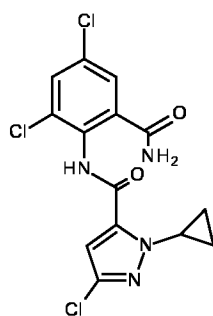


(Compound P108)

The desired compound was prepared as described for example 62 using 2-amino-5-cyano-3-methylbenzoic acid CAS 871239-18-8 and 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-

difluoroethyl)pyrazole-3-carboxylic acid, to afford 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P108)
LCMS (Method 2): 570 [M+H], Rt: 0.86 min

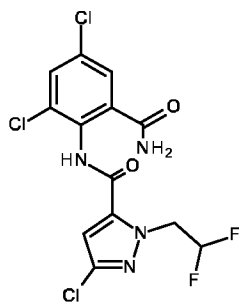
5 **Example 103: Preparation of N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P109)**



(Compound P109)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid, to afford N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P109)
LCMS (Method 2): 372 [M+H], Rt: 0.68 min.

10 **Example 104: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P110)**

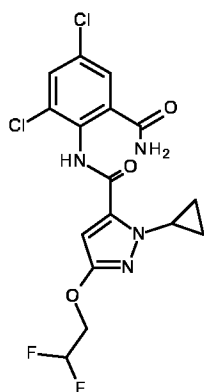


15 (Compound P110)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid CAS 1006486-42-5, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P110).

20 LCMS (Method 2): 396 [M+H], Rt: 0.67 min.

Example 105: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P111)

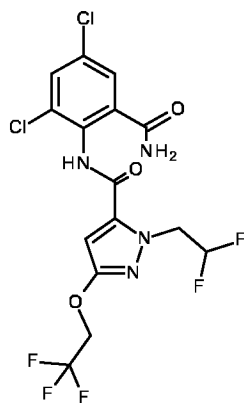


(Compound P111)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide (Compound P111).

LCMS (Method 2): 419 [M+H], Rt: 0.67 min.

Example 106: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P112)

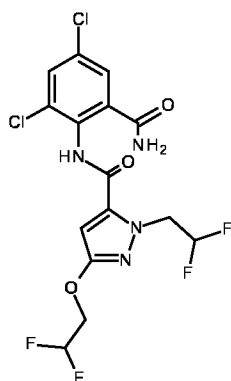


(Compound P112)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P112)

LCMS (Method 2): 461 [M+H], Rt: 0.78 min.

Example 107: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P113)

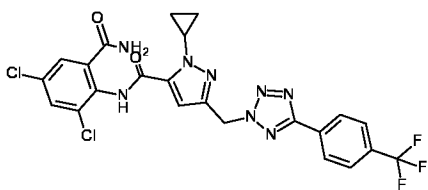


(Compound P113)

The desired compound was prepared as described for example 62 using 2-amino-3-bromo-5-chloro-benzoic acid CAS 41198-02-1 and 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P113).

LCMS (Method 2): 443 [M+H], Rt: 0.71 min.

Example 108: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P114)

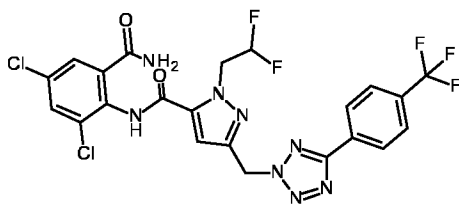


(Compound P114)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P114).

LCMS (Method 2): 565 [M+H], Rt: 1.01 min.

Example 109: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P115)



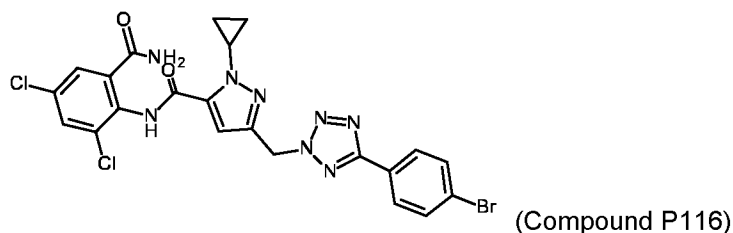
(Compound P115)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-

difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P115)

LCMS (Method 2): 589 [M+H], Rt: 0.93 min.

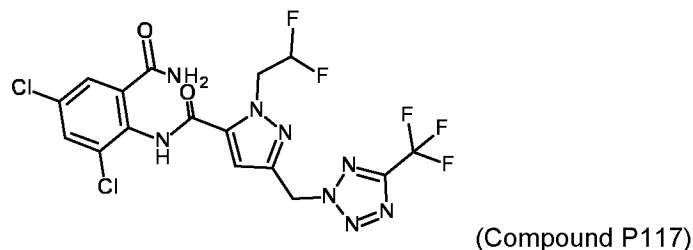
5 **Example 110: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P116)**



The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide (Compound P116).

LCMS (Method 2): 575 [M+H], Rt: 1.00 min.

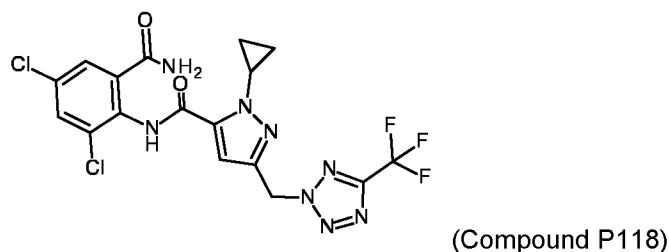
15 **Example 111: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P117)**



The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P117).

LCMS (Method 2): 513 [M+H], Rt: 0.79 min.

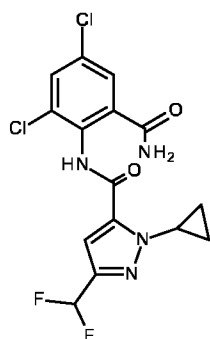
20 **Example 112: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P118)**



The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P118).

5 LCMS (Method 2): 488 [M+H], Rt: 0.79 min.

Example 113: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P119)



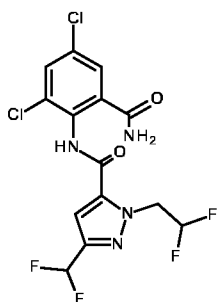
(Compound P119)

10 The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P119).

LCMS (Method 2): 413 [M+H], Rt: 0.67 min.

15

Example 114: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P120)

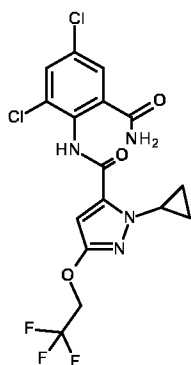


(Compound P120)

20 The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide (Compound P120).

LCMS (Method 2): 413 [M+H], Rt: 0.67 min.

25 **Example 115: Preparation of N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P121)**

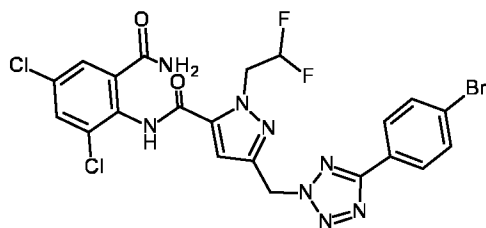


(Compound P121)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid, to afford N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide (Compound P121).

LCMS (Method 2): 437 [M+H], Rt: 0.79 min.

Example 116: Preparation of 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P122)

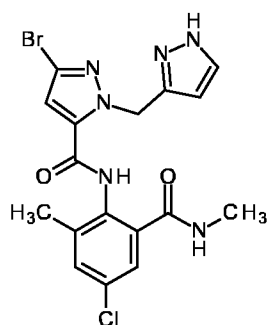


(Compound P122)

The desired compound was prepared as described for example 62 using 2-amino-3,5-dichloro-benzoic acid CAS 2789-92-6 and 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid, to afford 5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P122).

LCMS (Method 2): 599 [M+H], Rt: 0.92 min

Example 117: Preparation of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1H-pyrazol-3-ylmethyl)pyrazole-3-carboxamide (Compound P123)



(Compound P123)

The desired product was prepared as described for example 23 using tert-butyl 3-(bromomethyl)-1H-

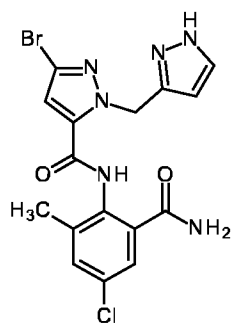
pyrazole-1-carboxylate CAS 186551-69-9 to afford of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1H-pyrazol-3-ylmethyl)pyrazole-3-carboxamide (Compound P123).

LCMS (Method 1): 451 [M+H], Rt: 0.81min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.21 (s, 3 H) 2.67 (d, J=4.72 Hz, 3 H) 5.65 (s, 2 H) 6.08 (d,

5 J=1.82 Hz, 1 H) 7.09 (s, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.59 (br s, 1 H) 8.31 (br d, J=4.36 Hz, 1 H) 10.11 (s, 1 H) 12.62 - 12.78 (br s, 1 H)

Example 118: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1H-pyrazol-3-ylmethyl)pyrazole-3-carboxamide (Compound P124)



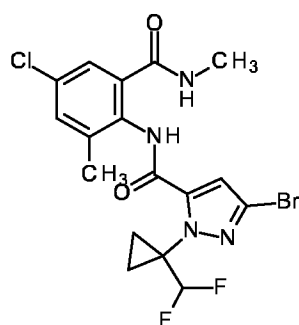
10 (Compound P124)

The desired product was prepared as described for example 21 using tert-butyl 3-(bromomethyl)-1H-pyrazole-1-carboxylate CAS 186551-69-9 to afford of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1H-pyrazol-3-ylmethyl)pyrazole-3-carboxamide (Compound P124).

LCMS (Method 1): 437 [M+H], Rt: 0.77min.

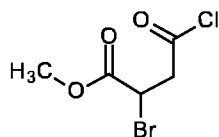
15 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.20 (s, 3 H) 5.66 (s, 2 H) 6.10 (s, 1 H) 7.09 (s, 1 H) 7.36 - 7.67 (m, 4 H) 7.82 (br s, 1 H) 8.17 (br s, 1 H) 10.14 (br s, 1 H).

Example 119: Preparation of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxamide (Compound P125)



20 (Compound P125)

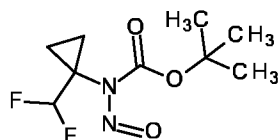
Step 1: Preparation of methyl 2-bromo-4-chloro-4-oxo-butanoate



To a solution of 3-bromo-4-methoxy-4-oxobutanoic acid CAS 98298-19-2 (5.2g, 25 mmol) in ethyl acetate (52 mL) were added DMF (2 drops) slowly followed by oxalyl chloride (3.3 mL, 37 mmol). The reaction was stirred at rt for 2h30. Then the solution was concentrated. The crude material was used as such in the following reaction.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.98 (d, *J*=6.18 Hz, 1 H) 3.12 (d, *J*=8.72 Hz, 1 H) 3.72 (s, 3 H) 4.67 (dd, *J*=8.54, 6.36 Hz, 1 H)

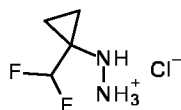
Step 2: Preparation of tert-butyl N-[1-(difluoromethyl)cyclopropyl]-N-nitroso-carbamate



To a solution of tert-butyl N-[1-(difluoromethyl)cyclopropyl]carbamate CAS 1996849-53-6 (980 mg, 4.73 mmol) in acetonitrile (7.09 mL) and pyridine (0.709 mL) was added in two portions at -30°C nitrosonium tetrafluoroborate (828 mg, 7.09 mmol). The mixture was stirred at the same temperature for 45 min. Then it was allowed to warm to 0°C and was stirred at this temperature for 7h. Then, ice (30mL) was added to the reaction followed by EA (50mL). The aq. layer was extracted with EA (2*30 mL). The combined org. layer were washed with aq. HCl (1N, 30mL) then with sat. aq. Na₂CO₃ (30mL), dried over Na₂SO₄, filtered and concentrated to afford tert-butyl N-[1-(difluoromethyl)cyclopropyl]-N-nitroso-carbamate (1.02g, 91% yield) as a yellow solid.

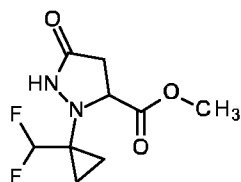
¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.85 - 1.21 (m, 2 H) 1.38 (br s, 2 H) 1.59 (s, 9 H) 5.63 - 5.98 (m, 1 H)

Step 3: Preparation of [[1-(difluoromethyl)cyclopropyl]amino]ammonium chloride



A solution of tert-butyl N-[1-(difluoromethyl)cyclopropyl]-N-nitroso-carbamate (1.8 g, 7.62 mmol) in MeOH (61 mL) was cooled to -78°C and stirred at this temperature for 30min. Then aq. HCl (12M, 6.35 mL, 76.2 mmol) was added dropwise and zinc (4.98 g, 76.2 mmol) was added in 2 portions. The mixture was stirred at -78°C for 4h. Then the suspension was filtered over celite and dried under reduced pressure. The residue was diluted with toluene (10 mL) and dried twice. The sticky solid was triturated with a mixture of TBME/toluene/EA (3:1:1) to afford the crude [[1-

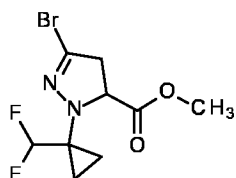
(difluoromethyl)cyclopropyl]amino]ammonium chloride (1.35g, 7.66 mmol, quant) as a beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.89 - 1.10 (m, 4 H) 5.79 - 6.15 (m, 1 H) 6.17 - 6.38 (m, 1 H) 9.00 - 9.27 (m, 3 H)

Step 4: Preparation of methyl 2-[1-(difluoromethyl)cyclopropyl]-5-oxo-pyrazolidine-3-carboxylate

To a solution of [[1-(difluoromethyl)cyclopropyl]amino]ammonium chloride (276 mg, 1.218 mmol) in acetonitrile (1.2 mL) was added at 0°C Na₂CO₃ (339 mg, 4.02 mmol). The beige suspension was stirred at 0°C for 30min. Then methyl 2-bromo-4-chloro-4-oxo-butanoate (279 mg, 1.218 mmol) diluted in acetonitrile (1.2 mL) was added dropwise to the suspension. The reaction was stirred at 0°C for 15min, then at 15°C for 12h. The reaction mixture was cooled with ice and acetic acid was added until pH=6. The mixture was extracted with EA (2 x 20 mL), the combined org. layers were dried over Na₂SO₄, filtered, and concentrated. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound (100mg, 0.427 mmol, 35% yield) as a colorless oil.

LCMS (Method 1): 235 [M+H], Rt: 0.55min.

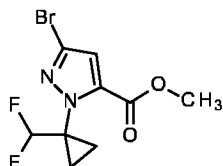
¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.91 (d, J=2.54 Hz, 4 H) 2.34 - 2.40 (m, 1 H) 2.91 - 3.06 (m, 1 H) 3.66 (s, 3 H) 4.30 - 4.49 (m, 1 H) 6.06 - 6.51 (m, 1 H) 9.79 (s, 1 H)

Step 5: Preparation of methyl 5-bromo-2-[1-(difluoromethyl)cyclopropyl]-3,4-dihydropyrazole-3-carboxylate

Under argon, a solution of methyl 2-[1-(difluoromethyl)cyclopropyl]-5-oxo-pyrazolidine-3-carboxylate (300 mg, 1.28 mmol) in acetonitrile (10.2 mL) was cooled at 0°C. N,N-diethylethanamine (0.197 mL, 1.409 mmol) was added dropwise followed 5min after by dropwise addition of POBr₃ (412 mg, 1.409 mmol). The reaction was stirred at 0°C for 3h30. Then ice and EA was added to the reaction. The org. layer was extracted with sat. aq. Na₂CO₃ (20 mL) and the aq. layer was extracted with EA. The combined org. layer were dried over Na₂SO₄, filtered and evaporated to afford the desired compound (313 mg, 1.053 mmol) as a white solid.

LCMS (Method 1): 299 [M+H], Rt: 0.86min.

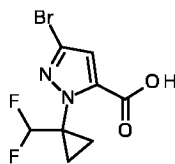
¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.90 - 1.06 (m, 4 H) 3.10 - 3.23 (m, 1 H) 3.40 - 3.56 (m, 1 H) 3.71 (s, 3 H) 4.40 - 4.57 (m, 1 H) 6.06 (s, 1 H)

Step 6: Preparation of methyl 5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxylate

Under Argon, to a solution of methyl 5-bromo-2-[1-(difluoromethyl)cyclopropyl]-3,4-dihydropyrazole-3-carboxylate (300 mg, 1.00 mmol) in acetone (4.04 mL) was added at 0°C potassium permanganate (481.8 mg, 3.03 mmol). The reaction was stirred at 0°C for 2h. The suspension was filtered over celite, and the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound (141 mg, 0.477 mmol, 47% yield) as a white solid.

LCMS (Method 1): 297 [M+H], Rt: 0.94min.

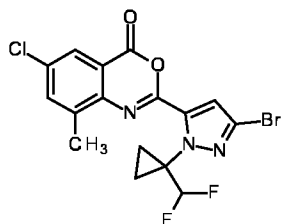
¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.45 - 1.52 (m, 4 H) 3.85 (s, 3 H) 6.09 - 6.45 (m, 1 H) 7.07 - 7.19 (m, 1 H)

Step 7: Preparation of 5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxylic acid

The desired product was prepared as described for example 1 step 2 using methyl 5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxylate (132 mg, 0.447 mmol) to afford of 5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxylic acid (119 mg, 0.409 mmol, 90% yield).

LCMS (Method 1): 283 [M+H], Rt: 0.75min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.15 (s, 3 H) 5.57 (s, 2 H) 7.02 (s, 1 H) 14.02 (s, 1 H)

Step 8: Preparation of 2-[5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one

The desired product was prepared as described for example 1 step 3 using 5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxylic acid (115 mg, 0.409 mmol) and 2-amino-5-chloro-3-methyl-benzoic acid CAS 20776-67-4 (75.95 mg, 0.409 mmol) to afford of 2-[5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (175 mg, 0.406 mmol, 99% yield).

LCMS (Method 1): 432 [M+H], Rt: 1.21 min.

¹H NMR (400 MHz, DMSO-d₆) δ 1.52 - 1.66 (m, 4 H) 2.54 - 2.54 (m, 3 H) 6.45 - 6.86 (m, 1 H) 7.30 (s, 1 H) 7.87 - 8.11 (m, 2 H)

5 **Step 9: Preparation of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxamide (Compound P125)**

The desired product was prepared as described for example 22 using 2-[5-bromo-2-[1-(difluoromethyl)cyclopropyl]pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (80 mg, 0.186 mmol) to afford of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[1-

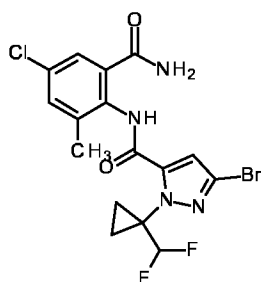
10 (difluoromethyl)cyclopropyl]pyrazole-3-carboxamide (Compound P125) (57 mg, 0.123 mmol, 66% yield).

LCMS (Method 1): 463 [M+H], Rt: 0.97 min.

¹H NMR (400 MHz, DMSO-d₆) 1.33 - 1.48 (m, 4 H) 2.25 (s, 3 H) 2.70 (d, J=4.36 Hz, 3 H) 6.17 - 6.57 (m, 1 H) 7.06 (s, 1 H) 7.34 - 7.59 (m, 2 H) 8.26 - 8.49 (m, 1 H) 9.85 - 10.46 (m, 1 H)

15

Example 120: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxamide (Compound P126)



(Compound P126)

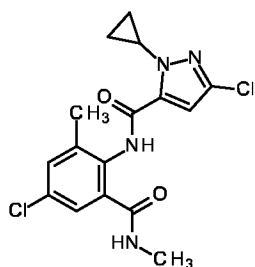
The desired product was prepared as described for example 1 step 4 using 2-[5-bromo-2-[1-

20 (difluoromethyl)cyclopropyl]pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (100 mg, 0.232 mmol) to afford of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxamide (Compound P126) (59 mg, 0.131 mmol, 57% yield).

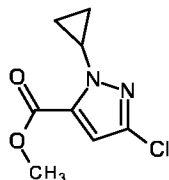
LCMS (Method 1): 449 [M+H], Rt: 0.91 min.

25 ¹H NMR (400 MHz, DMSO-d₆) 1.34 - 1.50 (m, 4 H) 2.21 - 2.27 (m, 3 H) 6.15 - 6.60 (m, 1 H) 6.95 - 7.12 (m, 1 H) 7.38 - 7.64 (m, 3 H) 7.76 - 7.96 (m, 1 H) 10.01 - 10.25 (m, 1 H)

Example 121: Preparation of 5-chloro-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P127)



(Compound P127)

Step 1: Preparation of methyl 5-chloro-2-cyclopropyl-pyrazole-3-carboxylate

To a solution of methyl 3-chloro-1H-pyrazole-5-carboxylate CAS 1810069-85-2 (500 mg, 3.11 mmol),
 5 cyclopropylboronic acid (535 mg, 6.22 mmol) and sodium carbonate (825 mg, 7.78 mmol) in 1,2-
 dichloroethane (12.4 mL) was added 2,2-bipyridine (1.02 g, 6.22 mmol) and copper acetate (1.41 g,
 7.78 mmol). The reaction was stirred overnight at 70°C. The suspension was filtered through celite
 pad, and solid was rinsed with EA. The filtrate was extracted with EA and the org. layer was washed
 with brine and NaHCO₃, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The
 10 crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound
 (282 mg, 1.27 mmol, 40% yield) as a yellow oil.

LCMS (Method 1): 201 [M+H], Rt: 0.94 min.

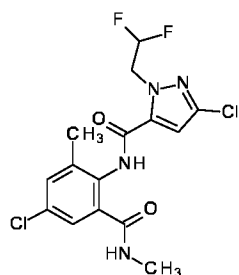
Step 2: Preparation of 5-chloro-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-
 15 pyrazole-3-carboxamide (Compound P127)

The desired product was prepared as described for example 23 step 2 to 4 using methyl 5-chloro-2-
 cyclopropyl-pyrazole-3-carboxylate in step 2, to afford 5-chloro-N-[4-chloro-2-methyl-6-
 (methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P127) as a solid.

20 LCMS (Method 1): 367 [M+H], Rt: 0.93 min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.35 (s, 1 H) 7.48 - 7.57 (m, 1 H) 7.36 - 7.46 (m, 1 H) 6.94 (s, 1
 H) 4.19 - 4.36 (m, 1 H) 2.68 - 2.72 (m, 3 H) 2.25 (s, 3 H) 0.93 - 1.15 (m, 4 H)

Example 122: Preparation of 5-chloro-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-
 25 difluoroethyl)pyrazole-3-carboxamide (Compound P128)



(Compound P128)

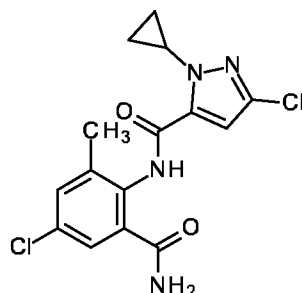
The desired product was prepared as described in example 23, using 1,1-difluoro-2-iodo-ethane CAS 598-39-0 and methyl 3-chloro-1H-pyrazole-5-carboxylate CAS 1810069-85-2 to afford 5-chloro-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P128) as a white solid.

LCMS (Method 1): 391 [M+H], Rt: 0.92 min

^1H NMR (400 MHz, DMSO- d_6) δ ppm 9.68 - 10.44 (m, 1 H) 8.29 - 8.40 (m, 1 H) 7.53 (m, 1 H) 7.42 (m, 1 H) 7.13 (s, 1 H) 6.34 (m, 1 H) 4.94 (m, 2 H) 2.67 (m, 3 H) 2.23 (s, 3 H)

^{19}F NMR (377 MHz, DMSO- d_6) δ ppm -122.62 (s, CF₃)

Example 123: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P129)



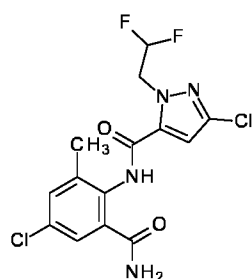
(Compound P129)

The desired product was prepared as described in example 21 step 3 to step 5, using methyl 5-chloro-2-cyclopropyl-pyrazole-3-carboxylate, preparation described in example 121 step 1, to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide (Compound P129) as a solid.

LCMS (Method 1): 354 [M+H], Rt: 0.87 min

^1H NMR (400 MHz, DMSO) δ ppm 0.83 - 1.11 (m, 4 H) 2.16 - 2.28 (m, 3 H) 4.23 - 4.39 (m, 1 H) 6.96 - 7.08 (m, 1 H) 7.39 - 7.57 (m, 3 H) 7.74 - 7.90 (m, 1 H) 9.65 - 10.21 (m, 1 H)

Example 124: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P130)



(Compound P130)

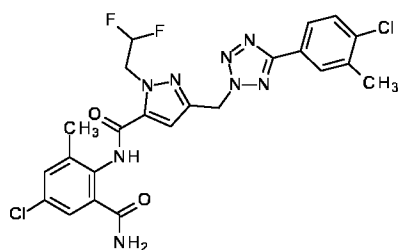
The desired product was prepared as described in example 21 step 2 to step 5, using 1,1-difluoro-2-iodo-ethane CAS 598-39-0 and methyl 3-chloro-1H-pyrazole-5-carboxylate CAS 1810069-85-2, to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P130) as a brown solid.

LCMS (Method 1): 377 [M+H], Rt: 0.88 min

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.23 (s, 1 H) 7.82 (s, 1 H) 7.42 - 7.57 (m, 3 H) 7.14 (s, 1 H) 6.35 (m, 1 H) 4.95 (m, 2 H) 2.22 (s, 3 H)

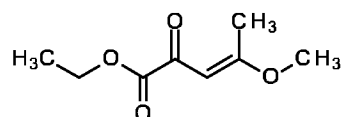
¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -122.55 (s, CF₃)

Example 125: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-[[5-(4-chloro-3-methyl-phenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P131)



(Compound P131)

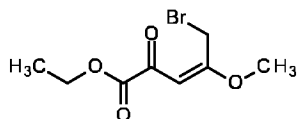
Step 1: Preparation of ethyl (E)-4-methoxy-2-oxo-pent-3-enoate



To a solution of 2-Methoxyprop-1-ene CAS 116-11-0 (10.0 g, 135 mmol) in dichloromethane (200 mL) was added at 0°C pyridine (10.9 mL, 135 mmol) followed by ethyl oxalyl chloride (15.0 mL, 135 mmol). The reaction was stirred at rt for 3h. Then, the reaction mixture was washed with water, then aq. HCL (2N) then brine. The combined aq. layers were extracted with EA. Combined org. layer were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford ethyl (E)-4-methoxy-2-oxo-pent-3-enoate (24.7 g, 143 mmol, quant) as an orange oil. The crude was used as such without further purification.

LCMS (Method 1): 173 [M+H], Rt: 0.74 min

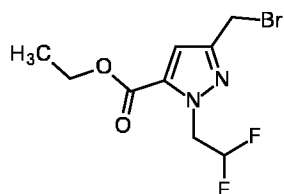
¹H NMR (400 MHz, CDCl₃) δ ppm 6.25 (s, 1 H) 4.31 (q, J=7.02 Hz, 2 H) 3.78 (s, 3 H) 2.39 (s, 3 H) 1.37 (t, J=7.27 Hz, 3 H)

Step 2: Preparation of ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate

To a solution of ethyl (E)-4-methoxy-2-oxo-pent-3-enoate (10 g, 58.1 mmol) in dichloromethane (90 mL) was added dropwise at 0°C a solution of bromine (3 mL, 58.1 mmol) in dichloromethane (30 mL). The reaction was stirred at this temperature for 20min. Then, pyridine (4.7 mL, 58.1 mmol) was added dropwise at 0°C. The reaction was stirred at 0°C for 2h30. Then, the mixture was quenched by adding aq. HCl (2M) and extracted. The aq. layer was extracted with EA. The combined org. layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound (5.21g, 18.7 mmol, 32% yield) as an orange oil.

LCMS (Method 1): 251 [M+H], Rt: 0.85 min

¹H NMR (400 MHz, CDCl₃) δ ppm 6.36 (s, 1 H) 4.49 (s, 2 H) 4.34 (q, J=7.27 Hz, 2 H) 3.86 (s, 3 H) 1.39 (t, J=7.08 Hz, 3 H)

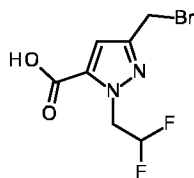
Step 3: Preparation of ethyl 5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxylate

A solution of ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate (2.38 g, 9.48 mmol) and (2,2-difluoroethyl) hydrazine hydrochloride CAS 1504582-53-9 (1.32 g, 9.48 mmol) in acetic acid (23.7 mL) was stirred at rt overnight. The reaction was diluted with EA and washed with water, sat. NaHCO₃, then brine. The combined aq. layers were extracted with EA. The combined org. layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound (200 mg, 0.67 mmol, 7% yield) as a yellowish oil.

LCMS (Method 1): 297 [M+H], Rt: 0.96 min

¹H NMR (400 MHz, CDCl₃) δ ppm 6.96 (s, 1 H) 5.98 - 6.30 (m, 1 H) 4.94 (td, J=13.08, 4.36 Hz, 2 H) 4.46 (s, 2 H) 4.37 (q, J=7.14 Hz, 2 H) 1.39 (t, J=7.27 Hz, 3 H)
¹⁹F NMR (377 MHz, CDCl₃) δ ppm -122.82 (s, -CH₂F)

Step 4: Preparation of 5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid



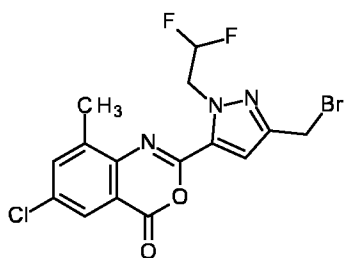
The desired product was prepared as described in example 1 step 2 using ethyl 5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxylate (185 mg, 0.623 mmol) to afford 5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid (168 mg, 0.64 mmol, quant) as a white solid.

5 LCMS (Method 1): 269 [M+H], Rt: 0.69 min

¹H NMR (400 MHz, CDCl₃) δ ppm 7.08 (s, 1 H) 6.15 (tt, J=55.59, 4.36 Hz, 1 H) 4.96 (td, J=13.08, 4.36 Hz, 3 H) 4.48 (s, 2 H)

¹⁹F NMR (377 MHz, CDCl₃) δ ppm -122.79 (s, 1 F)

10 Step 5: Preparation of 2-[5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one



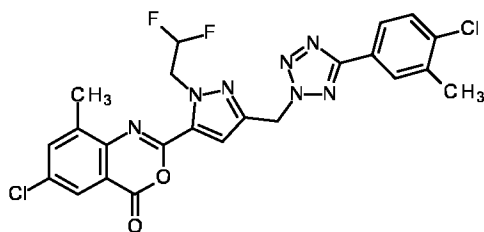
The desired product was prepared as described in example 1 step 3 using 5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid (160 mg, 0.595 mmol) and methyl 3-chloro-1H-pyrazole-5-carboxylate CAS 1810069-85-2 (110 mg, 0.595 mmol) to afford 2-[5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazol-3-yl]-6-chloro-8-methyl-3,1-benzoxazin-4-one (118 mg, 0.282 mmol, 47.4% yield) as yellow solid.

LCMS (Method 1): 420 [M+H], Rt: 1.16 min

¹H NMR (400 MHz, CDCl₃) δ ppm 8.07 (d, J=2.54 Hz, 1 H) 7.69 (d, J=1.82 Hz, 1 H) 7.23 (s, 1 H) 7.22 (s, 1 H) 6.11 - 6.42 (m, 1 H) 5.24 (td, J=12.72, 4.36 Hz, 2 H) 4.64 (s, 2 H) 4.50 (s, 1 H) 2.59 (s, 3 H)

¹⁹F NMR (377 MHz, CDCl₃) δ ppm -122.64 (s, -CH₂F)

Step 6: Preparation of 6-chloro-2-[5-[5-(4-chloro-3-methyl-phenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one



To a suspension of 6-chloro-2-[5-[[5-(4-chloro-3-methyl-phenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (110 mg, 0.294 mmol) in acetonitrile (2.94 mL) was added K₂CO₃ (81.3 mg, 0.588 mmol) and 5-(4-chloro-3-methylphenyl)-2H-tetrazole CAS 41421-29-8 (60.2 mg, 0.294 mmol). The reaction mixture was stirred at 70°C for 3h, then water was added. The aq. layer was extracted twice with EA. The combined org. layers were washed with brine, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified by flash chromatography using a CH/EA gradient to afford the desired compound (32mg, 0.060 mmol, 20% yield) as a white solid.

LCMS (Method 1): 532 [M+H], Rt: 1.31 min

¹H NMR (400 MHz, CDCl₃) δ ppm 8.04 (s, 2 H) 7.91 (dd, J=8.36, 1.82 Hz, 1 H) 7.67 (d, J=1.82 Hz, 1 H) 7.44 (d, J=8.36 Hz, 1 H) 7.19 (s, 1 H) 6.10 - 6.42 (m, 1 H) 5.90 (s, 2 H) 5.25 (td, J=12.72, 4.36 Hz, 2 H) 2.56 (s, 3 H) 2.45 (s, 3 H).

¹⁹F NMR (377 MHz, CDCl₃) δ ppm -122.64 (s, -CHF₂).

Step 7: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-[[5-(4-chloro-3-methyl-phenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P131)

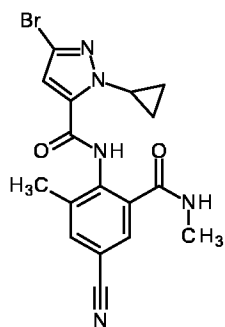
The desired product was prepared as described in example 2 step 2 using 6-chloro-2-[5-[[5-(4-chloro-3-methyl-phenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazol-3-yl]-8-methyl-3,1-benzoxazin-4-one (32 mg, 0.060 mmol) to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-5-[[5-(4-chloro-3-methyl-phenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide (Compound P131) (30 mg, 0.055 mmol, 91% yield) as a white solid.

LCMS (Method 1): 549 [M+H], Rt: 1.09 min

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.15 (s, 1 H) 8.03 (d, J=1.45 Hz, 1 H) 7.89 (dd, J=8.36, 1.82 Hz, 1 H) 7.77 (br s, 1 H) 7.60 (d, J=8.36 Hz, 1 H) 7.49 (d, J=1.82 Hz, 1 H) 7.41 (s, 2 H) 7.10 (s, 1 H) 6.15 - 6.47 (m, 1 H) 6.04 (s, 2 H) 4.88 - 5.01 (m, 2 H) 2.41 (s, 3 H) 2.17 (s, 3 H).

¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -122.22 (s, -CHF₂).

Example 126: Preparation of 5-bromo-N-[4-cyano-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-carboxamide (Compound P132)



(Compound P132)

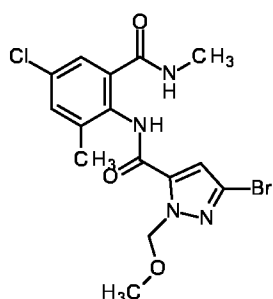
To a suspension of 2-(5-bromo-2-cyclopropyl-pyrazol-3-yl)-8-methyl-4-oxo-3,1-benzoxazine-6-carbonitrile, preparation described in example 1 step 3, (93 mg, 0.250 mmol) in EA (2 mL) was added

methyllamine (40 w% in water, to afford, 0.108 mL, 1.25 mmol). The reaction was stirred for 5 min. The reaction was concentrated, then the residue was suspended in water and stirred for 2h. The suspension was filtered and the solid was purified by reverse phase using a H₂O/ACN gradient to afford 5-bromo-N-[4-cyano-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-pyrazole-3-

carboxamide (Compound P132) (21 mg, 21% yield).

LCMS (Method 1): 402 [M+H], Rt: 0.88 min
1H NMR (400 MHz, DMSO-d₆) δ ppm 10.08 - 10.53 (m, 1 H) 8.34 - 8.71 (m, 1 H) 7.87 - 7.94 (m, 1 H) 7.79 - 7.85 (m, 1 H) 6.93 - 7.08 (m, 1 H) 4.19 - 4.39 (m, 1 H) 2.66 - 2.77 (m, 3 H) 2.21 - 2.32 (m, 3 H) 0.91 - 1.14 (m, 4 H)

Example 127: Preparation of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(methoxymethyl)pyrazole-3-carboxamide (Compound P133)



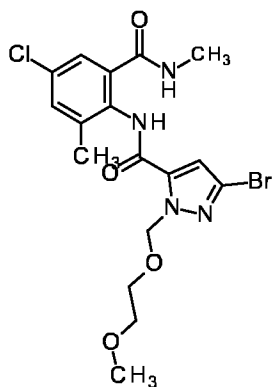
(Compound P133)

The desired product was prepared as described in example 23 using chloromethyl methyl ether CAS 107-30-2 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(methoxymethyl)pyrazole-3-carboxamide (Compound P133) as an off-white solid.

LCMS (Method 1): 415 [M+H], Rt: 0.88 min

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.22 (s, 3 H) 2.66 - 2.69 (m, 3 H) 3.23 - 3.26 (m, 3 H) 5.65 - 5.75 (m, 2 H) 7.14 - 7.20 (m, 1 H) 7.38 - 7.43 (m, 1 H) 7.50 - 7.56 (m, 1 H) 8.29 - 8.43 (m, 1 H) 10.02 - 10.19 (m, 1 H)

Example 128: Preparation of 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2-methoxyethoxymethyl)pyrazole-3-carboxamide (Compound P134)



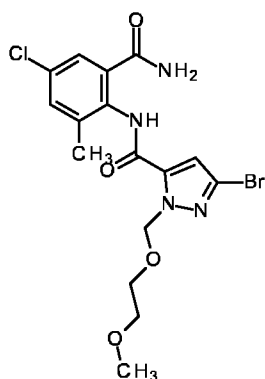
(Compound P134)

The desired product was prepared as described in example 23 using 1-(chloromethoxy)-2-methoxyethane CAS 3970-21-6 to afford 5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2-methoxyethoxymethyl)pyrazole-3-carboxamide (Compound P134) as an off-white solid.

LCMS (Method 1): 459 [M+H], Rt: 0.88 min

- 5 ¹H NMR (400 MHz, CDCl₃) δ ppm 9.92 (s, 1 H) 7.35 (d, J=2.18 Hz, 1 H) 7.29 (d, J=2.18 Hz, 1 H) 6.91 (s, 1 H) 6.13 - 6.23 (m, 1 H) 5.88 (s, 2 H) 3.70 - 3.79 (m, 2 H) 3.46 - 3.54 (m, 2 H) 3.30 (s, 3 H) 2.94 (d, J=4.72 Hz, 3 H) 2.29 (s, 3 H).

Example 129: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2-methoxyethoxymethyl)pyrazole-3-carboxamide (Compound P135)



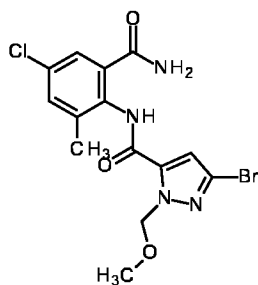
(Compound P135)

The desired product was prepared as described in example 21 using 1-(chloromethoxy)-2-methoxyethane CAS 3970-21-6 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2-methoxyethoxymethyl)pyrazole-3-carboxamide (Compound P135) as a brown solid.

- 15 LCMS (Method 1): 445 [M+H], Rt: 0.84 min

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.15 (s, 1 H) 7.82 (s, 1 H) 7.49 - 7.56 (m, 1 H) 7.41 - 7.49 (m, 2 H) 7.16 (s, 1 H) 5.76 (s, 2 H) 3.53 - 3.64 (m, 2 H) 3.34 - 3.42 (m, 2 H) 3.19 (s, 3 H) 2.21 (s, 3 H).

Example 130: Preparation of 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(methoxymethyl)pyrazole-3-carboxamide (Compound P136)



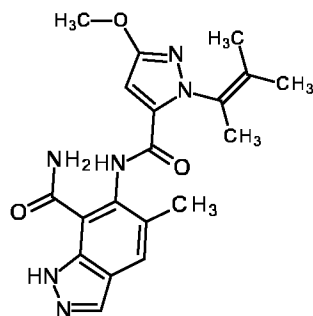
(Compound P136)

The desired product was prepared as described in example 21 using chloromethyl methyl ether CAS 107-30-2 to afford 5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(methoxymethyl)pyrazole-3-carboxamide (Compound P136) as a brown solid.

- 25 LCMS (Method 1): 401 [M+H], Rt: 0.83 min

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (s, 1 H) 7.81 (s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.47 (br s, 1 H) 7.43 - 7.45 (m, 1 H) 7.17 (s, 1 H) 5.69 (s, 2 H) 3.25 (s, 3 H) 2.21 (s, 3 H).

Example 131: Preparation of 6-[[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carbonyl]amino]-5-methyl-1H-indazole-7-carboxamide (Compound P138)



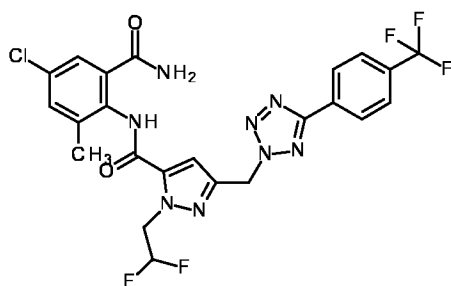
(Compound P138)

The desired compound was prepared as described in example 43 using 6-amino-5-methyl-1H-indazole-7-carboxylic acid CAS 946840-70-6, to afford 6-[[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carbonyl]amino]-5-methyl-1H-indazole-7-carboxamide (Compound P137) as beige solid.

LCMS (Method 1): 383 [M+H], Rt: 0.75 min

¹H NMR (400 MHz, acetonitrile-d₃) δ ppm 8.81 - 9.02 (m, 1 H) 7.91 - 8.10 (m, 1 H) 7.66 - 7.84 (m, 1 H) 6.32 - 6.42 (m, 1 H) 3.82 - 3.91 (m, 3 H) 2.27 - 2.33 (m, 3 H) 1.98 - 2.02 (m, 3 H) 1.73 - 1.80 (m, 3 H) 1.36 - 1.42 (m, 3 H)

Example 132: Preparation of N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P141)



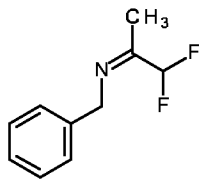
(Compound P141)

The desired compound was prepared as described in example 3 using 5-(bromomethyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxylate, preparation described in example 125 step 3, and 5-[4-(Trifluoromethyl)phenyl]-1H-tetrazole CAS 2251-79-8, to afford N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide (Compound P141) as beige solid.

LCMS (Method 1): 569 [M+H], Rt: 1.07 min

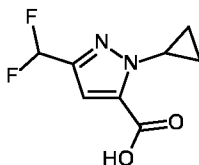
¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.18 (s, 1 H) 8.29 (d, J=7.99 Hz, 2 H) 7.95 (d, J=8.36 Hz, 2 H) 7.79 (s, 1 H) 7.50 (d, J=2.18 Hz, 1 H) 7.39 - 7.46 (m, 2 H) 7.15 (s, 1 H) 6.17 - 6.50 (m, 1 H) 6.11 (s, 2 H) 4.96 (br d, J=4.00 Hz, 2 H) 2.19 (s, 3 H).

¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -61.41 (s, -CF₃) -122.23 (s, -CHF₂).

Example 133: Preparation of 1-cyclopropyl-3-(difluoromethyl)-1H-pyrazole-5-carboxylic acidStep 1: Preparation of (Z)-N-benzyl-1,1-difluoro-propan-2-imine

A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with 1,1-difluoropropan-2-one (15.0 g, 159 mmol) in dichloromethane (150 mL) was added phenylmethanamine (17.1 g, 159 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 12 h. Reaction mixture was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100 mL) and dichloromethane, separated organic layer was concentrated under reduced pressure to afford (Z)-N-benzyl-1,1-difluoro-propan-2-imine (20.0 g, 109 mmol, yield: 68.5%) as light-yellow liquid.

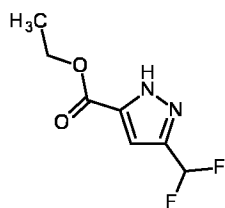
¹H NMR (400 MHz, DMSO-*d*₆): δ 7.37–7.24 (m, 5H), 5.93 (t, *J* = 55.6 Hz, 1H), 4.56 (s, 2H), 2.03 (s, 3H).

Step 2: Preparation of ethyl (Z)-4-(benzylamino)-5,5-difluoro-2-oxo-pent-3-enoate

A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with (Z)-N-benzyl-1,1-difluoro-propan-2-imine (20.0 g, 109 mmol) in dichloromethane (300 mL) was added pyridine (8.64 g, 109 mmol) at –20 °C then added ethyl 2-chloro-2-oxo-acetate (14.9 g, 109 mmol). The resulting reaction mixture was stirred at –20 °C to room temperature for 16 h. The reaction mixture was monitored by TLC (20% Ethyl acetate/Hexane), and it showed no starting material. Then the reaction mixture was treated with MTBE (100 mL) and the precipitate was filtered and filtrate was concentrated under reduced pressure to obtain ethyl (Z)-4-(benzylamino)-5,5-difluoro-2-oxo-pent-3-enoate (24.0 g, 84.7 mmol, yield: 77.6%) as light brown gum (crude product was used for next step).

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.36 – 7.26 (m, 6H), 6.91–6.61 (m, 1H), 4.52 (d, *J* = 6.0 Hz, 2H), 4.38 – 4.32 (m, 4H), 1.38 (t, *J* = 6.4 Hz, 3H).

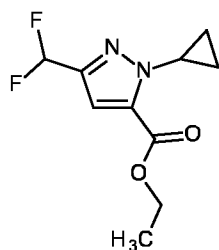
Step 3: Preparation of ethyl 3-(difluoromethyl)-1H-pyrazole-5-carboxylate



A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl (Z)-4-(benzylamino)-5,5-difluoro-2-oxo-pent-3-enoate (5.00 g, 17.7 mmol) in acetic acid (50.0 mL) was added, hydrazine hydrate (1.71 mL, 35.3 mmol) at rt. The resulting reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was monitored by TLC (40% Ethyl acetate/Hexane) and it showed no starting material. Then reaction mixture was concentrated under reduced pressure the residue was diluted with water and extracted the compound in EtOAc (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford desired compound. The crude reaction mixture was purified by CombiFlash column chromatography (CombiFlash 0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to afford ethyl 3-(difluoromethyl)-1H-pyrazole-5-carboxylate (4.02 g, 0.405 mmol, yield: 47.7%) as light-yellow solid.

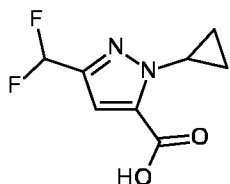
¹H NMR (400 MHz, DMSO-*d*₆): δ 14.48 (s, 1H), 7.19 – 6.92 (m, 2H), 4.33 (q, *J* = 6.8 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H).

Step 4: Preparation of ethyl 2-cyclopropyl-5-(difluoromethyl) pyrazole-3-carboxylate



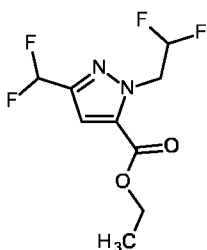
A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-(difluoromethyl)-1H-pyrazole-5-carboxylate (4.00 g, 21.0 mmol) was added cyclopropylboronic acid (2.71 g, 31.6 mmol), sodium carbonate (4.46 g, 42.1 mmol), 2-(2-pyridyl)pyridine (3.29 g, 21.0 mmol) and copper diacetate (3.83 g, 21.0 mmol) the resulting reaction mixture was stirred at 70 °C for 16 h. Reaction was monitored by TLC (50% Ethyl acetate/Hexane), it showed no starting material. The reaction mixture was poured into ice water extracted with EtOAc (2 x 200 mL) The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude reaction mixture was purified by CombiFlash column chromatography (CombiFlash, 0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to afford ethyl 2-cyclopropyl-5-(difluoromethyl) pyrazole-3-carboxylate (2.10 g, 9.12 mmol, yield: 43.4%) as light brown gum.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.14 – 6.87 (m, 2H), 4.37 – 4.31 (m, 3H), 1.33 (t, *J* = 6.8 Hz, 3H), 1.18 – 1.13 (m, 2H), 1.11 – 1.06 (m, 2H)

Step 5: Preparation of 2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxylic acid

A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-cyclopropyl-5-(difluoro methyl) pyrazole-3-carboxylate (6.00 g, 26.1 mmol) in ethanol (50.0 mL) was added lithium hydroxide hydrate (5.47 g, 130 mmol) in water (20.0 mL) at 0 °C. The resulting reaction mixture was stirred at rt 3 h. Reaction was monitor by TLC (50% Ethyl acetate/Hexane), it showed no starting material. Then The reaction mixture was concentrated under reduced pressure the residue was diluted with water and acidify with 2N HCl to pH 2 then extract the compound in EtOAc (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressure to afford 2-cyclopropyl-5-(difluoro methyl) pyrazole-3-carboxylic acid (5.00 g, 24.7 mmol, yield: 94.9%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 13.72 (s, 1H), 7.13 – 6.86 (m, 2H), 4.45 – 4.39 (m, 1H), 1.17 – 1.13 (m, 2H), 1.09 – 1.03 (m, 2H)

Example 134: Preparation of 1-(2,2-difluoroethyl)-3-(difluoromethyl)-1H-pyrazole-5-carboxylic acidStep 1: Preparation of ethyl 2-(2,2-difluoroethyl)-5-(difluoro methyl) pyrazole-3-carboxylate

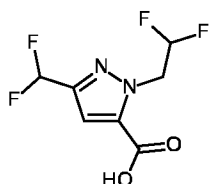
A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-(difluoro methyl)-1H-pyrazole-5-carboxylate (12.0 g, 63.1 mmol) (prepared in example 133) in N,N-dimethylformamide (150 mL) was added cesium carbonate (41.1 g, 126 mmol) and 1,1-difluoro-2-iodo-ethane (14.5 g, 75.7 mmol). The reaction mixture was stirred at 80 °C for 6 h. Reaction mixture was monitored by TLC (30% Ethyl acetate/Hexane), it showed no starting material. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressured to afford crude product. The crude product was purified by CombiFlash column chromatography (CombiFlash, 0 to 100% Hexane/EtOAc). Pure fractions were combined and

evaporated under reduced pressure to afford ethyl 2-(2,2-difluoroethyl)-5-(difluoromethyl) pyrazole-3-carboxylate (5.80 g, 22.8 mmol, yield: 36.2%) colourless gum.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.11 (s, 1H), 6.68 (t, *J* = 54.8 Hz, 1H), 6.15 (tt, *J* = 4.4 Hz, 55.6 Hz, 1H), 5.02 – 4.95 (m, 2H), 4.39 (q, *J* = 6.8 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

5

Step 2: Preparation of 2-(2,2-difluoroethyl)-5-(difluoro methyl) pyrazole-3-carboxylic acid



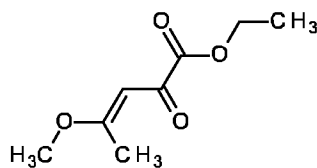
A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-(2,2-difluoroethyl)-5-(difluoro methyl) pyrazole-3-carboxylate (6.00 g, 23.6 mmol) in ethanol (50.0 mL) was added lithium hydroxide hydrate (4.95 g, 118 mmol) in water (20.0 mL) at 0 °C. The resulting reaction mixture was stirred at rt for 3 h. Reaction mixture was monitored by TLC (40% Ethyl acetate/Hexane), and it showed no starting material. Then The reaction mixture was concentrated under reduced pressure, the residue was diluted with water and acidify with 2N HCl to pH 2 then extracted the compound in EtOAc (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressure to afford 2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid (5.00 g, 22.1 mmol, yield: 93.7%) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 13.98 (s, 1H), 7.21 – 6.94 (m, 2H), 6.42 (tt, *J* = 3.6 Hz, 54.8 Hz, 1H), 5.08 – 4.99 (m, 2H)

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Example 135: Preparation of 1-cyclopropyl-3-((5-(trifluoromethyl)-2H-tetrazol-2-yl)methyl)-1H-pyrazole-5-carboxylic acid

Step 1: Preparation of ethyl (E)-4-methoxy-2-oxo-pent-3-enoate



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A 500 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-chloro-2-oxo-acetate (30.0 g, 220 mmol) in Dichloromethane (200 mL). Then added 2-methoxyprop-1-ene (19.0 g, 264 mmol) and pyridine (24.3 g, 308 mmol) in Dichloromethane (100 mL) at 0 °C in 30 min. The reaction mixture was stirred at rt for 16 h and was monitored by TLC (30% EtOAc/hexanes), it showed no starting material. Reaction mixture was diluted with Dichloromethane (300 mL) washed with 10% hydrochloric acid (150 mL), washed with water (300 mL) and brine solution (300 mL). The solvent was dried over anhydrous sodium sulfate and solvent was evaporated under

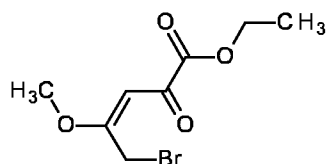
30

reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (CombiFlash 0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to obtain ethyl (E)-4-methoxy-2-oxo-pent-3-enoate (30.0 g, 174 mmol, yield: 79.3%) colour less gel.

5

^1H NMR (400 MHz, CDCl_3): δ 6.25 (s, 1H), 4.31 (q, J = 6.8 Hz, 2H), 3.78 (s, 3H), 2.39 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H).

Step 2: Preparation of ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate



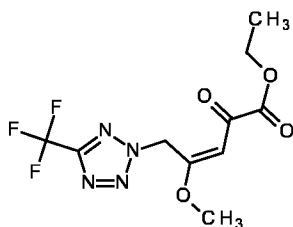
10

A 500 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with molecular bromine (10.8 mL, 209 mmol) in Dichloromethane (300 mL). Then added drop wise solution of ethyl (E)-4-methoxy-2-oxo-pent-3-enoate (30.0 g, 174 mmol) in Dichloromethane (250 mL) at 0 °C. The reaction mixture was further stirred at 0 °C for 1h, followed by the addition of a solution of pyridine (16.9 mL, 209 mmol) in Dichloromethane (50 mL) at 0 °C. The reaction mixture was slowly allowed to come at rt, stirred for 1 h. Reaction was monitored by TLC (20% EtOAc/hexanes) and it showed no starting material. Reaction mixture was diluted with Dichloromethane (100 mL) and added water (600 mL), 2N Hydrochloric acid (200 mL). The reaction mass was stirred 5 min, separated aqueous layer and organic layer. Aqueous layer extract with Dichloromethane (600 mL). Total organic layer washed with water (600 mL), brine solution (600 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by CombiFlash column chromatography (CombiFlash 0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to afford ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate (14.0 g, 55.8 mmol, yield: 32.0%) red colour gel.

20

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.25 (s, 1H), 4.50 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H).

Step 3: Preparation of ethyl (E)-4-methoxy-2-oxo-5-[5-(trifluoromethyl)tetrazol-2-yl]pent-3-enoate

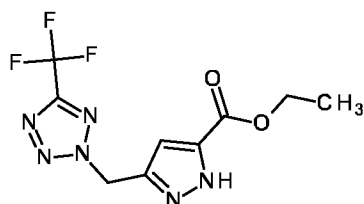


30

A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate (8.00 g, 31.9 mmol) in Acetonitrile (50.0 mL). Then added potassium carbonate (8.81 g, 63.7 mmol) and 5-(trifluoromethyl)-2H-tetrazole (5.28 g, 38.2 mmol) at rt. The reaction mixture was stirred at rt for 6 h. Reaction was monitored by TLC (30% EtOAc/hexanes) and it showed no starting material. Reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The separated organic layer was washed with water (200 mL), brine solution (100 mL), dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford crude compound. The crude material was purified by CombiFlash column chromatography (CombiFlash 0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to obtain ethyl (E)-4-methoxy-2-oxo-5-[5-(trifluoromethyl)tetrazol-2-yl]pent-3-enoate (2.50 g, 7.71 mmol, yield: 24.2%) as light brown liquid.

^1H NMR (400 MHz, CDCl_3): δ 6.56 (s, 1H), 6.10 (s, 2H), 4.37 (q, J = 6.8 Hz, 2H), 3.80 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

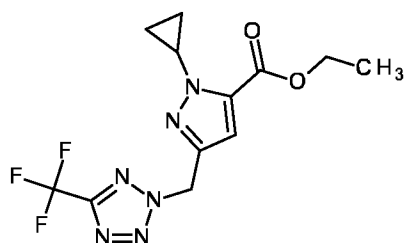
Step 4: Preparation of ethyl 3-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate



A 100 mL two-neck round bottom flask was equipped with nitrogen balloon, it was charged with ethyl (E)-4-methoxy-2-oxo-5-[5-(trifluoromethyl)tetrazol-2-yl]pent-3-enoate (2.30 g, 7.46 mmol) in Acetic acid (30.0 mL) and was added hydrazine hydrate (0.747 g, 14.9 mmol) at rt. The reaction mixture was stirred for 2 h at 60 °C. Reaction mixture was monitored by TLC (20% Ethyl acetate/Hexane) and it showed no starting material. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with 10% NaHCO_3 solution (50 mL), and washed with brine solution dried over sodium sulfate and concentrated under reduced pressure to afford ethyl 3-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate (1.50 g, 4.91 mmol, yield: 65.8%) crude product.

^1H NMR (400 MHz, CDCl_3): δ 6.92 (s, 1H), 5.97 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

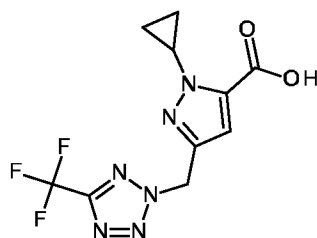
Step 5: Preparation of ethyl 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate



A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate (1.70 g, 5.86 mmol) in 1,2-dichloroethane (30.0 mL). Then at room temperature was added sodium carbonate (0.745 g, 7.03 mmol), cyclopropylboronic acid (0.604 g, 7.03 mmol), copper acetate (0.745 g, 4.10 mmol) and 2-(2-pyridyl)pyridine (0.640 g, 4.10 mmol), respectively. The reaction mixture was stirred for 5 h at 80 °C. Reaction progress was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. It was diluted with water (100 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with water (100 mL), brine and dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to obtain ethyl 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate (1.30 g, 3.74 mmol, yield: 63.8%) as an off-white solid.

¹H NMR (400 MHz, CDCl₃): 6.88 (s, 1H), 5.84 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.32 – 4.27 (m, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.27 – 1.25 (m, 2H), 1.07 – 1.05 (m, 2H).

Step 6: Preparation of 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid



A 100 mL two-neck round bottom flask was equipped with nitrogen balloon, charged with ethyl 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate (1.30 g, 3.94 mmol) in THF:MeOH (1:1) (10.0 mL). Then solution of lithium hydroxide hydrate (0.165 g, 3.94 mmol) in water (10mL) was added at rt. The reaction mixture was stirred at rt for 2 h. Reaction was monitored by TLC (10% Methanol/ CH₂Cl₂) and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude product. it was diluted with water (20 mL) and pH was adjusted to neutral with saturated citric acid solution, then extracted with ethyl acetate (2 x 100 mL). The combined organic layer washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced

pressure to obtained 2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid (1.05 g, 3.46 mmol, yield: 87.8%) as an off-white solid.

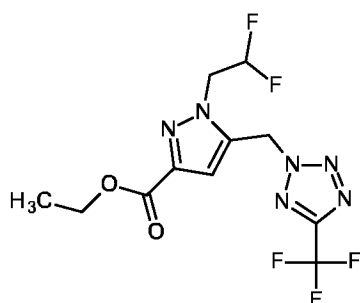
¹H NMR (400 MHz, CDCl₃): 7.03 (s, 1H), 5.88 (s, 2H), 4.30 – 4.25 (m, 1H), 1.30 – 1.28 (m, 2H), 1.10 – 1.08 (m, 2H)

5

Example 136: Preparation of 2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid

Step 1: Preparation of ethyl 1-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate

10



A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate (2.30 g, 7.93 mmol) (prepared in example 135) in N,N-dimethylformamide (30.0 mL). Then was added potassium carbonate (2.19 g, 15.9 mmol) and 1,1-difluoro-2-iodo-ethane (3.04 g, 15.9 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 5 h. Reaction progress was monitored by TLC (30% EtOAc/hexanes) and it showed no starting material. Reaction mixture was diluted with ice water (100 mL) and extracted with EtOAc (2 x 100 mL), washed with water (50 mL) brine solution (50 mL), dried over anhydrous sodium sulfate and solvent was evaporated under reduced pressure to afford crude product. The crude residue was purified by chromatography (CombiFlash, 0 to 70% EtOAc/Hexane). Pure fractions were combined and evaporated under reduced pressure to afford ethyl 2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate (1.30 g, 3.67 mmol, yield: 46.3%) as a light brown gum.

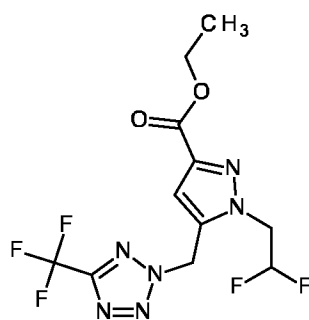
15

20

¹H NMR (400 MHz, CDCl₃): 6.96 (s, 1H), 6.92 – 6.12 (m, 1H), 5.90 (s, 2H), 4.95 (dt, *J* = 4.0 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.38 (t, 7.2 Hz, 3H).

25

Step 2: Preparation of ethyl 1-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate

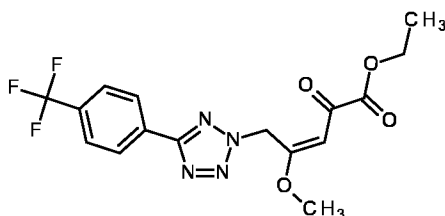


A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylate (1.40 g, 3.95 mmol) in THF:MeOH (1:1) (10.0 mL). Then solution of lithium hydroxide hydrate (0.166 g, 3.95 mmol) in water (10 mL) was added at rt. Stirred the reaction mixture at rt for 2 h. Reaction was monitor by TLC (10% Methanol/ CH₂Cl₂), it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude material. It was diluted with water (20 mL) and pH was adjusted to neutral with saturated citric acid solution, extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain 2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid (1.10 g, 3.36 mmol, yield: 84.9%) as an off-white solid.

¹H NMR (400 MHz, DMSO-d₆): 7.03 (s, 1H), 6.52 – 6.22 (m, 1H), 6.14 (s, 2H), 5.10 – 4.93 (m, 2H); MS: m/z = 325.0 [M – H][–]

Example 137: Preparation of 2-cyclopropyl-5-[[5-[4-(trifluoromethyl) phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid

Step 1: Preparation of ethyl (E)-4-methoxy-2-oxo-5-[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]pent-3-enoate

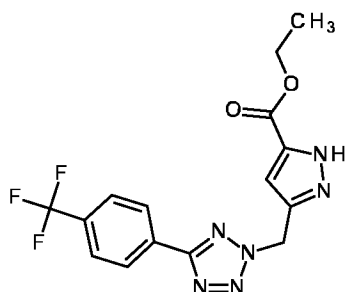


A 500 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl (E)-5-bromo-4-methoxy-2-oxo-pent-3-enoate (20.0 g, 79.7 mmol) in Acetonitrile (160.00 mL). Then added to it potassium carbonate (22.0 g, 159 mmol), 5-[4-(trifluoromethyl)phenyl]-2H-tetrazole (20.5 g, 95.6 mmol) at rt and stirred for 2 h. Reaction mixture was monitored by TLC (30% EtOAc/hexane), it showed no starting material. Reaction mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 200 mL), washed with water (100 mL) brine solution (100 mL), dried over anhydrous sodium sulfate, combined organic layer was evaporated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (CombiFlash 0

to 100% Hexane/EtOAc). Pure fractions were combined, evaporated under reduced pressure to obtain ethyl (E)-4-methoxy-2-oxo-5-[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]pent-3-enoate (20.0 g, 52.0 mmol, yield: 65.3%) off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.27 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 6.44 (s, 1H), 6.17 (s, 2H), 4.28 (d, *J* = 8.0 Hz, 2H), 3.78 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

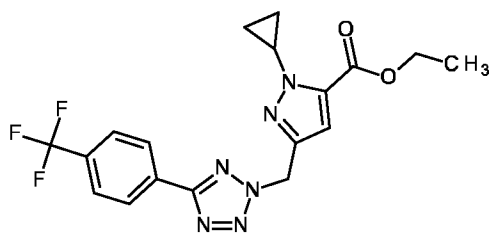
Step 2: Preparation of ethyl 3-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate



A 500 mL two-neck round bottom flask was equipped with nitrogen balloon, it was charged with ethyl (E)-4-methoxy-2-oxo-5-[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]pent-3-enoate (20.0 g, 52.0 mmol) in Acetic acid (20.00 mL) was added hydrazine hydrate (5.21 g, 104 mmol) at rt. The reaction mixture was stirred at 60 °C for 2 h. Reaction progress was monitored by TLC (20% Ethyl acetate/Hexane), it showed no starting material. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with 10% NaHCO₃ solution (200 mL), and washed with brine solution dried over sodium sulfate, concentrated under reduced pressure to afford ethyl 3-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate (17.0 g, 52.0 mmol, yield: 89.3%) light brown solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 14.10 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 6.91 (s, 1H), 6.08 (s, 2H), 4.29 (d, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 6.8 Hz, 3H).

Step 3: Preparation of ethyl 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylate

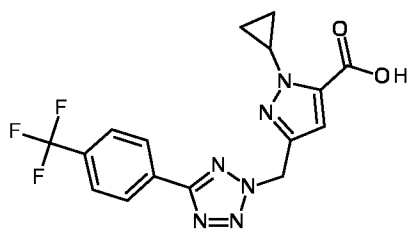


A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]-1H-pyrazole-5-carboxylate (8.00 g, 21.8 mmol) in 1,2-dichloroethane (100 mL). At room temperature was sodium carbonate (2.78 g, 26.2 mmol), cyclopropylboronic acid (3.75 g, 43.7 mmol), copper acetate (2.78 g, 15.3 mmol) and 2-(2-

pyridyl) pyridine (2.39 g, 15.3 mmol), respectively. The reaction mixture was stirred at 80°C for 5 h. Reaction mixture was monitored by TLC (30% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water and washed with brine solution dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to obtain ethyl 2-cyclopropyl-5-[[5-[4-(trifluoromethyl) phenyl] tetrazol-2-yl] methyl] pyrazole-3-carboxylate (4.00 g, 9.84 mmol, yield: 45.1%,) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.26 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 6.00 (s, 2H), 4.33 – 4.24 (m, 3H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.12 – 1.09 (m, 2H), 1.05 – 1.01 (m, 2H).

Step 4: Preparation of 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid

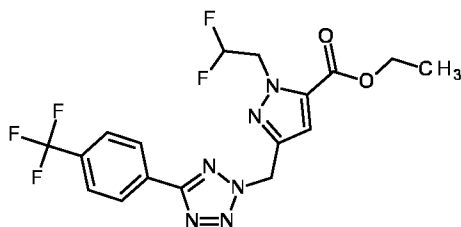


A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylate (6.00 g, 14.8 mmol) in Methanol: THF (1;1) (20 mL). Then lithiumhydroxide hydrate (3.10 g, 73.8 mmol) and water (6.00 mL) was added at 0 °C. The reaction mixture was stirred at rt for 4 h. Reaction progress was monitored by TLC (50% EtOAc/Hexane) and it showed no starting material. Solvent was evaporated under reduced pressure and pH was adjusted to 2.0 to 3.0 with saturated citric acid solution at 0 °C. Reaction mass was extracted with 10% MeOH/DCM (2 x 200 mL). The combined organic layers washed with brine (100 mL), water (100 mL), dried over sodium sulfate and evaporated under reduced pressure to obtain crude product. It was washed with n-pentane and dried with rotavapor under reduced pressure to obtain 2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid (5.50 g, 14.5 mmol, yield: 98.5%) off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.26 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 5.95 (s, 2H), 4.58 – 4.52 (m, 1H), 1.09 – 1.06 (m, 2H), 0.98 – 0.95 (m, 2H)

Example 138: Preparation of 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid

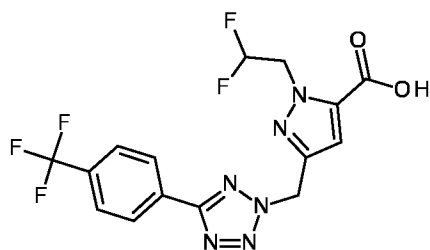
Step 1: Preparation of ethyl 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl) phenyl] tetrazol-2-yl] methyl] pyrazole-3-carboxylate



A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-[[5-[4-(trifluoromethyl) phenyl] tetrazol-2-yl] methyl]-1H-pyrazole-5-carboxylate (10.0 g, 27.3 mmol) (prepared in example 137) in N,N-dimethylformamide (10.0 mL) were added potassium carbonate (7.55 g, 54.6 mmol) and 1,1-difluoro-2-iodo-ethane (10.5 g, 54.6 mmol) at rt. The reaction mixture was stirred at 70 °C for 5 h. Reaction mixture was monitored by TLC (30% EtOAc/hexanes) and it showed no starting material. Ice was added to the reaction mixture was diluted with cold water (100 mL) and extracted with EtOAc (2 x 100 mL), washed with water (100 mL) brine solution (50 mL), dried over anhydrous sodium sulfate and solvent was evaporated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (0 to 100% Hexane/EtOAc). Pure fractions were combined and evaporated under reduced pressure to obtain ethyl 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl) phenyl] tetrazol-2-yl] methyl] pyrazole-3-carboxylate (7.00 g, 16.3 mmol, yield: 59.6%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.27 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 6.98 (s, 1H), 6.58 – 6.30 (m, 3H), 4.99 – 4.91 (m, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

Step 2: Preparation of 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid



A 250 mL two-neck round bottom flask was equipped with nitrogen balloon, charged with ethyl 2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylate (7.00 g, 16.3 mmol) in Methanol: THF (1:1) (20mL). Then solution of lithiumhydroxide hydrate (3.41 g, 81.3 mmol) in water (5.00 mL) at 0°C. The reaction mixture was stirred for 4 h at rt. Reaction mixture was monitored by TLC (50% EtOAc/n-Hexane) and it showed no starting material. Solvent was evaporated under reduced pressure, pH 2.0 to 3.0 was adjusted with saturated citric acid solution at 0 °C, extracted with 10% MeOH/DCM (2 x 200 mL). The combined organic layers washed with brine, water, dried over sodium sulfate and evaporated under reduced pressure to obtain crude product. It was washed with n-pentane and dried under rotavapor under reduced pressure to obtain 2-(2,2-difluoroethyl)-5-[[5-[4-

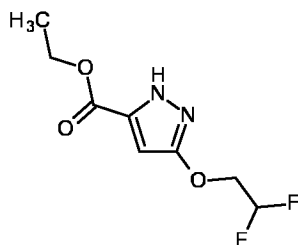
(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxylic acid (6.10 g, 15.2 mmol, yield: 93.2%) off white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 13.80 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 6.99 (s, 1H), 6.37 (tt, *J* = 4.0 Hz, 54.8 Hz, 1H), 6.06 (s, 2H), 5.01 – 4.90 (m, 2H)

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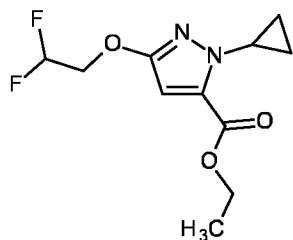
Example 139: Preparation of 2-cyclopropyl-5-(2,2-difluoroethoxy) pyrazole-3-carboxylic acid

Step 1: Preparation of ethyl 3-(2,2-difluoroethoxy)-1H-pyrazole-5-carboxylate



- 10 A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-hydroxy-1H-pyrazole-5-carboxylate (10.0 g, 64.0 mmol) in DMF (150 mL). Then added potassium carbonate (17.7 g, 128 mmol) and 1,1-difluoro-2-iodo-ethane (14.8 g, 76.9 mmol) at room temperature. Reaction mixture was stirred at 90°C for 15 min and monitored by TLC (30% Ethyl acetate/Hexane). It showed no starting material. Reaction mixture was quenched with ice -water and
- 15 extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (20% ethyl acetate/Hexane) pure fractions were collected and concentrated under reduced pressure to afford ethyl 3-(2,2-difluoroethoxy)-1H-pyrazole-5-carboxylate (4.50 g, 20.0 mmol, yield: 31.3%) as white solid.
- 20 ¹H NMR (400 MHz, CDCl₃): δ 10.89 (s, 1H), 6.27 (s, 1H), 6.26 – 5.98 (m, 1H), 4.47 – 4.36 (m, 4H), 1.39 (t, *J* = 14.4 Hz, 3H).

Step 2: Preparation of ethyl 2-cyclopropyl-5-(2,2-difluoroethoxy) pyrazole-3-carboxylate



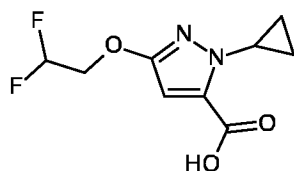
- 25 A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-(2,2-difluoroethoxy)-1H-pyrazole-5-carboxylate (9.00 g, 40.9 mmol) in 1,2-dichloroethane (500.0 mL). Then added to it cyclopropyl boronic acid (3.51 g, 40.9 mmol) and sodium carbonate (5.20 g, 49.1 mmol) at rt, reaction mixture was purged with oxygen gas for 10 min and copper acetate (5.71 g, 28.6 mmol), 2-(2-pyridyl) pyridine (4.47 g, 28.6 mmol) were added at rt. The reaction mixture was

stirred under oxygen atmosphere at 90 °C for 16 h. Reaction was monitor by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction mixture was quenched with water and extracted with Dichloromethane (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product.

The crude product was purified by CombiFlash column chromatography (0 - 100% ethyl acetate/Hexane) pure fraction was collected and concentrated under reduced pressure offered product ethyl 2-cyclopropyl-5-(2,2-difluoroethoxy) pyrazole-3-carboxylate (7.80 g, 29.4 mmol, yield: 71.9%) as colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 6.21 (s, 1H), 6.21 – 5.92 (m, 1H), 4.37 – 4.29 (m, 4H), 4.19 – 4.15 (m, 1H), 1.37 (t, *J* = 14.4 Hz, 3H), 1.18 (q, *J* = 1.2 Hz, 2H), 0.98 (q, *J* = 5.2 Hz, 2H)

Step 3: Preparation of 2-cyclopropyl-5-(2,2-difluoroethoxy) pyrazole-3-carboxylic acid

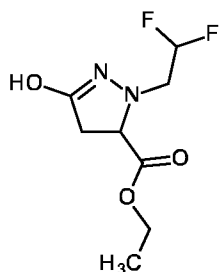


A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-cyclopropyl-5-(2,2-difluoroethoxy) pyrazole-3-carboxylate (7.80 g, 30.0 mmol) in THF:MeOH (1:1), (60mL) . Then solution of lithiumhydroxide hydrate (2.52 g, 59.9 mmol) in water (10 mL) was added at rt, stirred for 3 h at rt. Reaction was monitor by TLC (10% MeOH/CH₂Cl₂) and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude product, crude was diluted with water and quenched with saturated citric acid solution (10 mL, pH = 4) solid product was precipitated. Solid was filtered and washed with water and dried under vacuum to afford 2-cyclopropyl-5-(2,2-difluoroethoxy) pyrazole-3-carboxylic acid (5.20 g, 22.4 mmol, yield: 74.7%) as off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 6.32 (s, 1H), 6.47 – 6.18 (m, 1H), 4.38 – 4.23 (m, 3H), 1.08 – 1.04 (m, 2H), 0.95 – 0.92 (m, 2H)

Example 140: Preparation of 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl) pyrazole-3-carboxylic acid

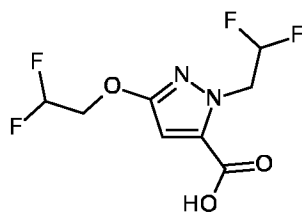
Step 1: Preparation of ethyl 2-(2,2-difluoroethyl)-5-hydroxy-3,4-dihydropyrazole-3-carboxylate



A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-hydroxy-1H-pyrazole-5-carboxylate (7.00 g, 44.8 mmol) in N,N-dimethylformamide (70.0 mL). Then potassium carbonate (18.6 g, 134 mmol) and 1,1-difluoro-2-iodo-ethane (25.8 g, 134 mmol) was added to it at rt. The resulting reaction mixture was stirred at 80 °C for 16 h. Reaction was monitored by TLC (20% Ethyl acetate/Hexane), and it showed no starting material. The reaction mixture was diluted with water (100 mL), extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by reverse phase column chromatography (CombiFlash 0 to 100% ACN/H₂O). Pure fractions were combined and evaporated under reduced pressure to obtain ethyl 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl) pyrazole-3-carboxylate (9.10 g, 30.4 mmol, yield: 67.8%) as white solid.

¹H NMR (400 MHz, CDCl₃): 6.30 (s, 1H), 6.24 – 5.92 (m, 2H), 4.80 (dt, J=4.4 Hz, 2H), 4.41 – 4.32 (m, 4H), 1.39 – 1.35 (t, 7.2 Hz, 3H)

Step 2: Preparation of 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl) pyrazole-3-carboxylic acid

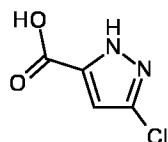


A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl) pyrazole-3-carboxylate (9.00 g, 30.1 mmol) in MeOH:THF (1:1) (60 mL) was added LiOH·H₂O (3.61 g, 90.3 mmol) and H₂O (10 mL) at rt. The resulting reaction mixture was stirred at rt for 16 h. Reaction mixture was monitored by TLC (50% Ethyl acetate/Hexane) and it showed no starting material. The reaction mixture was concentrated and diluted with water and pH was adjusted to acidic with saturated citric acid and extracted with EtOAc (2 X 100 mL) combined organic layer was washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain 5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid (7.10 g, 26.3 mmol, yield: 87.5%) as a white solid.

¹H NMR (400 MHz, CDCl₃): 6.44 (s, 1H), 6.50 – 6.17 (m, 2H), 4.84 (dt, J = 3.6 Hz, 2H), 4.40 (dt, J = 3.6 Hz, 2H)

Example 141: Preparation of 5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid

Step 1: Preparation of 3-chloro-1H-pyrazole-5-carboxylic acid

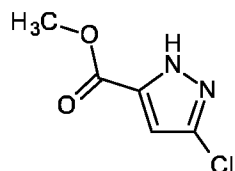


A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with 3-chloro-5-methyl-1H-pyrazole (2.50 g, 21.5 mmol) in water (100 mL) and t-Butanol (4.00 mL) was heated to 70 °C for 10 min, potassium permanganate (8.47 g, 53.6 mmol) in water (500 mL) was added drop wise over a period of 4 h. After addition reaction mixture was stirred at 70 °C for 16 h.

- 5 Reaction mixture was monitored by TLC (10% MeOH/ CH₂Cl₂) and it showed no starting material. The reaction mixture filtered through Celite bed and washed with water, aqueous layer was acidified with 1N HCl (pH = 2) and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with brine solution (100 mL), organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 3-chloro-1H-pyrazole-5-carboxylic acid (2.50 g, 16.7 mmol, yield: 77.9%) as white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 14.06 (s, 1H), 13.66 (s, 1H), 6.81 (s, 1H)

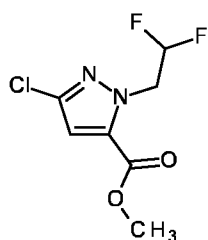
Step 2: Preparation of methyl 3-chloro-1H-pyrazole-5-carboxylate



- 15 A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with 3-chloro-1H-pyrazole-5-carboxylic acid (5.00 g, 34.1 mmol) in Methanol (50.0 mL) was added thionyl chloride (4.98 mL, 68.2 mmol) at 0 °C. The reaction mixture was stirred at rt for 16 h. Reaction was monitored by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude. Crude was dissolved in water and
- 20 extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product. It was purified by CombiFlash column chromatography (0-100% ethyl acetate/Hexane) pure fractions were collected and concentrated under reduced pressure to afford methyl 3-chloro-1H-pyrazole-5-carboxylate (10.2 g, 62.3 mmol, yield: 91.2%) as white solid.

- 25 ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.27 (s, 1H), 6.90 (s, 1H), 3.85 (s, 3H)

Step 3: Preparation of methyl 5-chloro-2-(2,2-difluoroethyl) pyrazole-3-carboxylate



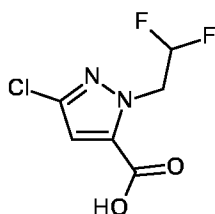
- A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with methyl 3-chloro-1H-pyrazole-5-carboxylate (5.20 g, 32.4 mmol) in DMF (50 mL). Then potassium carbonate (5.37 g, 38.9 mmol) and 1,1-difluoro-2-iodo-ethane (6.22 g, 32.4 mmol) was added at rt,
- 30

reaction mixture was stirred at 90 °C for 16 h. Reaction was monitored by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction mixture was quenched with ice -water and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product.

- 5 It was purified by CombiFlash column chromatography (0-100% ethyl acetate/Hexane), pure fractions were collected and concentrated under reduced pressure to afford methyl 5-chloro-2-(2,2-difluoroethyl) pyrazole-3-carboxylate (4.00 g, 17.5 mmol, yield: 53.9%) as white solid.

^1H NMR (400 MHz, DMSO- d_6): δ 7.09 (s, 1H), 6.56 – 6.26 (m, 1H), 6.90 (s, 1H), 3.86 (s, 3H)

10 **Step 4: Preparation of 5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxylic acid**

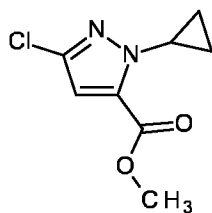


A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with methyl 5-chloro-2-(2,2-difluoroethyl) pyrazole-3-carboxylate (6.20 g, 27.6 mmol) in THF: MeOH (1:1) (100 mL). Then solution of lithium hydroxide hydrate (3.48 g, 82.8 mmol) in water (20 mL) was added
15 at rt. The reaction mixture was stirred at rt for 4 h. Reaction was monitored by TLC (10% Methanol/Dichloromethane), and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude product, crude was diluted with water and extracted with ethyl acetate (2 x 100 mL). Aqueous layer was acidified with 2 N HCl (pH = 2), obtained solid was filtered and collected to afford 5-chloro-2-(2,2-difluoroethyl) pyrazole-3-carboxylic acid (5.10 g, 23.7 mmol,
20 yield: 86.0%) as white solid.

^1H NMR (400 MHz, DMSO- d_6): δ 6.99 (s, 1H), 6.52 - 6.25 (m, 1H), 4.99 – 4.91 (m, 2H)

Example 142: Preparation of 5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid

25 **Step 1: Preparation of methyl 5-chloro-2-cyclopropyl-pyrazole-3-carboxylate**

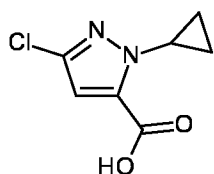


A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with methyl 3-chloro-1H-pyrazole-5-carboxylate (9.00 g, 56.1 mmol) (prepared in example 141) in 1,2-dichloroethane (100 mL). Then cyclopropylboronic acid (4.81 g, 56.1 mmol) and sodium carbonate (7.13 g, 67.3 mmol) was added at rt. Reaction mixture was purged with Oxygen gas for 10 min and
30

copper acetate (7.83 g, 39.2 mmol), 2-(2-pyridyl)pyridine (6.13 g, 39.2 mmol) were added at rt. The reaction mixture stirred under oxygen atmosphere at 90 °C for 16 h. Reaction was monitored by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction mixture was quenched with water and extracted with Dichloromethane (2 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (0-100% ethyl acetate/Hexane) pure fractions were collected and concentrated under reduced pressure to afford methyl 5-chloro-2-cyclopropyl-pyrazole-3-carboxylate (4.50 g, 22.0 mmol, yield: 39.2%) as colourless oil.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.95 (s, 1H), 4.27 – 4.23 (m, 1H), 3.85 (s, 3H), 1.13 – 1.11 (m, 2H), 1.04 – 1.02 (m, 2H).

Step 2: Preparation of 5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid

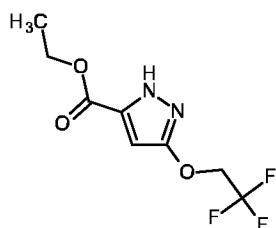


A 100 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with methyl 5-chloro-2-cyclopropyl-pyrazole-3-carboxylate (4.50 g, 22.4 mmol) in THF: MeOH (1:1) (50.0 mL). Then added solution of lithium hydroxide hydrate (1.88 g, 44.9 mmol) in water (10 mL) at room temperature. The reaction mixture was stirred at rt for 4 h. Reaction was monitored by TLC (10% Methanol/Dichloromethane), and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude product, crude was diluted with water and extracted with ethyl acetate (2 x 100 mL). Aqueous layer was acidified with 2 N HCl (pH = 2), obtained solid was filtered and collected to afford 5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid (2.60 g, 13.7 mmol, yield: 60.9%) as white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.82 (s, 1H), 4.36 – 4.32 (m, 1H), 1.12 – 1.10 (m, 2H), 1.02 – 0.99 (m, 2H)

Example 143: Preparation of 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid

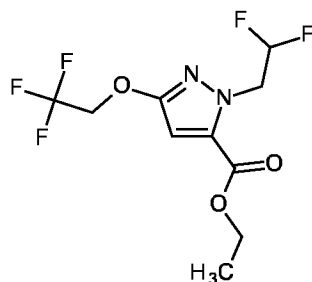
Step 1: Preparation of ethyl 3-(2,2,2-trifluoroethoxy)-1H-pyrazole-5-carboxylate



A 1 L two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-hydroxy-1H-pyrazole-5-carboxylate (30.0 g, 192 mmol) in DMF (500 mL) was added potassium carbonate (53.1 g, 384 mmol) and 1,1,1-trifluoro-2-iodo-ethane (48.4 g, 231 mmol) at rt, reaction mixture was stirred at 90°C for 24 h. Reaction was monitored by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction mixture was quenched with ice -water and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (0-100% ethyl acetate/Hexane) pure fraction were collected and concentrated under reduced pressure to afford ethyl 3-(2,2,2-trifluoroethoxy)-1H-pyrazole-5-carboxylate (15.0 g, 63.0 mmol, yield: 32.8%) as white solid.

¹H NMR (400 MHz, CDCl₃): δ 10.39 (s, 1H), 6.30 (s, 1H), 4.62 (q, *J* = 8.4 Hz, 2H), 4.38 (q, *J* = 6.8 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

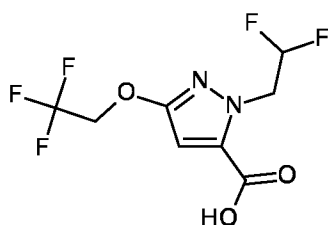
Step 2: Preparation of ethyl 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylate



A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-(2,2,2-trifluoroethoxy)-1H-pyrazole-5-carboxylate (8.00 g, 33.6 mmol) in DMF (300 mL) was added potassium carbonate (9.28 g, 67.2 mmol) and 1,1-difluoro-2-iodo-ethane (7.74 g, 40.3 mmol) at rt, reaction mixture was stirred at 90°C for 3 h. Reaction was monitored by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction mixture was quenched with ice water and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by CombiFlash column chromatography (0-100% ethyl acetate/Hexane) pure fractions were collected and concentrated under reduced pressure to afford ethyl 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy) pyrazole-3-carboxylate (9.00 g, 29.2 mmol, yield: 86.9%) as colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 6.26 (s, 1H), 6.26 – 5.86 (m, 1H), 4.76 – 4.69 (m, 2H), 4.52 (q, *J* = 8.4 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 8.0 Hz, 3H).

Step 3: Preparation of 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy) pyrazole-3-carboxylic acid



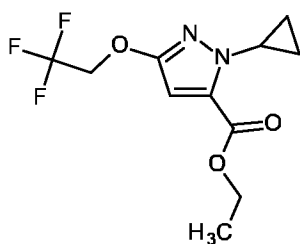
A stirred solution of ethyl 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylate (9.00 g, 29.8 mmol) in THF: MeOH (50.0 mL). Then added solution of lithium hydroxide hydrate (2.50 g, 59.6 mmol) in water (20 mL) at rt. The reaction mixture was stirred at rt for 3 h. Reaction was monitored by

5 TLC (10% MeOH/CH₂Cl₂) and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude, crude was diluted with water and quenched with saturated citric acid solution (10 mL, pH = 4) solid was precipitated. Solid was filtered, washed with water and dried to afford 2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid (6.02 g, 21.8 mmol, yield: 73.4%) as an off-white solid.

10 ¹H NMR (400 MHz, DMSO-d₆): δ 13.85 (s, 1H), 6.54 (s, 1H), 6.48 – 6.18 (m, 1H), 4.87 – 4.80 (m, 4H)

Example 144: Preparation of 5-chloro-2-cyclopropyl-pyrazole-3-carboxylic acid

Step 1: Preparation of ethyl 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylate

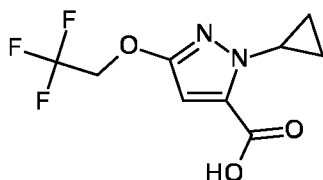


15 A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 3-(2,2,2-trifluoroethoxy)-1H-pyrazole-5-carboxylate (6.00 g, 25.2 mmol) (Prepared in example 143) in 1,2-dichloroethane (300 mL). Then added to it cyclopropylboronic acid (2.16 g, 25.2 mmol) and sodium carbonate (3.20 g, 30.2 mmol) at rt. Reaction mixture was purged with oxygen gas for 10 min

20 and copper acetate (3.52 g, 17.6 mmol), 2-(2-pyridyl) pyridine (2.75 g, 17.6 mmol) was added at rt. The reaction was stirred under oxygen atmosphere at 90 °C for 16 h. Reaction was monitored by TLC (30% Ethyl acetate/Hexane) and it showed no starting material. Reaction was quenched with water and extracted with Dichloromethane (2 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate and concentrated under reduced pressure to afford crude

25 product. The crude product was purified by CombiFlash column chromatography (0-100% ethyl acetate/Hexane) pure fractions were collected and concentrated under reduced pressure to afford ethyl 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylate (4.00 g, 14.2 mmol, yield: 56.5%) as colourless oil.

30 ¹H NMR (400 MHz, DMSO-d₆): δ 6.46 (s, 1H), 4.79 (q, *J* = 8.8 Hz, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.19 – 4.15 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.10 – 1.06 (m, 2H), 0.99 – 0.94 (m, 2H).

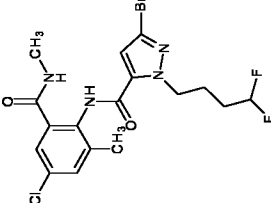
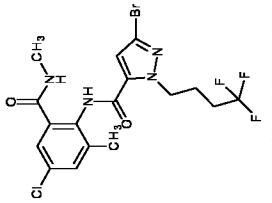
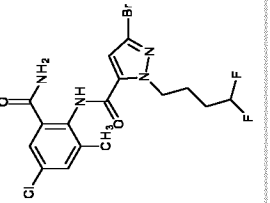
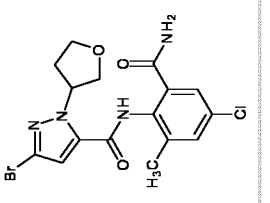
Step 2: Preparation of 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylic acid

A 250 mL two-neck round bottom flask was equipped with nitrogen balloon and it was charged with ethyl 2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxylate (6.20 g, 22.3 mmol) in THF: MeOH (60.0 mL). Then a solution of lithium hydroxide hydrate (1.87 g, 44.6 mmol) in water (20 mL) was added at rt, and resulting reaction mixture was stirred at for 3 h. Reaction was monitored by TLC (10% MeOH/CH₂Cl₂) and it showed no starting material. Reaction mixture was concentrated under reduced pressure to obtain crude product, crude product was diluted with water and added saturated citric acid solution (10 mL, pH = 4) precipitated solid was filtered, washed with water dried to afford. 2-cyclopropyl-5-(2,2,2-trifluoroethoxy) pyrazole-3-carboxylic acid (5.20 g, 20.8 mmol, yield: 93.3%) as off-white solid.

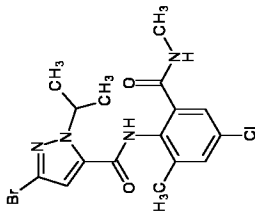
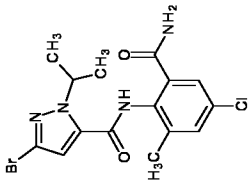
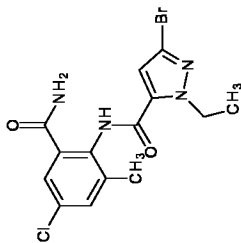
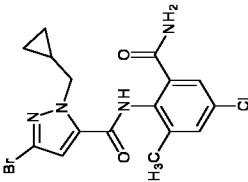
¹H NMR (400 MHz, DMSO-d₆): δ 6.40 (s, 1H), 4.77 (q, *J* = 8.8 Hz, 2H), 4.30 – 4.24 (m, 1H), 1.07 – 1.04 (m, 2H), 0.96 – 0.91 (m, 2H)

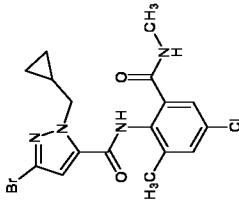
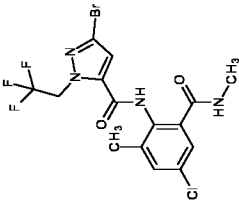
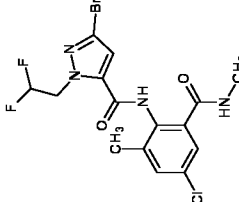
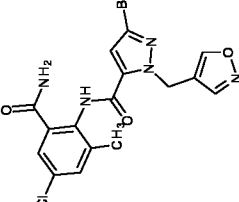
Table P: Physical data of compounds of formula I

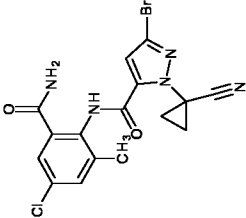
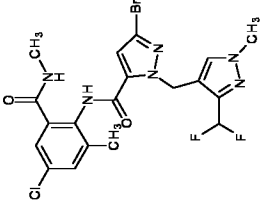
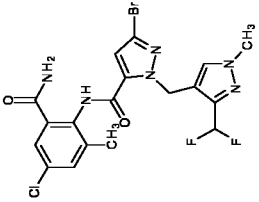
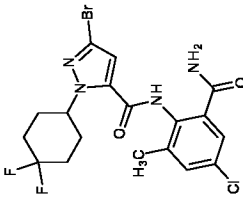
Entry	IUPAC name	STRUCTURE	RT (min)	[M+H] (measured)	Method	NMR	NMR 19F
P1	5-bromo-N-(2-carbamoyl-4-chloro-6-methylphenyl)-2-(3,3-difluoropropyl)pyrazole-3-carboxamide		0.92	437	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.12 (s, 1 H) 7.82 (br s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.41 - 7.48 (m, 2 H) 7.11 (s, 1 H) 5.96 - 6.30 (m, 1 H) 4.62 (t, J=7.08 Hz, 2 H) 2.26 - 2.42 (m, 2 H) 2.22 (s, 3 H).	¹⁹ F NMR (377 MHz, DMSO-d ₆) δ ppm -116.13 (s, -CHF ₂).
P2	2-tert-butyl-N-[4-chloro-2-(cyclopropylmethylcarbamoyl)-6-methylphenyl]-5-(trifluoromethyl)pyrazole-3-carboxamide		1.20	457	1		
P3	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(3,3-difluoropropyl)pyrazole-3-carboxamide		0.96	451	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.11 (s, 1 H) 8.28 - 8.37 (m, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.39 (d, J=2.54 Hz, 1 H) 7.11 (s, 1 H) 5.96 - 6.28 (m, 1 H) 4.61 (t, J=6.90 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H) 2.29 - 2.40 (m, 2 H) 2.23 (s, 3 H).	¹⁹ F NMR (377 MHz, DMSO-d ₆) δ ppm -116.12 (s, -CHF ₂).

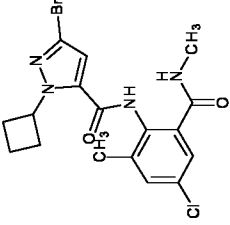
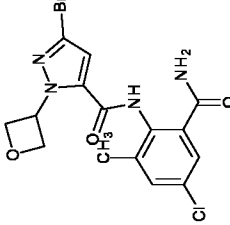
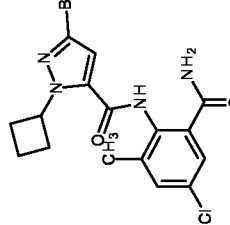
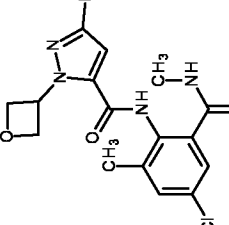
P4	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4-difluorobutyl)pyrazole-3-carboxamide		0.99	465	1	¹ H NMR (400 MHz, DMSO) δ ppm 10.09 (s, 1 H) 8.32 (br d, J=4.72 Hz, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.08 (s, 1 H) 5.90 - 6.23 (m, 1 H) 4.48 (t, J=6.72 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H) 2.22 (s, 3 H) 1.72 - 1.92 (m, 4 H).	¹⁹ F NMR (377 MHz, DMSO) δ ppm -115.60 (s, -CHF ₂).
P5	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(4,4-trifluorobutyl)pyrazole-3-carboxamide		1.04	483	1	¹ H NMR (400 MHz, DMSO) δ ppm 10.10 (s, 1 H) 8.28 - 8.37 (m, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.09 (s, 1 H) 4.51 (t, J=7.08 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H) 2.18 - 2.29 (m, 5 H) 1.94 - 2.02 (m, 2 H).	¹⁹ F NMR (377 MHz, DMSO) δ ppm -64.89 (s, -CF ₃).
P6	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorobutyl)pyrazole-3-carboxamide		0.94	451	1	¹ H NMR (400 MHz, DMSO) δ ppm 10.11 (s, 1 H) 7.82 (br s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.41 - 7.47 (m, 2 H) 7.09 (s, 1 H) 5.91 - 6.24 (m, 1 H) 4.49 (t, J=6.90 Hz, 2 H) 2.22 (s, 3 H) 1.72 - 1.92 (m, 4 H).	¹⁹ F NMR (377 MHz, DMSO) δ ppm -115.59 (s, -CHF ₂).
P7	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorobutyl)pyrazole-3-carboxamide		0.86	429	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.10 (1 H, br s), 7.80 (1 H, br s), 7.52 (1 H, d, J=2.18 Hz), 7.47 (1 H, br s), 7.43 (1 H, d, J=2.54 Hz), 7.08 (1 H, s), 5.66-5.73 (1 H, m), 3.93-3.99 (2 H, m), 3.77-3.83 (2 H, m), 2.27-2.39 (2 H, m), 2.23 (3 H, s).	

P8	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-ethyl-pyrazole-3-carboxamide		0.93	399	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.06 (s, 1 H) 8.31 (br d, J=4.72 Hz, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.05 (s, 1 H) 4.44 (q, J=7.02 Hz, 2 H) 2.67 (d, J=4.72 Hz, 3 H) 2.23 (s, 3 H) 1.31 (t, J=7.27 Hz, 3 H).	
P9	5-bromo-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.83	414	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 10.48 (s, 1 H) 7.95 (br s, 2 H) 7.86 (s, 1 H) 7.59 (s, 1 H) 7.22 (s, 1 H) 6.36 (tt, J=1.00 Hz, 1 H) 4.97 (td, J=1.00 Hz, 2 H) 2.26 - 2.30 (m, 3 H)	
P10	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-trifluorobutyl)pyrazole-3-carboxamide		0.99	469	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.12 (s, 1 H) 7.82 (br s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.40 - 7.48 (m, 2 H) 7.09 (s, 1 H) 4.51 (t, J=7.08 Hz, 2 H) 2.19 - 2.30 (m, 5 H) 1.94 - 2.02 (m, 2 H).	¹⁹ F NMR (377 MHz, DMSO-d ₆) δ ppm -64.84 (s, -CF ₃).
P11	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydrofuran-3-yl-pyrazole-3-carboxamide		0.91	443	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.10 (1 H, br. s), 8.31 (1 H, br. q, J=4.72 Hz), 7.51 (1 H, d, J=1.82 Hz), 7.39 (1 H, d, J=2.18 Hz), 7.07 (1 H, s), 5.64-5.71 (1 H, m), 3.93-3.99 (2 H, m), 3.77-3.83 (2 H, m), 2.68 (3 H, d, J=4.36 Hz), 2.27-2.40 (2 H, m), 2.23 (3 H, s).	

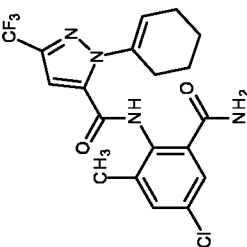
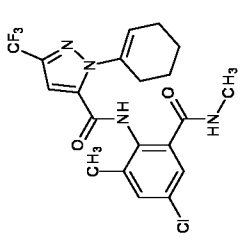
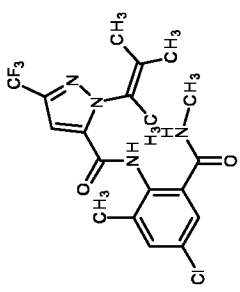
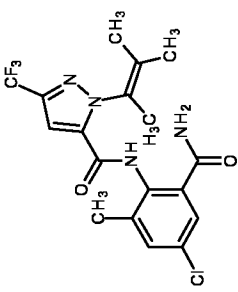
P12	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydrofuran-3-yl-pyrazole-3-carboxamide		0.99	415	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.06 (1 H, br. s), 8.30 (1 H, br. q, J=4.72 Hz), 7.51 (1 H, d, J=2.18 Hz), 7.38 (1 H, d, J=2.54 Hz), 6.99 (1 H, s), 5.27-5.38 (1 H, m), 2.67 (3 H, d, J=4.36 Hz), 2.23 (3 H, s), 1.38 (6 H, d, J=6.54 Hz).
P13	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-isopropyl-pyrazole-3-carboxamide		0.94	401	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 7.80 (1 H, br. s), 7.52 (1 H, d, J=2.18 Hz), 7.47 (1 H, br. s), 7.44 (1 H, d, J=2.54 Hz), 7.00 (1 H, s), 5.28-5.39 (1 H, m), 2.23 (3 H, s), 1.38 (6 H, d, J=6.54 Hz).
P14	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-ethyl-pyrazole-3-carboxamide		0.88	387	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.06 (s, 1 H) 7.80 (br s, 1 H) 7.52 (d, J=1.82 Hz, 1 H) 7.45 - 7.49 (m, 1 H) 7.42 - 7.45 (m, 1 H) 7.06 (s, 1 H) 4.45 (q, J=7.27 Hz, 2 H) 2.22 (s, 3 H) 1.31 (t, J=7.27 Hz, 3 H).
P15	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(cyclopropylmethyl)pyrazole-3-carboxamide		0.94	413	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.01 - 10.17 (m, 1 H) 7.74 - 7.88 (m, 1 H) 7.46 - 7.49 (m, 1 H) 7.41 - 7.55 (m, 2 H) 7.07 - 7.12 (m, 1 H) 4.28 - 4.36 (m, 2 H) 2.19 - 2.26 (m, 3 H) 1.22 - 1.33 (m, 1 H) 0.31 - 0.51 (m, 4 H)

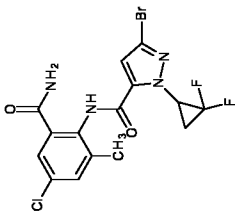
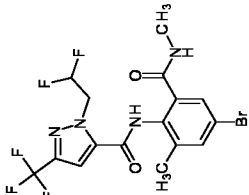
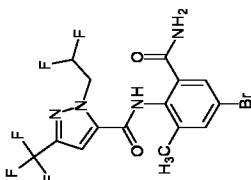
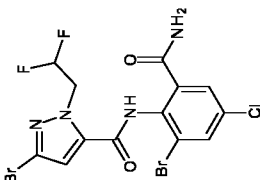
P16	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclopropylmethyl)pyrazole-3-carboxamide		1	427	1	1H NMR (400 MHz, DMSO-d6) δ ppm 8.32 (1 H, br. q, J=4.72 Hz), 7.51 (1 H, d, J=2.18 Hz), 7.40 (1 H, br. s), 7.38 (1 H, d, J=2.18 Hz), 7.07 (1 H, s), 4.30 (2 H, d, J=7.27 Hz), 2.66 (3 H, d, J=4.72 Hz), 2.22 (3 H, s), 1.21-1.31 (1 H, m), 0.42-0.47 (2 H, m), 0.31-0.35 (2 H, m).	
P23	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2,2-trifluoroethyl)pyrazole-3-carboxamide		1.02	455	1	1H NMR (400 MHz, DMSO-d6) δ ppm 10.13 - 10.31 (m, 1 H) 8.21 - 8.40 (m, 1 H) 7.46 - 7.58 (m, 1 H) 7.35 - 7.45 (m, 1 H) 7.19 - 7.34 (m, 1 H) 5.39 - 5.56 (m, 2 H) 2.64 - 2.69 (m, 3 H) 2.18 - 2.22 (m, 3 H)	
P25	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.94	437	1	1H NMR (400 MHz, DMSO-d6) δ ppm 10.13 - 10.25 (m, 1 H) 8.23 - 8.39 (m, 1 H) 7.51 - 7.54 (m, 1 H) 7.39 - 7.42 (m, 1 H) 7.15 - 7.21 (m, 1 H) 6.35 (m, 1 H) 4.95 (m, 2 H) 2.68 (m, 3 H) 2.23 (s, 3 H)	¹⁹ F NMR (377 MHz, DMSO-d6) δ ppm -122.67 (s, CHF2)
P30	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(isoxazol-4-ylmethyl)pyrazole-3-carboxamide		0.86	440	1	1H NMR (400 MHz, DMSO-d6) δ ppm 10.17 (s, 1 H) 8.96 (s, 1 H) 8.58 (s, 1 H) 7.86 (br s, 1 H) 7.53 (d, J=2.18 Hz, 1 H) 7.47 - 7.51 (m, 1 H) 7.44 - 7.47 (m, 1 H) 7.13 (s, 1 H) 5.58 (s, 2 H) 2.22 (s, 3 H).	

P31	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1-cyanocyclopropyl)pyrazole-3-carboxamide		0.83	424	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.46 - 7.56 (m, 2 H) 6.95 - 6.96 (m, 1 H) 5.88 - 6.07 (m, 1 H) 5.45 - 5.85 (m, 2 H) 2.16 (s, 3 H) 1.88 - 2.01 (m, 2 H) 1.57 - 1.70 (m, 2 H).
P32	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[[3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl]pyrazole-3-carboxamide		0.94	517	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 2.29 - 2.31 (m, 3 H) 2.96 - 2.99 (m, 3 H) 3.86 - 3.89 (m, 3 H) 5.72 - 5.75 (m, 2 H) 6.12 - 6.18 (m, 1 H) 6.66 - 6.96 (m, 2 H) 7.31 - 7.33 (m, 1 H) 7.39 - 7.42 (m, 1 H) 7.42 - 7.45 (m, 1 H) 9.93 - 10.02 (m, 1 H)
P33	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-[[3-(difluoromethyl)-1-methyl-pyrazol-4-yl]methyl]pyrazole-3-carboxamide		0.9	503	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.12 (s, 1 H) 7.84 (s, 1 H) 7.68 (s, 1 H) 7.53 (d, J=2.18 Hz, 1 H) 7.42 - 7.49 (m, 2 H) 6.86 - 7.16 (m, 2 H) 5.63 (s, 2 H) 3.82 (s, 3 H) 2.20 (s, 3 H). ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ ppm -111.18 (-CHF ₂).
P34	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(4,4-difluorocyclohexyl)pyrazole-3-carboxamide		1.02	477	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.09 - 10.15 (m, 1 H) 7.74 - 7.85 (m, 1 H) 7.39 - 7.54 (m, 2 H) 7.45 - 7.49 (m, 1 H) 7.00 - 7.07 (m, 1 H) 5.06 - 5.18 (m, 1 H) 2.21 - 2.25 (m, 3 H) 1.89 - 2.19 (m, 9 H)

P35	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclobutyl-pyrazole-3-carboxamide		1.04	425	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.87 - 10.00 (m, 1 H) 7.28 - 7.39 (m, 2 H) 6.79 - 6.85 (m, 1 H) 6.11 - 6.23 (m, 1 H) 5.56 - 5.68 (m, 1 H) 2.92 - 3.00 (m, 3 H) 2.62 - 2.77 (m, 2 H) 2.35 - 2.49 (m, 2 H) 2.25 - 2.33 (m, 2 H) 1.72 - 1.94 (m, 2 H)
P36	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(oxetan-3-yl)pyrazole-3-carboxamide		0.77	415	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.30 - 10.45 (m, 1 H) 7.91 - 8.04 (m, 1 H) 7.58 - 7.71 (m, 1 H) 7.42 - 7.58 (m, 2 H) 6.96 - 7.05 (m, 1 H) 5.66 - 5.85 (m, 1 H) 4.89 - 5.11 (m, 4 H) 2.14 - 2.30 (m, 3 H)
P37	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-cyclobutyl-pyrazole-3-carboxamide		0.97	413	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.82 - 9.91 (m, 1 H) 7.36 - 7.46 (m, 2 H) 6.76 - 6.82 (m, 1 H) 5.93 - 6.15 (m, 1 H) 5.55 - 5.70 (m, 2 H) 2.62 - 2.76 (m, 2 H) 2.36 - 2.47 (m, 2 H) 2.27 - 2.35 (m, 3 H) 1.70 - 1.93 (m, 2 H)
P38	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(oxetan-3-yl)pyrazole-3-carboxamide		0.81	429	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.58 - 9.67 (m, 1 H) 7.30 - 7.37 (m, 2 H) 6.92 - 6.95 (m, 1 H) 6.23 - 6.32 (m, 1 H) 5.63 - 5.72 (m, 1 H) 5.22 - 5.29 (m, 2 H) 5.00 - 5.08 (m, 2 H) 2.87 - 2.92 (m, 3 H) 2.28 - 2.34 (m, 3 H)

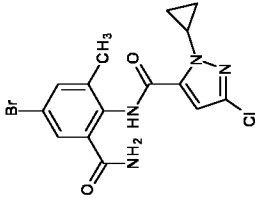
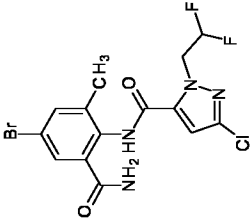
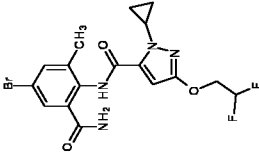
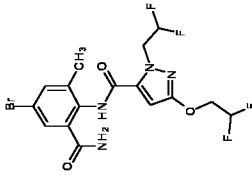
P41	N-(2-carbamoyl-4-chloro-6-methylphenyl)-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1.1	417	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.87 - 9.97 (m, 1 H) 7.35 - 7.47 (m, 2 H) 7.01 - 7.08 (m, 1 H) 5.65 - 6.21 (m, 2 H) 5.08 - 5.22 (m, 1 H) 2.27 - 2.39 (m, 3 H) 2.16 - 2.27 (m, 1 H) 1.42 - 1.58 (m, 3 H) 0.94 - 1.03 (m, 3 H) 0.64 - 0.76 (m, 3 H)	¹⁹ F NMR (376 MHz, CDCl ₃) δ ppm -61.94 (s, CF ₃)
P42	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylpropyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1.15	431	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.88 - 10.00 (m, 1 H) 7.33 - 7.42 (m, 1 H) 7.03 - 7.17 (m, 1 H) 6.13 - 6.27 (m, 1 H) 5.08 - 5.21 (m, 1 H) 2.90 - 3.00 (m, 4 H) 2.26 - 2.35 (m, 4 H) 2.14 - 2.26 (m, 1 H) 1.46 - 1.58 (m, 4 H) 0.94 - 1.04 (m, 3 H) 0.63 - 0.77 (m, 3 H)	¹⁹ F NMR (376 MHz, CDCl ₃) δ ppm -61.96 (m, CF ₃)
P43	N-(2-carbamoyl-4-chloro-6-methylphenyl)-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide		0.9	377	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.52 - 9.59 (m, 1 H) 7.34 - 7.39 (m, 2 H) 6.25 - 6.29 (m, 1 H) 5.63 - 6.20 (m, 2 H) 3.91 - 3.97 (m, 3 H) 2.25 - 2.28 (m, 3 H) 2.06 - 2.11 (m, 3 H) 1.81 - 1.84 (m, 3 H) 1.44 - 1.49 (m, 3 H)	
P44	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carboxamide		0.95	391	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.57 - 9.63 (m, 1 H) 7.25 - 7.27 (m, 1 H) 7.21 (d, J=2.54 Hz, 1 H) 6.36 - 6.44 (m, 1 H) 6.30 - 6.33 (m, 1 H) 3.91 - 3.95 (m, 3 H) 2.88 (d, J=4.72 Hz, 4 H) 2.19 - 2.25 (m, 3 H) 2.06 - 2.09 (m, 3 H) 1.80 - 1.85 (m, 3 H) 1.44 - 1.47 (m, 3 H)	

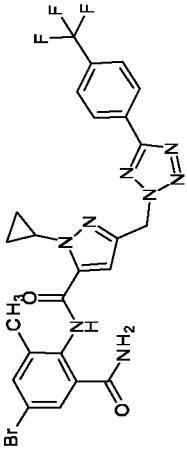
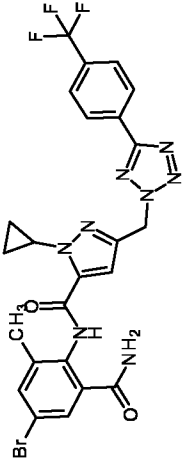
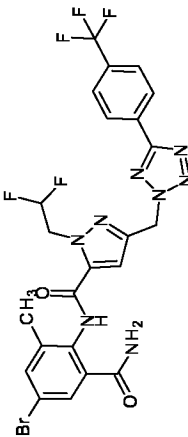
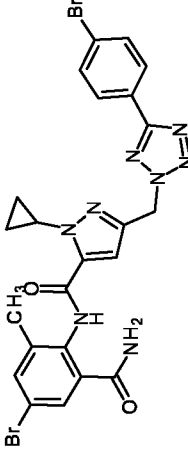
P45	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide					¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.20 - 10.33 (m, 1 H) 7.78 - 7.90 (m, 1 H) 7.47 - 7.51 (m, 1 H) 7.42 - 7.55 (m, 3 H) 5.88 - 5.97 (m, 1 H) 3.27 - 3.36 (m, 1 H) 2.35 - 2.44 (m, 2 H) 2.21 - 2.27 (m, 2 H) 2.12 - 2.20 (m, 2 H) 1.69 - 1.79 (m, 2 H) 1.53 - 1.66 (m, 2 H)	¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm - 60.73 (s, CF ₃)
P46	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclohexen-1-yl)-5-(trifluoromethyl)pyrazole-3-carboxamide					¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.91 - 10.00 (m, 1 H) 7.32 - 7.41 (m, 1 H) 7.09 - 7.18 (m, 1 H) 6.18 - 6.31 (m, 1 H) 5.92 - 6.10 (m, 1 H) 2.88 - 3.03 (m, 3 H) 2.42 - 2.55 (m, 2 H) 2.28 (s, 3 H) 2.20 - 2.26 (m, 2 H) 1.81 - 1.91 (m, 2 H) 1.66 - 1.76 (m, 2 H) 1.56 - 1.64 (m, 1 H)	¹⁹ F NMR (376 MHz, CDCl ₃) δ ppm -62.15 (s, CF ₃)
P47	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1	429	1.07	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.86 - 9.97 (m, 1 H) 7.33 - 7.39 (m, 1 H) 7.26 - 7.28 (m, 1 H) 7.17 - 7.22 (m, 1 H) 6.17 - 6.24 (m, 1 H) 2.89 - 3.00 (m, 3 H) 2.22 - 2.31 (m, 3 H) 2.10 - 2.20 (m, 3 H) 1.83 - 1.91 (m, 3 H) 1.39 - 1.45 (m, 3 H)	¹⁹ F NMR (376 MHz, CDCl ₃) δ ppm -62.09 (s, CF ₃)
P48	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1,2-dimethylprop-1-enyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1	415	1.02	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.12 - 10.22 (m, 1 H) 7.74 - 7.88 (m, 1 H) 7.47 - 7.50 (m, 1 H) 7.42 - 7.45 (m, 1 H) 7.36 - 7.41 (m, 1 H) 2.21 (s, 3 H) 2.00 - 2.03 (m, 3 H) 1.74 - 1.80 (m, 3 H) 1.26 - 1.34 (m, 3 H)	¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm - 60.64 (s, CF ₃)

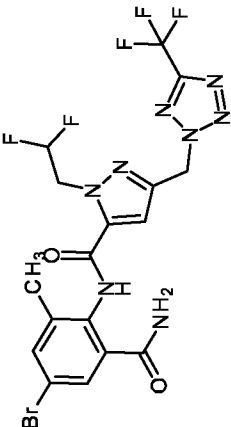
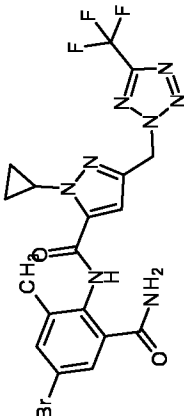
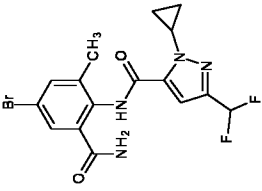
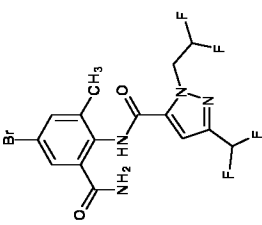
P49	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluorocyclopropyl)pyrazole-3-carboxamide		0.91	435	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (s, 1 H) 7.82 (br s, 1 H) 7.53 (d, J=2.18 Hz, 1 H) 7.47-7.50 (m, 1 H) 7.44-7.47 (m, 1 H) 7.18 (s, 1 H) 4.64 (br d, J=8.36 Hz, 1 H) 2.29-2.40 (m, 2 H) 2.22 (s, 3 H).	¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm -131.01 (d, J=159.75 Hz, 1 F) -142.28 (d, J=159.74 Hz, 1 F).
P57	N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1.01	471	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.24-10.40 (m, 1 H) 8.25-8.40 (m, 1 H) 7.48-7.72 (m, 3 H) 6.40 (tt, J=1.00 Hz, 1 H) 5.08 (td, J=1.00 Hz, 2 H) 2.68 (d, J=1.00 Hz, 4 H) 2.23 (s, 3 H)	
P58	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		0.97	457	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.32 (s, 1 H) 7.84 (s, 1 H) 7.64-7.71 (m, 1 H) 7.46-7.62 (m, 3 H) 6.41 (tt, J=1.00 Hz, 1 H) 5.09 (td, J=1.00 Hz, 2 H) 2.23 (s, 3 H)	
P59	5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.91	487	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.34-10.49 (m, 1 H) 7.19-8.06 (m, 5 H) 6.33 (tt, J=1.00 Hz, 1 H) 4.93 (td, J=1.00 Hz, 2 H)	

P60	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide		0.98	433	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.11 - 10.25 (m, 1 H) 7.79 - 7.92 (m, 1 H) 7.29 - 7.71 (m, 4 H) 4.31 - 4.52 (m, 1 H) 2.21 - 2.31 (m, 3 H) 0.94 - 1.23 (m, 4 H)	
P61	N-[4-bromo-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropyl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.03	445	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.99 - 10.26 (m, 1 H) 8.22 - 8.43 (m, 1 H) 7.61 - 7.72 (m, 1 H) 7.47 - 7.58 (m, 1 H) 7.27 - 7.39 (m, 1 H) 4.29 - 4.46 (m, 1 H) 2.65 - 2.73 (m, 3 H) 2.19 - 2.30 (m, 3 H) 0.97 - 1.23 (m, 4 H)	¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm -60.56 (s, CF ₃)
P62	5-bromo-N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide		0.91	463	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.22 - 10.29 (m, 1 H) 7.98 - 8.04 (m, 1 H) 7.81 - 7.87 (m, 1 H) 7.62 - 7.66 (m, 1 H) 7.52 - 7.62 (m, 1 H) 6.99 - 7.09 (m, 1 H) 4.24 - 4.36 (m, 1 H) 1.07 - 1.14 (m, 2 H) 0.94 - 1.03 (m, 2 H)	
P63	2-tert-butyl-N-[4-chloro-2-(isopropylcarbamoyl)-6-methyl-phenyl]-5-(trifluoromethyl)pyrazole-3-carboxamide		1.19	445	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.51 - 9.61 (m, 1 H) 7.67 - 7.78 (m, 1 H) 7.49 - 7.60 (m, 1 H) 7.35 - 7.42 (m, 1 H) 6.96 - 7.04 (m, 1 H) 5.88 - 5.97 (m, 1 H) 2.32 - 2.37 (m, 3 H) 1.73 - 1.75 (m, 9 H) 1.23 - 1.26 (m, 6 H)	

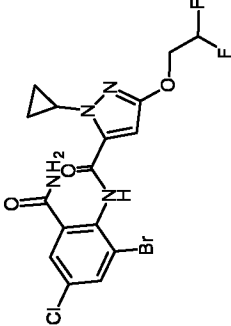
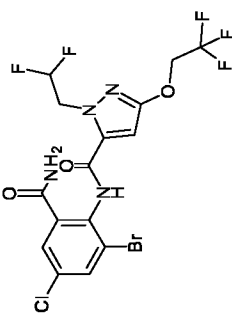
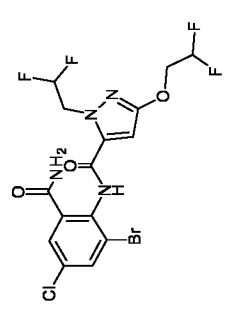
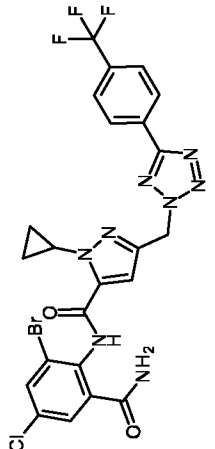
P64	N-[4-chloro-2-(cyclopropylmethyl/carbamoyl)-6-methyl-phenyl]-2-ethyl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.12	429	1				
P65	N-[4-chloro-2-(isobutyl/carbamoyl)-6-methyl-phenyl]-2-ethyl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.11	417	1				
P66	N-[4-chloro-2-(cyclopropylmethyl/carbamoyl)-6-methyl-phenyl]-2-propyl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.17	443	1			1H NMR (400 MHz, DMSO-d6) δ ppm 10.05 - 10.27 (m, 1 H) 8.37 - 8.53 (m, 1 H) 7.51 - 7.56 (m, 1 H) 7.41 - 7.47 (m, 1 H) 7.36 - 7.41 (m, 1 H) 4.50 (m, 2 H) 2.98 - 3.07 (m, 2 H) 2.20 - 2.28 (m, 3 H) 1.70 - 1.83 (m, 3 H) 0.86 - 0.95 (m, 1 H) 0.77 - 0.85 (m, 3 H) 0.25 - 0.35 (m, 2 H) 0.09 - 0.20 (m, 2 H)	19F NMR (376 MHz, DMSO-d6) δ ppm -60.73 (s, CF3)
P67	N-[4-chloro-2-(isopropyl/carbamoyl)-6-methyl-phenyl]-2-propyl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.16	431	1				

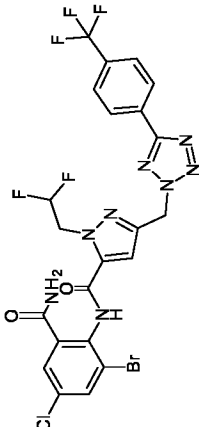
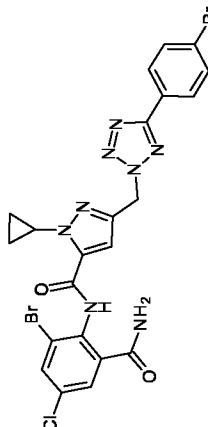
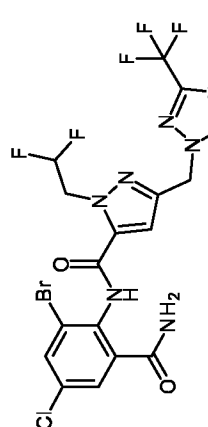
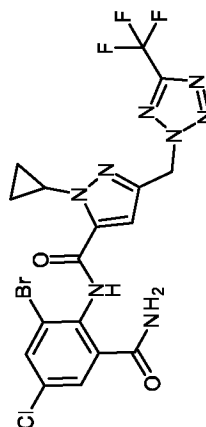
P68	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide		0.69	397	2		
P69	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		1.08	403.99	2		
P70	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide		0.72	443	2		
P71	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.8	485	2		

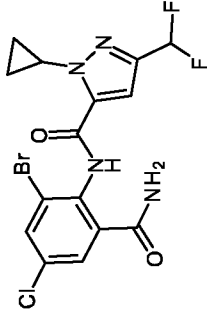
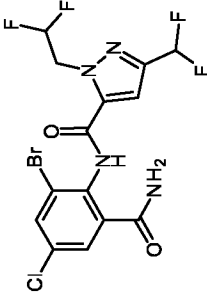
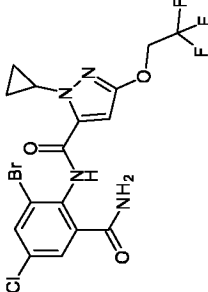
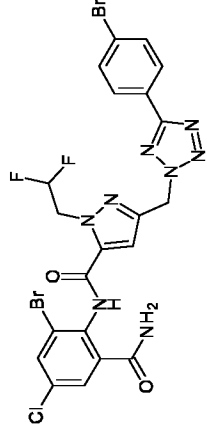
P72	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.73	467	2	
P73	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.97	589	2	
P74	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.95	613	2	
P75	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]cyclopropylpyrazole-3-carboxamide		0.95	599	2	

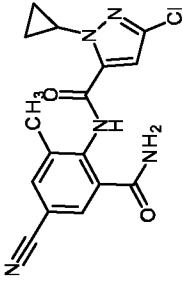
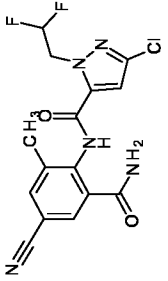
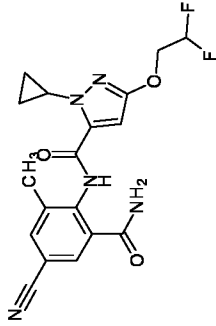
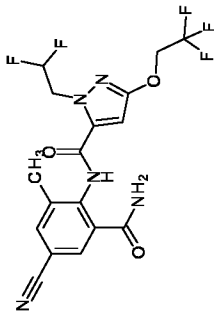
P76	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.78	537	2	
P77	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.82	513	2	
P78	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide		0.69	413	2	
P79	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide		0.69	437	2	

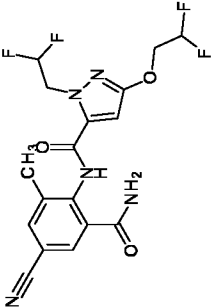
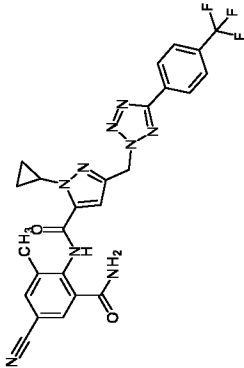
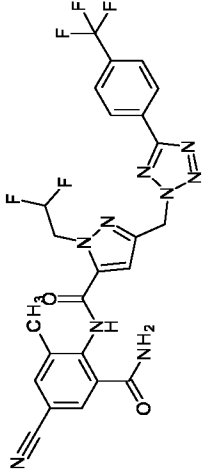
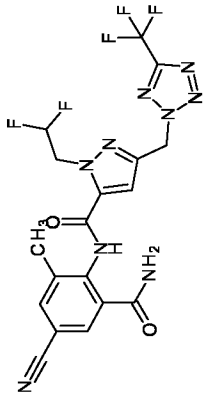
P80	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.81	461	2	
P81	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.94	523	2	
P82	N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-chloro-2-cyclopropyl-pyrazole-3-carboxamide		0.68	416	2	
P83	N-(4-bromo-2-carbamoyl-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.68	440	2	

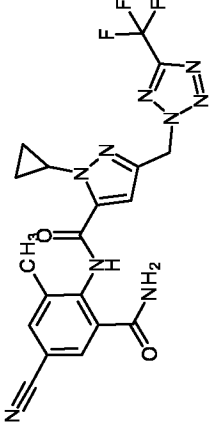
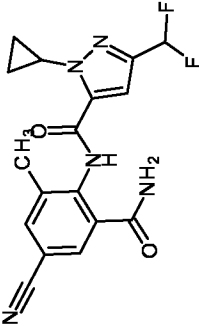
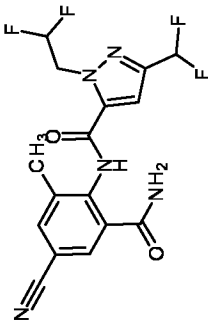
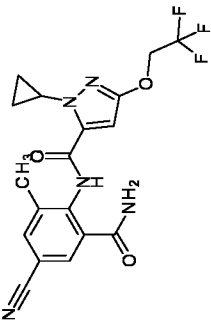
P84	N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide		0.71	463	2	
P85	N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.79	504	2	
P86	N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-5-(2,2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.71	486	2	
P87	N-(2-bromo-6-carbamoyl-4-chloro-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		1.02	609	2	

P88	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-2-(2-(2-difluoroethyl)-5-[[5-(4-(trifluoromethyl)phenyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.95	633	2		
P89	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-cyclopropylpyrazole-3-carboxamide		0.95	599	2		
P90	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-2-(2-(2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.82	557	2		
P91	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.8	533	2		

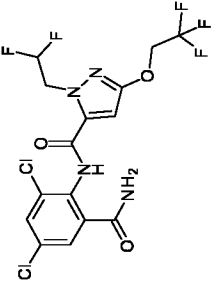
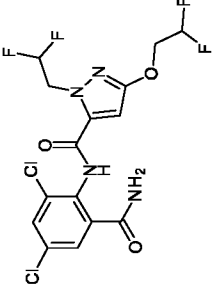
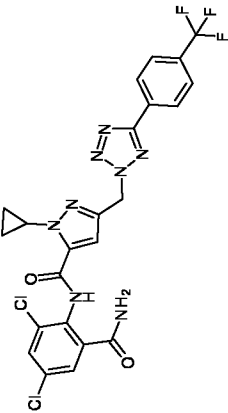
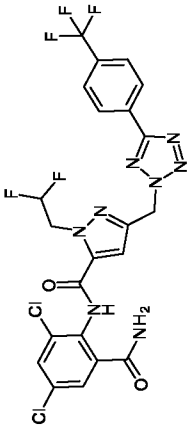
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P93	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide		0.67	456	2	
P94	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.79	480	2	
P95	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.94	643	2	

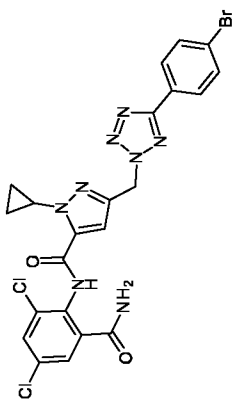
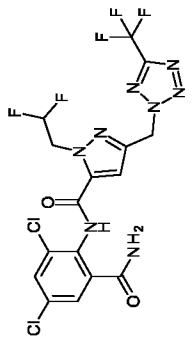
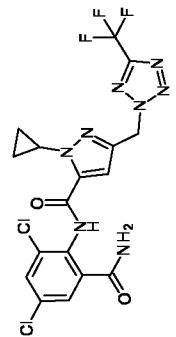
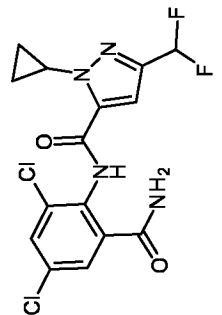
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P97	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.57	368	2	
P98	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide		0.62	390	2	
P99	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.7	432	2	

P100	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-5-(2-(2-difluoroethoxy)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.62	390	2		
P101	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.94	536	2		
P102	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2-(2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.91	560	2		
P103	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2-(2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.71	484	2		

P104	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-[(5-(trifluoromethyl)tetrazol-2-yl)methyl]pyrazole-3-carboxamide		0.78	460	2		
P105	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide		0.58	360	2		
P106	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide		0.57	384	2		
P107	N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.71	407	2		

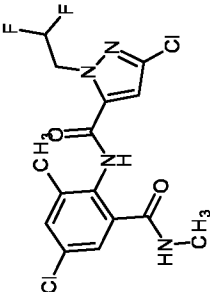
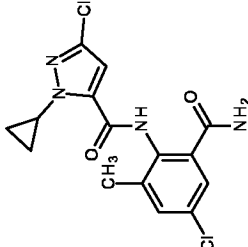
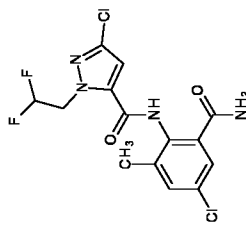
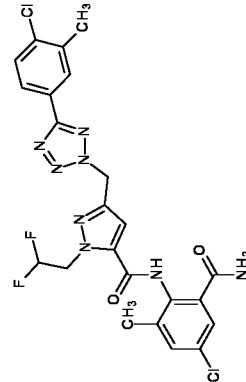
P108	5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4-cyano-6-methyl-phenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.86	570	2		
P109	N-(2-bromo-6-carbamoyl-4-chlorophenyl)-5-chloro-2-cyclopropylpyrazole-3-carboxamide		0.68	372	2		
P110	N-(2-carbamoyl-4,6-dichlorophenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.67	396	2		
P111	N-(2-carbamoyl-4,6-dichlorophenyl)-2-cyclopropyl-5-(2,2-difluoroethoxy)pyrazole-3-carboxamide		0.67	419	2		

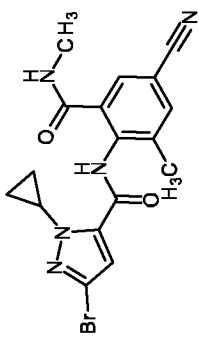
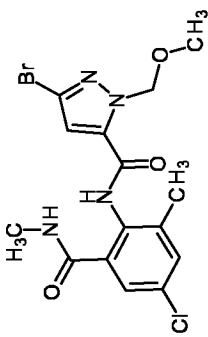
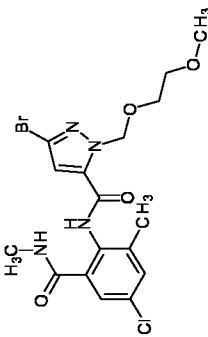
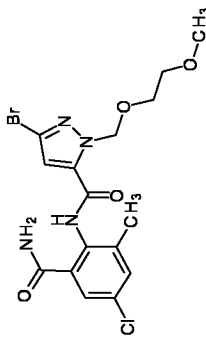
P112	N-(2-carbamoyl-4,6-dichlorophenyl)-2-(2-(2-difluoroethoxy)-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.78	461	2	
P113	N-(2-carbamoyl-4,6-dichlorophenyl)-5-(2-(2-difluoroethoxy)-2-(2,2-difluoroethoxy)pyrazole-3-carboxamide		0.81	443	2	
P114	N-(2-carbamoyl-4,6-dichlorophenyl)-2-cyclopropyl-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		1.01	565	2	
P115	N-(2-carbamoyl-4,6-dichlorophenyl)-2-(2-(2-difluoroethoxy)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.93	589	2	

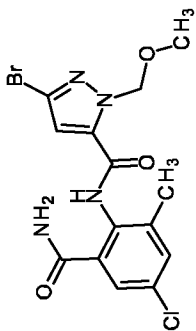
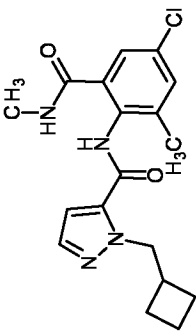
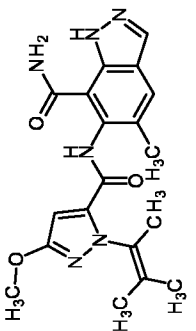
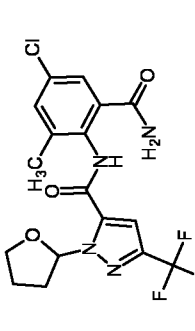
P116	5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-pyrazole-3-carboxamide		1	575	2	
P117	N-(2-carbamoyl-4,6-dichloro-phenyl)-2-(2-(2,2-difluoroethyl)-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.79	513	2	
P118	N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-[[5-(trifluoromethyl)tetrazol-2-yl]methyl]pyrazole-3-carboxamide		0.79	488	2	
P119	N-(2-carbamoyl-4,6-dichloro-phenyl)-2-cyclopropyl-5-(difluoromethyl)pyrazole-3-carboxamide		0.67	413	2	

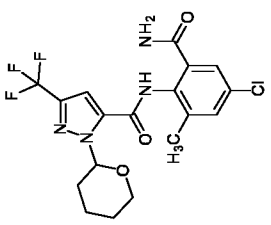
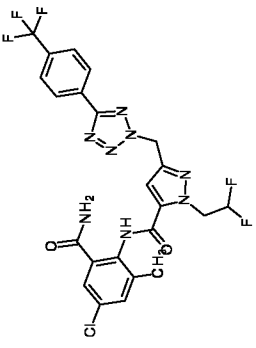
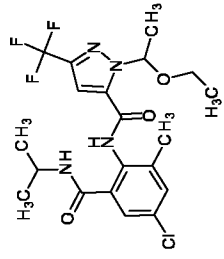
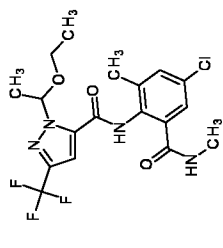
P120	N-(2-carbamoyl-4,6-dichlorophenyl)-2-(2,2-difluoroethyl)-5-(difluoromethyl)pyrazole-3-carboxamide		0.67	413	2		
P121	N-(2-carbamoyl-4,6-dichlorophenyl)-2-cyclopropyl-5-(2,2,2-trifluoroethoxy)pyrazole-3-carboxamide		0.79	437	2		
P122	5-[[5-(4-bromophenyl)tetrazol-2-yl]methyl]-N-(2-carbamoyl-4,6-dichlorophenyl)-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.92	599	2		
P123	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(1H-pyrazol-3-ylmethyl)pyrazole-3-carboxamide		0.81	451	1		1H NMR (400 MHz, DMSO-d6) δ ppm 2.21 (s, 3 H) 2.67 (d, J=4.72 Hz, 3 H) 5.65 (s, 2 H) 6.08 (d, J=1.82 Hz, 1 H) 7.09 (s, 1 H) 7.39 (d, J=2.18 Hz, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.59 (br s, 1 H) 8.31 (br d, J=4.36 Hz, 1 H) 10.11 (s, 1 H) 12.62 - 12.78 (br s, 1 H)

P124	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1H-pyrazol-3-ylmethyl)pyrazole-3-carboxamide		0.77	437	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 2.20 (s, 3 H) 5.66 (s, 2 H) 6.10 (s, 1 H) 7.09 (s, 1 H) 7.36 - 7.67 (m, 4 H) 7.82 (br s, 1 H) 8.17 (br s, 1 H) 10.14 (br s, 1 H).
P125	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxamide		0.97	463	1	¹ H NMR (400 MHz, DMSO-d ₆) 1.33 - 1.48 (m, 4 H) 2.25 (s, 3 H) 2.70 (d, J=4.36 Hz, 3 H) 6.17 - 6.57 (m, 1 H) 7.06 (s, 1 H) 7.34 - 7.59 (m, 2 H) 8.26 - 8.49 (m, 1 H) 9.85 - 10.46 (m, 1 H)
P126	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-[1-(difluoromethyl)cyclopropyl]pyrazole-3-carboxamide		0.91	449	1	¹ H NMR (400 MHz, DMSO-d ₆) 1.34 - 1.50 (m, 4 H) 2.21 - 2.27 (m, 3 H) 6.15 - 6.60 (m, 1 H) 6.95 - 7.12 (m, 1 H) 7.38 - 7.64 (m, 3 H) 7.76 - 7.96 (m, 1 H) 10.01 - 10.25 (m, 1 H)
P127	5-chloro-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-cyclopropylpyrazole-3-carboxamide		0.93	367	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.35 (s, 1 H) 7.48 - 7.57 (m, 1 H) 7.36 - 7.46 (m, 1 H) 6.94 (s, 1 H) 4.19 - 4.36 (m, 1 H) 2.68 - 2.72 (m, 3 H) 2.25 (s, 3 H) 0.93 - 1.15 (m, 4 H)

P128	5-chloro-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.92	391	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.68 - 10.44 (m, 1 H) 8.29 - 8.40 (m, 1 H) 7.53 (m, 1 H) 7.42 (m, 1 H) 7.13 (s, 1 H) 6.34 (m, 1 H) 4.94 (m, 2 H) 2.67 (m, 3 H) 2.23 (s, 3 H)	¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm 122.62 (s, CF₃)
P129	N-(2-carbamoyl-4-chloro-6-methylphenyl)-5-chloro-2-cyclopropylpyrazole-3-carboxamide		0.87	354	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.83 - 1.11 (m, 4 H) 2.16 - 2.28 (m, 3 H) 4.23 - 4.39 (m, 1 H) 6.96 - 7.08 (m, 1 H) 7.39 - 7.57 (m, 3 H) 7.74 - 7.90 (m, 1 H) 9.65 - 10.21 (m, 1 H)	
P130	N-(2-carbamoyl-4-chloro-6-methylphenyl)-5-chloro-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		0.88	377	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.23 (s, 1 H) 7.82 (s, 1 H) 7.42 - 7.57 (m, 3 H) 7.14 (s, 1 H) 6.35 (m, 1 H) 4.95 (m, 2 H) 2.22 (s, 3 H)	¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm 122.55 (s, CF₃)
P131	N-(2-carbamoyl-4-chloro-6-methylphenyl)-5-[[5-(4-chloro-3-methylphenyl)tetrazol-2-yl]methyl]-2-(2,2-difluoroethyl)pyrazole-3-carboxamide		1.09	549	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.15 (s, 1 H) 8.03 (d, J=1.45 Hz, 1 H) 7.89 (dd, J=8.36, 1.82 Hz, 1 H) 7.77 (br s, 1 H) 7.60 (d, J=8.36 Hz, 1 H) 7.49 (d, J=1.82 Hz, 1 H) 7.41 (s, 2 H) 7.10 (s, 1 H) 6.15 - 6.47 (m, 1 H) 6.04 (s, 2 H) 4.88 - 5.01 (m, 2 H) 2.41 (s, 3 H) 2.17 (s, 3 H)	¹⁹F NMR (377 MHz, DMSO-d₆) δ ppm 122.22 (s, CHF₂)

P132	5-bromo-N-[4-cyano-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclopropyl-pyrazole-3-carboxamide		0.88	402	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.08 - 10.53 (m, 1 H) 8.34 - 8.71 (m, 1 H) 7.87 - 7.94 (m, 1 H) 7.79 - 7.85 (m, 1 H) 6.93 - 7.08 (m, 1 H) 4.19 - 4.39 (m, 1 H) 2.66 - 2.77 (m, 3 H) 2.21 - 2.32 (m, 3 H) 0.91 - 1.14 (m, 4 H)
P133	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(methoxymethyl)pyrazole-3-carboxamide		0.88	415	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 2.22 (s, 3 H) 2.66 - 2.69 (m, 3 H) 3.23 - 3.26 (m, 3 H) 5.65 - 5.75 (m, 2 H) 7.14 - 7.20 (m, 1 H) 7.38 - 7.43 (m, 1 H) 7.50 - 7.56 (m, 1 H) 8.29 - 8.43 (m, 1 H) 10.02 - 10.19 (m, 1 H)
P134	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(2-methoxyethoxymethyl)pyrazole-3-carboxamide		0.88	459	1	¹ H NMR (400 MHz, CDCl ₃) δ ppm 9.92 (s, 1 H) 7.35 (d, J=2.18 Hz, 1 H) 7.29 (d, J=2.18 Hz, 1 H) 6.91 (s, 1 H) 6.13 - 6.23 (m, 1 H) 5.88 (s, 2 H) 3.70 - 3.79 (m, 2 H) 3.46 - 3.54 (m, 2 H) 3.30 (s, 3 H) 2.94 (d, J=4.72 Hz, 3 H) 2.29 (s, 3 H)
P135	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2-methoxyethoxymethyl)pyrazole-3-carboxamide		0.84	445	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.15 (s, 1 H) 7.82 (s, 1 H) 7.49 - 7.56 (m, 1 H) 7.41 - 7.49 (m, 2 H) 7.16 (s, 1 H) 5.76 (s, 2 H) 3.53 - 3.64 (m, 2 H) 3.34 - 3.42 (m, 2 H) 3.19 (s, 3 H) 2.21 (s, 3 H)

P136	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(methoxymethyl)pyrazole-3-carboxamide		0.83	401	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.17 (s, 1 H) 7.81 (s, 1 H) 7.52 (d, J=2.18 Hz, 1 H) 7.47 (br s, 1 H) 7.43 - 7.45 (m, 1 H) 7.17 (s, 1 H) 5.69 (s, 2 H) 3.25 (s, 3 H) 2.21 (s, 3 H).
P137	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(cyclobutylmethyl)pyrazole-3-carboxamide		0.96	361	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.91 - 10.04 (m, 1 H) 8.25 - 8.37 (m, 1 H) 7.49 - 7.57 (m, 2 H) 7.34 - 7.45 (m, 1 H) 6.93 - 7.03 (m, 1 H) 4.44 - 4.57 (m, 2 H) 2.70 - 2.77 (m, 1 H) 2.66 - 2.70 (m, 3 H) 2.17 - 2.29 (m, 3 H) 1.84 - 1.92 (m, 2 H) 1.68 - 1.84 (m, 4 H)
P138	6-[[2-(1,2-dimethylprop-1-enyl)-5-methoxy-pyrazole-3-carbonyl]amino]-5-methyl-1H-indazole-7-carboxamide		0.75	383	1	¹ H NMR (400 MHz, acetonitrile-d ₃) δ ppm 8.81 - 9.02 (m, 1 H) 7.91 - 8.10 (m, 1 H) 7.66 - 7.84 (m, 1 H) 6.32 - 6.42 (m, 1 H) 3.82 - 3.91 (m, 3 H) 2.27 - 2.33 (m, 3 H) 1.98 - 2.02 (m, 3 H) 1.73 - 1.80 (m, 3 H) 1.36 - 1.42 (m, 3 H)
P139	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-tetrahydrofuran-2-yl-5-(trifluoromethyl)pyrazole-3-carboxamide		0.99	415 (-H)	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.18 - 10.28 (m, 1 H) 7.78 - 7.87 (m, 1 H) 7.52 - 7.55 (m, 1 H) 7.48 - 7.52 (m, 1 H) 7.44 - 7.47 (m, 1 H) 7.39 - 7.43 (m, 1 H) 6.85 - 6.93 (m, 1 H) 3.87 - 4.06 (m, 2 H) 2.30 - 2.43 (m, 2 H) 2.23 - 2.27 (m, 3 H) 2.17 - 2.23 (m, 1 H) 1.93 - 2.05 (m, 1 H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm -61.3 (s, -CF ₃)

P140	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-tetrahydropyran-2-yl-5-(trifluoromethyl)pyrazole-3-carboxamide		0.95	419	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.22 - 10.32 (m, 1 H) 7.60 - 7.79 (m, 1 H) 7.41 - 7.47 (m, 2 H) 7.37 - 7.40 (m, 1 H) 7.25 - 7.34 (m, 1 H) 6.16 - 6.25 (m, 1 H) 3.86 - 3.98 (m, 1 H) 3.50 - 3.61 (m, 1 H) 2.22 - 2.28 (m, 3 H) 2.15 - 2.21 (m, 1 H) 1.88 - 2.01 (m, 2 H) 1.59 - 1.71 (m, 1 H) 1.48 - 1.57 (m, 2 H)	¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm -60.86 (s, -CF ₃)
P141	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(2,2-difluoroethyl)-5-[[5-[4-(trifluoromethyl)phenyl]tetrazol-2-yl]methyl]pyrazole-3-carboxamide		1.07	569	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.18 (s, 1 H) 8.29 (d, J=7.99 Hz, 2 H) 7.95 (d, J=8.36 Hz, 2 H) 7.79 (s, 1 H) 7.50 (d, J=2.18 Hz, 1 H) 7.39 - 7.46 (m, 2 H) 7.15 (s, 1 H) 6.17 - 6.50 (m, 1 H) 6.11 (s, 2 H) 4.96 (br d, J=4.00 Hz, 2 H) 2.19 (s, 3 H).	
P142	N-[4-chloro-2-(isopropylcarbamoyl)-6-methyl-phenyl]-2-(1-ethoxyethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1.14	461	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.25 (s, 1 H) 8.25 (s, 1 H) 7.49 - 7.55 (m, 1 H) 7.42 (s, 1 H) 7.32 - 7.39 (m, 1 H) 6.47 - 6.54 (m, 1 H) 3.85 - 4.00 (m, 1 H) 3.43 - 3.53 (m, 1 H) 3.17 - 3.27 (m, 1 H) 2.26 (s, 3 H) 1.61 (m, 3 H) 1.08 (m, 6 H) 1.02 (m, 3 H)	¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm -60.89 (s, -CF ₃)
P143	N-[4-chloro-2-methyl-6-(methoxycarbonyl)phenyl]-2-(1-ethoxyethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1.05	431 [M-H]	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.26 - 10.33 (m, 1 H) 8.31 - 8.39 (m, 1 H) 7.52 - 7.56 (m, 1 H) 7.36 - 7.44 (m, 2 H) 6.42 - 6.52 (m, 1 H) 3.40 - 3.52 (m, 1 H) 3.18 - 3.27 (m, 1 H) 2.64 - 2.70 (m, 3 H) 2.22 - 2.27 (m, 3 H) 1.59 - 1.66 (m, 3 H) 0.99 - 1.06 (m, 3 H)	¹⁹ F NMR (376 MHz, DMSO-d ₆) δ ppm -60.75 (s, -CF ₃)

P144	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(1-ethoxyethyl)-5-(trifluoromethyl)pyrazole-3-carboxamide		1.00	417 [M-H]	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.30 (s, 1 H) 7.84 (s, 1 H) 7.52 - 7.56 (m, 1 H) 7.47 - 7.49 (m, 1 H) 7.44 - 7.46 (m, 1 H) 7.38 - 7.41 (m, 1 H) 6.45 - 6.51 (m, 1 H) 3.42 - 3.51 (m, 1 H) 3.20 - 3.27 (m, 1 H) 2.22 - 2.26 (m, 3 H) 1.63 (m, 3 H) 1.04 (m, 3 H)	¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -60.79 (s, -CF₃)
P145	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydrofuran-2-yl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.03	431	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.24 (s, 1 H) 8.28 - 8.37 (m, 1 H) 7.47 (m, 2 H) 7.40 (s, 1 H) 6.83 - 6.90 (m, 1 H) 3.86 - 4.08 (m, 2 H) 2.69 (m, 3 H) 2.30 - 2.43 (m, 2 H) 2.25 (s, 3 H) 2.19 - 2.23 (m, 1 H) 1.95 - 2.03 (m, 1 H)	¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -60.79 (s, -CF₃)
P146	N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-tetrahydropyran-2-yl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.07	445	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.25 (s, 1 H) 8.32 (m, 1 H) 7.47 (m, 2 H) 7.37 (s, 1 H) 6.15 - 6.21 (m, 1 H) 3.88 - 3.95 (m, 1 H) 3.52 - 3.61 (m, 1 H) 2.70 (m, 3 H) 2.25 (s, 3 H) 2.16 - 2.23 (m, 1 H) 1.90 - 2.02 (m, 2 H) 1.59 - 1.70 (m, 1 H) 1.50 - 1.58 (m, 2 H)	¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -60.84 (s, -CF₃)
P147	N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-tetrahydropyran-2-yl-5-(trifluoromethyl)pyrazole-3-carboxamide		1.01	429 [M-H]	1	¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.24 - 10.28 (m, 1 H) 7.80 - 7.86 (m, 1 H) 7.52 - 7.55 (m, 1 H) 7.49 - 7.52 (m, 1 H) 7.44 - 7.47 (m, 1 H) 7.37 - 7.41 (m, 1 H) 6.16 - 6.21 (m, 1 H) 3.87 - 3.95 (m, 1 H) 3.53 - 3.61 (m, 1 H) 2.23 - 2.25 (m, 3 H) 2.16 - 2.22 (m, 1 H) 1.90 - 2.03 (m, 2 H) 1.58 - 1.72 (m, 1 H) 1.49 - 1.58 (m, 2 H)	¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -60.85 (s, -CF₃)

The activity of the compositions according to the invention can be broadened considerably, and adapted to prevailing circumstances, by adding other insecticidally, acaricidally and/or fungicidally active ingredients. The mixtures of the compounds of formula I with other insecticidally, acaricidally and/or fungicidally active ingredients may also have further surprising advantages which can also be described, in a wider sense, as synergistic activity. For example, better tolerance by plants, reduced phytotoxicity, insects can be controlled in their different development stages or better behaviour during their production, for example during grinding or mixing, during their storage or during their use.

Suitable additions to active ingredients here are, for example, representatives of the following classes of active ingredients: organophosphorus compounds, nitrophenol derivatives, thioureas, juvenile hormones, formamidines, benzophenone derivatives, ureas, pyrrole derivatives, carbamates, pyrethroids, chlorinated hydrocarbons, acylureas, pyridylmethyleamino derivatives, macrolides, neonicotinoids and *Bacillus thuringiensis* preparations.

The following combinations of a compound of formula I with another active substance in a weight ratio of 1:1 are preferred (where the abbreviation "TX" means "one compound selected from the compounds defined in the Tables A-1 to A-10 and P"):

(7E,9Z)-dodeca-7,9-dien-1-yl acetate + TX, (9Z,11E)-tetradeca-9,11-dien-1-yl acetate + TX, (9Z,12E)-tetradeca-9,12-dien-1-yl acetate + TX, (E)-6-methylhept-2-en-4-ol + TX, (E)-dec-5-en-1-yl acetate with (E)-dec-5-en-1-ol + TX, (E)-tridec-4-en-1-yl acetate + TX, (E,Z)-tetradeca-4,10-dien-1-yl acetate + TX, (Z)-dodec-7-en-1-yl acetate + TX, (Z)-hexadec-11-en-1-yl acetate + TX, (Z)-hexadec-11-enal + TX, (Z)-hexadec-13-en-11-yn-1-yl acetate + TX, (Z)-icos-13-en-10-one + TX, (Z)-tetradec-7-en-1-al + TX, (Z)-tetradec-9-en-1-ol + TX, (Z)-tetradec-9-en-1-yl acetate + TX, 1,2-dibromo-3-chloropropane + TX, 1,2-dichloropropane + TX, 1,2-dichloropropane with 1,3-dichloropropene + TX, 1,3-dichloropropene + TX, 14-methyloctadec-1-ene + TX, 1-hydroxy-1H-pyridine-2-thione + TX, 2-(octylthio)ethanol + TX, 2-chlorophenyl N-methylcarbamate (CPMC) + TX, 3-(4-chlorophenyl)-5-methylrhodanine + TX, 3,4-dichlorotetrahydrothiophene 1,1-dioxide + TX, 4-(quinoxalin-2-ylamino)benzenesulfonamide + TX, 4-methylnonan-5-ol with 4-methylnonan-5-one + TX, 5-methyl-6-thioxo-1,3,5-thiadiazinan-3-ylacetic acid + TX, 6-isopentenylaminopurine + TX, 8-hydroxyquinoline sulfate + TX, abamectin + TX, acequinocyl + TX, acetamiprid + TX, acetoprole + TX, acrinathrin + TX, acynonapyr + TX, *Adoxophyes orana* GV + TX, *afidopyropen* + TX, *afoxalaner* + TX, *Agrobacterium radiobacter* + TX, AKD-3088 + TX, *alanycarb* + TX, *aldicarb* + TX, *aldoxycarb* + TX, *allethrin* + TX, *alpha-cypermethrin* + TX, *alphamethrin* + TX, *alpha-multistriatin* + TX, *Amblyseius* spp. + TX, *amidoflumet* + TX, amino acids + TX, *aminocarb* + TX, *Anagrapta falcifera* NPV + TX, *Anagrus atomus* + TX, *Aphelinus abdominalis* + TX, *Aphidius colemani* + TX, *Aphidoletes aphidimyza* + TX, *apholate* + TX, *Autographa californica* NPV + TX, AZ 60541 + TX, *azadirachtin* + TX, *azocyclotin* + TX, *Bacillus aizawai* + TX, *Bacillus chitosporus* AQ746 (NRRL Accession No B-21 618) + TX, *Bacillus firmus* + TX, *Bacillus kurstaki* + TX, *Bacillus mycoides* AQ726 (NRRL Accession No. B-21664) + TX, *Bacillus pumilus* (NRRL Accession No B-30087) + TX, *Bacillus pumilus* AQ717 (NRRL Accession No. B-21662) + TX, *Bacillus* sp. AQ175 (ATCC Accession No.

55608) + TX, *Bacillus* sp. AQ177 (ATCC Accession No. 55609) + TX, *Bacillus* sp. AQ178 (ATCC Accession No. 53522) + TX, *Bacillus sphaericus* Neide + TX, *Bacillus subtilis* AQ153 (ATCC Accession No. 55614) + TX, *Bacillus subtilis* AQ30002 (NRRL Accession No. B-50421) + TX, *Bacillus subtilis* AQ30004 (NRRL Accession No. B- 50455) + TX, *Bacillus subtilis* AQ713 (NRRL Accession No. B-21661) + TX, *Bacillus subtilis* AQ743 (NRRL Accession No. B-21665) + TX, *Bacillus subtilis* unspecified + TX, *Bacillus thuringiensis* AQ52 (NRRL Accession No. B-21619) + TX, *Bacillus thuringiensis* BD#32 (NRRL Accession No B-21530) + TX, *Bacillus thuringiensis* Berliner + TX, *Bacillus thuringiensis* subsp. Aizawai + TX, *Bacillus thuringiensis* subsp. Israelensis + TX, *Bacillus thuringiensis* subsp. Japonensis + TX, *Bacillus thuringiensis* subsp. Kurstaki + TX, *Bacillus thuringiensis* subsp. Tenebrionis + TX, *Bacillus thuringiensis* subspec. kurstaki BMP 123 + TX, *Beauveria bassiana* + TX, *Beauveria brongniartii* + TX, benclotiaz + TX, benomyl + TX, bensultap + TX, benzoximate + TX, benzpyrimoxan + TX, betacyfluthrin + TX, beta-cypermethrin + TX, bethoxazin + TX, bifenazate + TX, bifenthrin + TX, binapacryl + TX, bioallethrin + TX, bioresmethrin + TX, bis(tributyltin) oxide + TX, bisazir + TX, bistrifluron + TX, brevicomin + TX, broflanilide + TX, brofluthrin + TX, bromoacetamide + TX, bromophos-ethyl + TX, bronopol + TX, buprofezine + TX, busulfan + TX, butocarboxim + TX, butopyronoxyl + TX, butoxy(polypropylene glycol) + TX, butylpyridaben + TX, cadusafos + TX, calcium arsenate + TX, carbaryl + TX, carbofuran + TX, carbon disulfide + TX, carbosulfan + TX, cartap + TX, CAS number: 1594624-87-9 + TX, CAS number: 1922957-47-8 + TX, CAS number: 1255091-74-7 + TX, CAS number: 1365070-72-9 + TX, CAS number: 1445683-71-5 + TX, CAS number: 1445684-82-1 + TX, CAS number: 1594626-19-3 + TX, CAS number: 1594637-65-6 + TX, CAS number: 1632218-00-8 + TX, CAS number: 1808115-49-2 + TX, CAS number: 1922957-45-6 + TX, CAS number: 1922957-46-7 + TX, CAS number: 1922957-48-9 + TX, CAS number: 1956329-03-5 + TX, CAS number: 1990457-52-7 + TX, CAS number: 1990457-55-0 + TX, CAS number: 1990457-57-2 + TX, CAS number: 1990457-66-3 + TX, CAS number: 1990457-77-6 + TX, CAS number: 1990457-85-6 + TX, CAS number: 2032403-97-5 + TX, CAS number: 2044701-44-0 + TX, CAS number: 2095470-94-1 + TX, CAS number: 2128706-05-6 + TX, CAS number: 2133042-31-4 + TX, CAS number: 2133042-44-9 + TX, CAS number: 2171099-09-3 + TX, CAS number: 2220132-55-6 + TX, CAS number: 2368920-61-8 + TX, CAS number: 2377084-09-6 + TX, CAS number: 2396747-83-2 + TX, CAS number: 2408220-91-5 + TX, CAS number: 2408220-94-8 + TX, CAS number: 2415706-16-8 + TX, CAS number: 2615135-05-0 + TX, CAS number: 2719848-60-7 + TX, CAS number: RNA (*Leptinotarsa decemlineata*-specific recombinant double-stranded interfering GS2) + TX, chlorantraniliprole + TX, chlordane + TX, chlorfenapyr + TX, chloropicrin + TX, chloroprallethrin + TX, chlorpyrifos + TX, chromafenozide + TX, *Chrysoperla carnea* + TX, clenpirin + TX, cloethocarb + TX, clothianidin + TX, codlure + TX, codlemone + TX, copper acetoarsenite + TX, copper dioctanoate + TX, copper hydroxide + TX, copper sulfate + TX, cresol + TX, crufomate + TX, *Cryptolaemus montrouzieri* + TX, cuclure + TX, cyanofenphos + TX, cyantraniliprole + TX, cybutryne + TX, cyclaniliprole + TX, cyclobutirfluram + TX, cycloprothrin + TX, cycloxaprid + TX, *Cydia pomonella* GV + TX, cyenopyrafen + TX, cyetpyrafen + TX, cyflumetofen + TX, cyfluthrin + TX, cyhalodiamide + TX, cyhalothrin + TX, cypermethrin + TX, cyphenothrin + TX, cyproflanilide + TX, cyromazine + TX, cytokinins + TX, *Dacnusa*

sibirica + TX, dazomet + TX, DBCP + TX, DCIP + TX, deltamethrin + TX, diafenthiuron + TX, dialifos + TX, diamidafos + TX, dibrom + TX, dibutyl adipate + TX, dibutyl phthalate + TX, dibutyl succinate + TX, dichlofenthion + TX, dichlone + TX, dichlorophen + TX, dicliphos + TX, dicloromezotiaz + TX, diethyltoluamide + TX, diflubenzuron + TX, Diglyphus isaea + TX, dimatif + TX, dimethoate + TX, dimethyl carbate + TX, dimethyl phthalate + TX, dimpropyridaz + TX, dinactin + TX, dinocap + TX, dinotefuran + TX, dioxabenzofos + TX, dipyrithione + TX, disparture + TX, D-limonene + TX, dodec-8-en-1-yl acetate + TX, dodec-9-en-1-yl acetate + TX, dodeca-8,10-dien-1-yl acetate + TX, dodicin + TX, dominicalure + TX, doramectin + TX, emamectin + TX, emamectin benzoate + TX, empenethrin + TX, Encarsia formosa + TX, endothal + TX, endrin + TX, eprinomectin + TX, epsilon - momfluorothrin + TX, epsilon-metofluthrin + TX, Eretmocerus eremicus + TX, esfenvalerate + TX, ethion + TX, ethiprole + TX, ethoprophos + TX, ethyl 4-methyloctanoate + TX, ethyl hexanediol + TX, ethylene dibromide + TX, etofenprox + TX, etoxazole + TX, etpyrafen + TX, eugenol + TX, Extract of seaweed and fermentation product derived from melasse + TX, Extract of seaweed and fermentation product derived from melasse comprising urea + TX, Extract of seaweed and fermented plant products + TX, Extract of seaweed and fermented plant products comprising phytohormones + TX, vitamins + TX, EDTA-chelated copper + TX, zinc + TX, and iron + TX, famphur + TX, fenaminosulf + TX, fenamiphos + TX, fenazaquin + TX, fenfluthrin + TX, fenitrothion + TX, fenmezoditiaz + TX, fenobucarb + TX, fenothiocarb + TX, fenoxycarb + TX, fenpropathrin + TX, fenpyrad + TX, fenpyroximate + TX, fensulfothion + TX, fenthion + TX, fentin + TX, fentinacetate + TX, fenvalerate + TX, ferric phosphate + TX, fipronil + TX, flometoquin + TX, flonicamid + TX, fluacrypyrim + TX, fluazaindolizine + TX, fluazuron + TX, flubendiamide + TX, flubenzimine + TX, fluchlordiniliprole + TX, flucitrate + TX, flucycloxuron + TX, flucythrinate + TX, fluensulfone + TX, fluensulfone [318290-98-1] + TX, flufenerim + TX, flufenprox + TX, flufiprole + TX, fluhexafon + TX, flumethrin + TX, fluopyram + TX, flupentiofenox flupyradifurone + TX, flupyrimin + TX, flupyroxystrobin + TX, fluralaner + TX, fluvalinate + TX, fluxametamide + TX, formaldehyde + TX, fosthiazate + TX, fosthietan + TX, frontaline + TX, furfural + TX, gamma-cyhalothrin + TX, Gossyplure® (1:1 mixture of the (Z,E) and (Z,Z) isomers of hexadeca-7,11-dien-1-yl-acetate) + TX, grandlure + TX, grandlure I + TX, grandlure II + TX, grandlure III + TX, grandlure IV + TX, Granulovirus + TX, guadipyr + TX, GY-81 + TX, halfenprox + TX, halofenozide + TX, Harpin + TX, Helicoverpa armigera Nucleopolyhedrovirus + TX, Helicoverpa zea NPV + TX, Helicoverpa zea Nucleopolyhedrovirus + TX, Heliothis punctigera Nucleopolyhedrovirus + TX, Heliothis virescens Nucleopolyhedrovirus + TX, hemel + TX, hempa + TX, heptafluthrin + TX, heterophos + TX, Heterorhabditis bacteriophora and H. megidis + TX, hexalure + TX, hexamide + TX, hexythiazox + TX, Hippodamia convergens + TX, hydramethylnon + TX, hydrargaphen + TX, hydrated lime + TX, imicyafos + TX, imidacloprid + TX, imiprothrin + TX, Indazaproxamet + TX, indoxacarb + TX, iodomethane + TX, iprodione + TX, ipsdienol + TX, ipsenol + TX, isamidofos + TX, isazofos + TX, isocycloseram + TX, Isoflualanam (CAS number: 2892524-05-7) + TX, isothioate + TX, ivermectin + TX, japonilure + TX, kappa-bifenthrin + TX, kappa-tefluthrin + TX, kasugamycin + TX, kasugamycin hydrochloride hydrate + TX, kinetin + TX, lambda-cyhalothrin + TX, ledprona + TX, lepimectin + TX, Leptomastix dactylopii + TX, lineatin + TX, litlure + TX, looplure + TX, lotilaner + TX, lufenuron + TX,

Macrolophus caliginosus + TX, Mamestra brassicae NPV + TX, mecarphon + TX, medlure + TX, megatomoic acid + TX, metaflumizone + TX, metaldehyde + TX, metam + TX, metam-potassium + TX, metam-sodium + TX, Metaphycus helvolus + TX, Metarhizium anisopliae var. acridum + TX, Metarhizium anisopliae var. anisopliae + TX, Metarhizium spp. + TX, metepa + TX, methiocarb + TX, methiotepa + TX, methomyl + TX, methoquin-butyl + TX, methoxyfenozide + TX, methyl apholate + TX, methyl bromide + TX, methyl eugenol + TX, methyl isothiocyanate + TX, methylneodecanamide + TX, metofluthrin + TX, metolcarb + TX, mexacarbate + TX, milbemectin + TX, milbemycin oxime + TX, momfluorothrin + TX, morzid + TX, moxidectin + TX, muscalure + TX, Muscodor albus 620 (NRRL Accession No. 30547) + TX, Muscodor roseus A3-5 (NRRL Accession No. 30548) + TX, Myrothecium verrucaria composition + TX, nabam + TX, NC-184 + TX, Neem tree based products + TX, Neodiprion sertifer NPV and N. lecontei NPV + TX, nickel bis(dimethyldithiocarbamate) + TX, niclosamide + TX, niclosamide-olamine + TX, nicofluprole + TX, nitenpyram + TX, nithiazine + TX, nitrapyrin + TX, octadeca-2,13-dien-1-yl acetate + TX, octadeca-3,13-dien-1-yl acetate + TX, octhilinone + TX, omethoate + TX, orfuralure + TX, Orius spp. + TX, oryctalure + TX, ostramone + TX, oxamate + TX, oxamyl + TX, oxazosulfonyl + TX, oxolinic acid + TX, oxytetracycline + TX, Paecilomyces fumosoroseus + TX, Paecilomyces lilacinus + TX, parathion-ethyl + TX, Pasteuria nishizawae + TX, Pasteuria penetrans + TX, Pasteuria ramosa + TX, Pasteuria thornei + TX, Pasteuria usgae + TX, P-cymene + TX, penfluron + TX, pentachlorophenol + TX, permethrin + TX, phenothrin + TX, phorate + TX, phosphamidon + TX, phosphocarb + TX, Phytoseiulus persimilis + TX, picaridin + TX, piperazine + TX, piperonylbutoxide + TX, pirimicarb + TX, pirimiphos-ethyl + TX, pirimiphos-methyl + TX, Plutella xylostella Granulosis virus + TX, Plutella xylostella Nucleopolyhedrovirus + TX, Polyhedrosis virus + TX, potassium and molybdenum and EDTA-chelated manganese + TX, potassium ethylxanthate + TX, potassium hydroxyquinoline sulfate + TX, prallethrin + TX, probenazole + TX, profenofos + TX, profluthrin + TX, propargite + TX, propetamphos + TX, propoxur + TX, prothiophos + TX, protrifenbute + TX, pyflubumide + TX, pymetrozine + TX, pyraclofos + TX, pyrafluprole + TX, pyrethrum + TX, pyridaben + TX, pyridalyl + TX, pyridin-4-amine + TX, pyrifluquinazon + TX, pyrimidifen + TX, pyriminostrobin + TX, pyriprole + TX, pyriprole [394730-71-3] + TX, pyriproxyfen + TX, QRD 420 (a terpenoid blend) + TX, QRD 452 (a terpenoid blend) + TX, QRD 460 (a terpenoid blend) + TX, Quillaja saponaria + TX, quinochloramine + TX, quinonamid + TX, resmethrin + TX, Rhodococcus globerulus AQ719 (NRRL Accession No B-21663) + TX, sarolaner + TX, S-bioallethrin + TX, sebufos + TX, selamectin + TX, siglure + TX, silafluofen + TX, simazine + TX, sodium pentachlorophenoxide + TX, sordidin + TX, spidoxamat + TX, spinetoram + TX, spinosad + TX, spirotetramat + TX, Spirothrips + TX, spiromesifen + TX, spiropidion + TX, spirotetramat + TX, Spodoptera exigua multicapsid nuclear polyhedrosis virus + TX, Spodoptera frugiperda Nucleopolyhedrovirus + TX, Steinernema bibionis + TX, Steinernema carpocapsae + TX, Steinernema feltiae + TX, Steinernema glaseri + TX, Steinernema riobrave + TX, Steinernema riobrave + TX, Steinernema scapterisci + TX, Steinernema spp. + TX, Streptomyces galbus (NRRL Accession No. 30232) + TX, Streptomyces sp. (NRRL Accession No. B-30145) + TX, streptomycin + TX, streptomycin sesquisulfate + TX, strychnine + TX, sulcatol + TX, sulfoxaflor + TX, tazimcarb + TX, tebufenozide + TX, tebufenpyrad + TX, tebupirimiphos + TX,

tecloftalam + TX, tefluthrin + TX, temephos + TX, tepa + TX, terbam + TX, terbufos + TX, terpenoid blend + TX, tetrachlorantraniliprole + TX, tetrachlorothiophene + TX, tetradec-11-en-1-yl acetate + TX, tetradiphon + TX, tetramethrin + TX, tetramethylfluthrin + TX, tetranactin + TX, tetraniliprole + TX, theta-cypermethrin + TX, thiacloprid + TX, thiafenox + TX, thiamethoxam + TX, thiocyclam + TX, thiodicarb + TX, thiofanox + TX, thiohempa + TX, thiomersal + TX, thiometon + TX, thionazin + TX, thiophanate + TX, thiosultap + TX, thiotepa + TX, tigolaner + TX, tiorantraniliprole + TX, tioazafen + TX, tolfenpyrad + TX, toxaphene + TX, tralomethrin + TX, transfluthrin + TX, tretamine + TX, triazamate + TX, triazophos + TX, triazuron + TX, tributyltin oxide + TX, trichlorfon + TX, trichloronate + TX, trichlorphon + TX, Trichogramma spp. + TX, trifenmorph + TX, trifluenfurinate + TX, triflumezopyrim + TX, trimedlure + TX, trimedlure A + TX, trimedlure B1 + TX, trimedlure B2 + TX, trimedlure C + TX, trimethacarb + TX, triphenyltin acetate + TX, triphenyltin hydroxide + TX, trunc-call + TX, tyclopyrazoflor + TX, Typhlodromus occidentalis + TX, uredepa + TX, Verticillium lecanii + TX, Verticillium spp. + TX, xylenols + TX, YI-5302 + TX, zeatin + TX, zeta-Cypermethrin + TX;

N-[(1R)-1-benzyl-3-chloro-1-methyl-but-3-enyl]-8-fluoro-quinoline-3-carboxamide + TX, N-[(1S)-1-benzyl-3-chloro-1-methyl-but-3-enyl]-8-fluoro-quinoline-3-carboxamide + TX, N-ethyl-N'-[5-methoxy-2-methyl-4-[(2-trifluoromethyl)tetrahydrofuran-2-yl]phenyl]-N-methyl-formamidine (these compounds may be prepared from the methods described in WO2019/110427) + TX, (3',4',5'-trifluoro-biphenyl-2-yl)-amide + TX, (3-methylisoxazol-5-yl)-[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methanone (these compounds may be prepared from the methods described in WO 2017/220485) + TX, (4-phenoxyphenyl)methyl 2-amino-6-methyl-pyridine-3-carboxylate (this compound may be prepared from the methods described in WO 2014/006945) + TX, (5-methyl-2-pyridyl)-[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methanone + TX, (7E,9Z)-dodeca-7,9-dien-1-yl acetate + TX, (9Z,11E)-tetradeca-9,11-dien-1-yl acetate + TX, (9Z,12E)-tetradeca-9,12-dien-1-yl acetate + TX, (E)-6-methylhept-2-en-4-ol + TX, (E)-dec-5-en-1-yl acetate with (E)-dec-5-en-1-ol + TX, (E)-tridec-4-en-1-yl acetate + TX, (E,Z)-tetradeca-4,10-dien-1-yl acetate + TX, + TX, (R)-3-(difluoromethyl)-1-methyl-N-[1,1,3-trimethylindan-4-yl]pyrazole-4-carboxamide + TX, (Z)-dodec-7-en-1-yl acetate + TX, (Z)-hexadec-11-en-1-yl acetate + TX, (Z)-hexadec-11-enal + TX, (Z)-hexadec-13-en-11-yn-1-yl acetate + TX, (Z)-icos-13-en-10-one + TX, (Z)-tetradec-7-en-1-ol + TX, (Z)-tetradec-9-en-1-ol + TX, (Z)-tetradec-9-en-1-yl acetate + TX, (Z,2E)-5-[1-(2,4-dichlorophenyl)pyrazol-3-yl]oxy-2-methoxyimino-N,3-dimethyl-pent-3-enamide (this compound may be prepared from the methods described in WO 2018/153707) + TX, (Z,2E)-5-[1-(4-chlorophenyl)pyrazol-3-yl]oxy-2-methoxyimino-N,3-dimethyl-pent-3-enamide + TX, + TX, [2-[3-[2-[1-[2-[3,5-bis(difluoromethyl)pyrazol-1-yl]acetyl]-4-piperidyl]thiazol-4-yl]-4,5-dihydroisoxazol-5-yl]-3-chloro-phenyl] methanesulfonate + TX, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline + TX, 1-(4,5-dimethylbenzimidazol-1-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline + TX, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,5-trifluoro-3,3-dimethyl-isoquinoline + TX, 1-(6,7-dimethylpyrazolo[1,5-a]pyridin-3-yl)-4,4,6-trifluoro-3,3-dimethyl-isoquinoline + TX, 1-(6-chloro-7-methyl-pyrazolo[1,5-a]pyridin-3-yl)-4,4-difluoro-3,3-dimethyl-isoquinoline (these

compounds may be prepared from the methods described in WO2017/025510) + TX, 1,1-bis(4-chlorophenyl)-2-ethoxyethanol + TX, 1,1-dichloro-2,2-bis(4-ethylphenyl)ethane + TX, 1,2-dibromo-3-chloropropane + TX, 1,2-dichloropropane with 1,3-dichloropropene + TX, 1,3-dichloropropene + TX, 1,3-dimethoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea + TX, 1-[2-[[1-(4-chlorophenyl)pyrazol-3-yl]oxymethyl]-3-methyl-phenyl]-4-methyl-tetrazol-5-one + TX, 10-dien-1-yl acetate + TX, 14-methyloctadec-1-ene + TX, 1-bromo-2-chloroethane + TX, 1-dichloro-1-nitroethane + TX, 1-hydroxy-1H-pyridine-2-thione + TX, 1-methoxy-3-methyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea + TX, 1-methyl-4-[3-methyl-2-[[2-methyl-4-(3,4,5-trimethylpyrazol-1-yl)phenoxy]methyl]phenyl]tetrazol-5-one + TX, 2-(difluoromethyl)-N-((3R)-1 + TX, 1 + TX, 3-trimethylindan-4-yl)pyridine-3-carboxamide + TX, 2-(difluoromethyl)-N-((3R)-1 + TX, 1 + TX, 3-trimethylindan-4-yl)pyridine-3-carboxamide + TX, 2-(1,3-dithiolan-2-yl)phenyl dimethylcarbamate + TX, 2-(2-butoxyethoxy)ethyl piperonylate + TX, 2-(2-butoxyethoxy)ethyl thiocyanate + TX, 2-(4,5-dimethyl-1,3-dioxolan-2-yl)phenyl methylcarbamate + TX, 2-(4-chloro-3,5-xylyloxy)ethanol + TX, 2-(difluoromethyl)-N-(3-ethyl-1,1-dimethyl-indan-4-yl)pyridine-3-carboxamide + TX, 2-(difluoromethyl)-N-[(3R)-3-ethyl-1,1-dimethyl-indan-4-yl]pyridine-3-carboxamide + TX, 2-(difluoromethyl)-N-[(3S)-3-ethyl-1,1-dimethyl-indan-4-yl]pyridine-3-carboxamide (this compound may be prepared from the methods described in WO 2014/095675) + TX, 2-(difluoromethyl)-N-[3-ethyl-1,1-dimethyl-indan-4-yl]pyridine-3-carboxamide + TX, 2-(octylthio)ethanol + TX, 2,2,2-trichloro-1-(3,4-dichlorophenyl)ethyl acetate + TX, 2,2-dichlorovinyl 2-ethylsulfinyethyl methyl phosphate + TX, 2,2-difluoro-N-methyl-2-[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]acetamide + TX, 2,4-dichlorophenyl benzenesulfonate + TX, 2,6-Dimethyl-1H,5H-[1,4]dithiino[2,3-c:5,6-c']dipyrrole-1,3,5,7(2H,6H)-tetrone (this compound may be prepared from the methods described in WO 2011/138281) + TX, 2-[2-fluoro-6-[(8-fluoro-2-methyl-3-quinolyl)oxy]phenyl]propan-2-ol + TX, 2-[6-(4-bromophenoxy)-2-(trifluoromethyl)-3-pyridyl]-1-(1,2,4-triazol-1-yl)propan-2-ol (this compound may be prepared from the methods described in WO 2017/029179) + TX, 2-[6-(4-chlorophenoxy)-2-(trifluoromethyl)-3-pyridyl]-1-(1,2,4-triazol-1-yl)propan-2-ol (this compound may be prepared from the methods described in WO 2017/029179) + TX, 2-chlorovinyl diethyl phosphate + TX, 2-fluoro-N-methyl-N-1-naphthylacetamide + TX, 2-imidazolidone + TX, 2-isovalerylindan-1,3-dione + TX, 2-methyl(prop-2-ynyl)aminophenyl methylcarbamate + TX, 2-oxo-N-propyl-2-[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]acetamide (this compound may be prepared from the methods described in WO 2018/065414) + TX, 2-thiocyanatoethyl laurate + TX, 3-(4,4-difluoro-3,3-dimethyl-1-isoquinolyl)-7,8-dihydro-6H-cyclopenta[e]benzimidazole (these compounds may be prepared from the methods described in WO2016/156085) + TX, 3-(4,4-difluoro-3,4-dihydro-3,3-dimethylisoquinolin-1-yl)quinolone + TX, 3-(4-chlorophenyl)-5-methylrhodanine + TX, 3-(difluoromethyl)-1-methyl-N-[1,1,3-trimethylindan-4-yl]pyrazole-4-carboxamide + TX, 3,4-dichlorotetrahydrothiophene 1,1-dioxide + TX, 3-[2-(1-chlorocyclopropyl)-3-(2-fluorophenyl)-2-hydroxypropyl]imidazole-4-carbonitrile (this compound may be prepared from the methods described in WO 2016/156290) + TX, 3-[2-(1-chlorocyclopropyl)-3-(3-chloro-2-fluoro-phenyl)-2-hydroxypropyl]imidazole-4-carbonitrile (this compound may be prepared from the methods described in WO 2016/156290) + TX, 3-bromo-1-chloroprop-1-ene + TX, 3-chloro-6-methyl-5-phenyl-4-(2,4,6-

trifluorophenyl)pyridazine + TX, 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid + TX, 3-ethyl-1-methoxy-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]urea + TX, 3-methyl-1-phenylpyrazol-5-yl dimethylcarbamate + TX, 4-(2-bromo-4-fluorophenyl)-N-(2-chloro-6-fluorophenyl)-1 + TX, 3-dimethyl-1H-pyrazol-5-amine + TX, 4-(2,6-difluorophenyl)-6-methyl-5-phenyl-pyridazine-3-carbonitrile + TX, 4-(2-bromo-4-fluoro-phenyl)-N-(2-chloro-6-fluoro-phenyl)-2,5-dimethyl-pyrazol-3-amine + TX, 4-(quinoxalin-2-ylamino)benzenesulfonamide + TX, 4,4-difluoro-1-(5-fluoro-4-methyl-benzimidazol-1-yl)-3,3-dimethyl-isoquinoline + TX, 4,4-difluoro-3,3-dimethyl-1-(6-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline + TX, 4,4-difluoro-3,3-dimethyl-1-(7-methylpyrazolo[1,5-a]pyridin-3-yl)isoquinoline + TX, 4,4-dimethyl-2-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]isoxazolidin-3-one + TX, 4-[[6-[2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-(1,2,4-triazol-1-yl)propyl]-3-pyridyl]oxy] benzonitrile + TX, 4-[[6-[2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-(5-sulfanyl-1,2,4-triazol-1-yl)propyl]-3-pyridyl]oxy] benzonitrile + TX, 4-[[6-[2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-(5-thioxo-4H-1,2,4-triazol-1-yl)propyl]-3-pyridyl]oxy] benzonitrile + TX, 4-chloro-2-(2-chloro-2-methyl-propyl)-5-[(6-iodo-3-pyridyl)methoxy]pyridazin-3-one + TX, 4-chlorophenyl phenyl sulfone + TX, 4-methyl(prop-2-ynyl)amino-3,5-xylyl methylcarbamate + TX, 4-methylnonan-5-ol with 4-methylnonan-5-one + TX, 5-(1,3-benzodioxol-5-yl)-3-hexylcyclohex-2-enone + TX, 5,5-dimethyl-2-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]isoxazolidin-3-one + TX, 5,5-dimethyl-3-oxocyclohex-1-enyl dimethylcarbamate + TX, 5-amino-1,3,4-thiadiazole-2-thiol zinc salt (2:1) + TX, 5-methyl-6-thioxo-1,3,5-thiadiazinan-3-ylacetic acid + TX, 6-chloro-3-(3-cyclopropyl-2-fluoro-phenoxy)-N-[2-(2,4-dimethylphenyl)-2,2-difluoro-ethyl]-5-methyl-pyridazine-4-carboxamide (may be prepared from the methods described in WO 2020/109391) + TX, 6-chloro-3-(3-cyclopropyl-2-fluoro-phenoxy)-N-[2-(3,4-dimethylphenyl)-2,2-difluoro-ethyl]-5-methyl-pyridazine-4-carboxamide (may be prepared from the methods described in WO 2020/109391) + TX, 6-chloro-4,4-difluoro-3,3-dimethyl-1-(4-methylbenzimidazol-1-yl)isoquinoline + TX, 6-chloro-N-[2-(2-chloro-4-methyl-phenyl)-2,2-difluoro-ethyl]-3-(3-cyclopropyl-2-fluoro-phenoxy)-5-methyl-pyridazine-4-carboxamide (may be prepared from the methods described in WO 2020/109391) + TX, 6-ethyl-5,7-dioxo-pyrrolo[4,5][1,4]dithiino[1,2-c]isothiazole-3-carbonitrile + TX, 6-isopentenylaminopurine + TX, 8-fluoro-N-[(1R)-1-[(3-fluorophenyl)methyl]-1,3-dimethyl-butyl]quinoline-3-carboxamide + TX, 8-fluoro-N-[(1S)-1-[(3-fluorophenyl)methyl]-1,3-dimethyl-butyl]quinoline-3-carboxamide + TX, 8-hydroxyquinoline sulfate + TX, acetion + TX, acetoprole + TX, acibenzolar + TX, acibenzolar-S-methyl + TX, acrylonitrile + TX, Adoxophyes orana GV + TX, Agrobacterium radiobacter + TX, aldoxycarb + TX, aldrin + TX, allosamidin + TX, allyxycarb + TX, alpha-chlorohydrin + TX, alpha-ecdysone + TX, alpha-multistriatin + TX, aluminium phosphide + TX, Amblyseius spp. + TX, amectotractin + TX, ametotradin + TX, amidithion + TX, amidothioate + TX, aminocarb + TX, aminopyrifin + TX, amisulbrom + TX, amiton + TX, amiton hydrogen oxalate + TX, amitraz + TX, anabasine + TX, Anagrapta falcifera NPV + TX, Anagrus atomus + TX, ancymidol + TX, anilazine + TX, anisiflupurin + TX, anthraquinone + TX, antu + TX, Aphelinus abdominalis + TX, Aphidius colemani + TX, Aphidoletes aphidimyza + TX, apholate + TX, aramite + TX, arsenous oxide + TX, athidathion + TX, Autographa californica NPV + TX, azaconazole + TX, azamethiphos + TX, azobenzene + TX, azothoate + TX, azoxystrobin + TX, Bacillus

sphaericus Neide + TX, *Bacillus thuringiensis* delta endotoxins + TX, barium carbonate + TX, barium hexafluorosilicate + TX, barium polysulfide + TX, barthrin + TX, Bayer 22/190 + TX, Bayer 22408 + TX, *Beauveria brongniartii* + TX, benalaxyl + TX, benclothiaz + TX, benomyl + TX, benoxafos + TX, benthiavalicarb + TX, benzothiofostrobin + TX, benzovindiflupyr + TX, benzyl benzoate + TX, beta-cyfluthrin + TX, beta-cypermethrin + TX, bethoxazin + TX, bioethanomethrin + TX, biopermethrin + TX, bis(2-chloroethyl) ether + TX, bis(tributyltin) oxide + TX, bisazir + TX, bisthiosemi + TX, bitertanol + TX, bixafen + TX, blasticidin-S + TX, borax + TX, bordeaux mixture + TX, boscalid + TX, brevicomin + TX, brodifacoum + TX, brofenvalerate + TX, bromadiolone + TX, bromethalin + TX, bromfenvinfos + TX, bromoacetamide + TX, bromocyclen + TX, bromo-DDT + TX, bromophos + TX, bromopropylate + TX, bromuconazole + TX, bronopol + TX, bufencarb + TX, bupirimate + TX, buprofezin + TX, busulfan + TX, but-3-ynyl N-[6-[(Z)-[(1-methyltetrazol-5-yl)-phenyl-methylene]amino]oxymethyl]-2-pyridyl]carbamate + TX, butacarb + TX, butathiofos + TX, butocarboxim + TX, butonate + TX, butopyronoxyl + TX, butoxy(polypropylene glycol) + TX, butoxycarboxim + TX, butylpyridaben + TX, calcium arsenate + TX, calcium cyanide + TX, calcium polysulfide + TX, camphechlor + TX, captafol + TX, captan + TX, carbanolate + TX, carbendazim + TX, carbon disulfide + TX, carbon tetrachloride + TX, carbophenothion + TX, carboxin + TX, cartap hydrochloride + TX, cevadine + TX, chinomethionat + TX, chloralose + TX, chlorbenside + TX, chlorbicyclen + TX, chlordane + TX, chlordecone + TX, chlordimeform + TX, chlordimeform hydrochloride + TX, chlorfenethol + TX, chlorfenson + TX, chlorfensulfide + TX, chlorobenzilate + TX, chloroform + TX, chloroinconazide + TX, chloromebuform + TX, chloromethiuron + TX, chloroneb + TX, chlorophacinone + TX, chloropicrin + TX, chloropropylate + TX, chlorothalonil + TX, chlorphoxim + TX, chlorprazophos + TX, chlorthiophos + TX, chlozolate + TX, cholecalciferol + TX, *Chrysoperla carnea* + TX, cinerin I + TX, cinerin II + TX, cinerins + TX, cismethrin + TX, cis-resmethrin + TX, clocythrins + TX, closantel + TX, codlelure + TX, codlemone + TX, copper acetoarsenite + TX, copper arsenate + TX, copper dioctanoate + TX, copper hydroxide + TX, copper naphthenate + TX, copper oleate + TX, copper oxide + TX, copper oxychloride + TX, copper sulfate + TX, coumachlor + TX, coumafuryl + TX, coumaphos + TX, coumatetralyl + TX, coumethoxystrobin (jiaxiangjunzhi) + TX, coumithoate + TX, coumoxystrobin + TX, cresol + TX, crimidine + TX, crotamiton + TX, crotoxyphos + TX, cruformate + TX, cryolite + TX, *Cryptolaemus montrouzieri* + TX, CS 708 + TX, cuelure + TX, cufraneb + TX, cyanofenphos + TX, cyanophos + TX, cyanthoate + TX, cyazofamid + TX, cybutryne + TX, cyclothrin + TX, cyclobutrifluram + TX, *Cydia pomonella* GV + TX, cyflufenamid + TX, cymiazole + TX, cymoxanil + TX, cyproconazole + TX, cyprodinil + TX, cythioate + TX, cytokinins + TX, *Dacnusa sibirica* + TX, DAEP + TX, dazomet + TX, DCIP + TX, DCPM + TX, DDT + TX, debacarb + TX, decarbofuran + TX, demephion + TX, demephion-O + TX, demephion-S + TX, demeton-methyl + TX, demeton-O + TX, demeton-O-methyl + TX, demeton-S + TX, demeton-S-methyl + TX, demeton-S-methylsulfon + TX, diamidafos + TX, dibutyl adipate + TX, dibutyl phthalate + TX, dibutyl succinate + TX, dicapthon + TX, dichlobentiazox + TX, dichlofenthion + TX, dichlofluanid + TX, dichlone + TX, dichlorophen + TX, dichlorvos + TX, dichlozoline + TX, dicliphos + TX, diclocymet + TX, diclomezine + TX, dicloran + TX, dicresyl + TX, dicyclanil + TX, dicyclopentadiene + TX, dieldrin + TX, dienochlor + TX, diethofencarb + TX, diethyl 5-methylpyrazol-

3-yl phosphate + TX, diethyltoluamide + TX, difenacoum + TX, difenoconazole + TX, difethialone + TX, diflovidazin + TX, Diglyphus isaea + TX, dilor + TX, dimatif + TX, dimefluthrin + TX, dimefox + TX, dimetan + TX, dimethirimol + TX, dimethomorph + TX, dimethrin + TX, dimethyl carbate + TX, dimethyl phthalate + TX, dimethylvinphos + TX, dimetilan + TX, dimoxystrobin + TX, dinex + TX, dinex-diclexine + TX, diniconazole + TX, dinocap-4 + TX, dinocap-6 + TX, dinocton + TX, dinopenton + TX, dinoprop + TX, dinosam + TX, dinoseb + TX, dinosulfon + TX, dinoterbon + TX, diofenolan + TX, dioxabenzofos + TX, dioxathion + TX, diphacinone + TX, diphenyl sulfone + TX, dipymetitrone + TX, dipyrithione + TX, disparlure + TX, disulfiram + TX, dithianon + TX, dithicrofos + TX, DNOC + TX, dodec-8-en-1-yl acetate + TX, dodec-9-en-1-yl acetate + TX, dodeca-8 + TX, dodemorph + TX, dodicin + TX, dodine + TX, dofenapyn + TX, dominicalure + TX, doramectin + TX, DSP + TX, d-tetramethrin + TX, ecdysterone + TX, edifenphos + TX, EI 1642 + TX, EMPC + TX, Encarsia formosa + TX, endothal + TX, endothion + TX, enestroburin + TX, enoxastrobin + TX, EPBP + TX, epoxiconazole + TX, eprinomectin + TX, Eretmocerus eremicus + TX, ergocalciferol + TX, etaphos + TX, ethaboxam + TX, ethiofencarb + TX, ethirimol + TX, ethoate-methyl + TX, ethyl 1-[[4-[(Z)-2-ethoxy-3,3,3-trifluoro-prop-1-en-1-yl]oxy]phenyl]methyl]pyrazole-3-carboxylate (may be prepared from the methods described in WO 2020/056090) + TX, ethyl 1-[[4-[[2-(trifluoromethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]methyl]pyrazole-3-carboxylate (may be prepared from the methods described in WO 2020/056090) + TX, ethyl 1-[[4-[[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]pyrazole-4-carboxylate + TX, ethyl 1-[[5-[[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-thienyl]methyl]pyrazole-4-carboxylate (this compound may be prepared from the methods described in WO 2018/158365) + TX, ethyl 4-methyloctanoate + TX, ethyl formate + TX, ethyl hexanediol + TX, ethylene dibromide + TX, ethylene dichloride + TX, ethylene oxide + TX, etridiazole + TX, etrimfos + TX, eugenol + TX, EXD + TX, famoxadone + TX, farnesol + TX, farnesol with nerolidol + TX, fenamidone + TX, fenaminosulf + TX, fenaminstrobin + TX, fenarimol + TX, fenazaflor + TX, fenbuconazole + TX, fenbutatin oxide + TX, fenchlorphos + TX, fenethacarb + TX, fenfuram + TX, fenhexamid + TX, fenitrothion + TX, fenothiocarb + TX, fenoxacrim + TX, fenoxanil + TX, fenpiclonil + TX, fempicoxamid + TX, fenpirithrin + TX, fenpropidin + TX, fenpropimorph + TX, fenpyrad + TX, fenpyrazamine + TX, fenpyroximate + TX, fenson + TX, fensulfothion + TX, fenthion + TX, fenthion-ethyl + TX, fentin + TX, fentrifanil + TX, ferbam + TX, ferimzone + TX, ferric phosphate + TX, flocoumafen + TX, florylpicoxamid + TX, fluazinam + TX, flubeneteram + TX, flubenzimine + TX, flucofuron + TX, flucycloxuron + TX, fludioxonil + TX, fluenetil + TX, flufenoxadiazam + TX, flufenoxystrobin + TX, fluindapyr + TX, flumetylsulfonimide + TX, flumorph + TX, fluopicolide + TX, fluopimomide + TX, fluopyram + TX, fluorbenside + TX, fluoroacetamide + TX, fluoroimide + TX, fluoxapiprolin + TX, fluoxastrobin + TX, fluoxytioconazole + TX, flupropadine + TX, flupropadine hydrochloride + TX, fluquinconazole + TX, flusilazole + TX, flusulfamide + TX, flutianil + TX, flutolanil + TX, flutriafol + TX, fluxapyroxad + TX, FMC 1137 + TX, folpet + TX, formaldehyde + TX, formetanate + TX, formetanate hydrochloride + TX, formparanate + TX, fosetyl-aluminium + TX, fosmethilan + TX, fospirate + TX, fosthietan + TX, frontalinal + TX, fuberidazole + TX, furalaxyl + TX, furametpyr + TX, furathiocarb + TX, furethrin + TX, furfural + TX, gamma-HCH + TX, glyodin + TX, grandlure + TX, grandlure I + TX, grandlure II + TX, grandlure III + TX, grandlure IV + TX, guazatine + TX, guazatine

acetates + TX, halfenprox + TX, HCH + TX, hemel + TX, hempa + TX, HEOD + TX, heptachlor + TX, heterophos + TX, Heterorhabditis bacteriophora and H. megidis + TX, hexaconazole + TX, hexadecyl cyclopropanecarboxylate + TX, hexalure + TX, hexamide + TX, HHDN + TX, Hippodamia convergens + TX, hydrargaphen + TX, hydrated lime + TX, hydrogen cyanide + TX, hymexazol + TX, hyquincarb + TX, imanin + TX, imazalil + TX, imibenconazole + TX, iminoctadine + TX, inpyrfluxam + TX, ipconazole + TX, ipfentrifluconazole + TX, ipflufenquin + TX, iprobenphos + TX, iprodione + TX, iprovalicarb + TX, ipsdienol + TX, ipsenol + TX, IPSP + TX, isamidofos + TX, isazofos + TX, isobenzan + TX, isocarbophos + TX, isodrin + TX, isofenphos + TX, isofetamid + TX, isoflucypram + TX, isolane + TX, isoprothiolane + TX, isopyrazam + TX, isotianil + TX, isoxathion + TX, japonilure + TX, jasmolin I + TX, jasmolin II + TX, jodfenphos + TX, juvenile hormone I + TX, juvenile hormone II + TX, juvenile hormone III + TX, kadethrin + TX, kasugamycin + TX, kasugamycin hydrochloride hydrate + TX, kelevan + TX, kinetin + TX, kinoprene + TX, kresoxim-methyl + TX, lead arsenate + TX, Leptomastix dactylopii + TX, leptophos + TX, lindane + TX, lineatin + TX, lirimfos + TX, litlure + TX, looplure + TX, lvbenmixianan + TX, lythidathion + TX, Macrolophus caliginosus + TX, magnesium phosphide + TX, malonoben + TX, Mamestra brassicae NPV + TX, mancopper + TX, mancozeb + TX, mandestrobin + TX, mandipropamid + TX, maneb + TX, mazidox + TX, m-cumenyl methylcarbamate + TX, mecarbam + TX, mecarphon + TX, medlure + TX, mefentrifluconazole + TX, megatomoic acid + TX, menazon + TX, mepanipyrim + TX, meperfluthrin + TX, mephosfolan + TX, mepronil + TX, mercuric oxide + TX, mercurous chloride + TX, mesulfen + TX, mesulfenfos + TX, metalaxyl + TX, metam + TX, metam-potassium + TX, metam-sodium + TX, Metaphycus helvolus + TX, Metarhizium anisopliae var. acridum + TX, Metarhizium anisopliae var. anisopliae + TX, metarylpicoxamid + TX, metconazole + TX, metepa + TX, methacrifos + TX, methanesulfonyl fluoride + TX, methasulfocarb + TX, methiotepa + TX, methocrotophos + TX, methoprene + TX, methoquin-butyl + TX, methothrin + TX, methoxychlor + TX, methyl (Z)-2-(5-cyclohexyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate + TX, methyl (Z)-2-(5-cyclopentyl-2-methyl-phenoxy)-3-methoxy-prop-2-enoate (these compounds may be prepared from the methods described in WO2020/193387) + TX, methyl (Z)-2-[5-(3-isopropylpyrazol-1-yl)-2-methyl-phenoxy]-3-methoxy-prop-2-enoate + TX, methyl (Z)-3-methoxy-2-[2-methyl-5-(3-propylpyrazol-1-yl)phenoxy]prop-2-enoate + TX, methyl (Z)-3-methoxy-2-[2-methyl-5-(4-propyltriazol-2-yl)phenoxy]prop-2-enoate + TX, methyl (Z)-3-methoxy-2-[2-methyl-5-[3-(trifluoromethyl)pyrazol-1-yl]phenoxy]prop-2-enoate (these compounds may be prepared from the methods described in WO2020/079111) + TX, methyl (Z)-3-methoxy-2-[2-methyl-5-[4-(trifluoromethyl)triazol-2-yl]phenoxy]prop-2-enoate + TX, methyl apholate + TX, methyl bromide + TX, methyl eugenol + TX, methyl isothiocyanate + TX, methyl N-[[4-[1-(2,6-difluoro-4-isopropyl-phenyl)pyrazol-4-yl]-2-methyl-phenyl]methyl]carbamate (may be prepared from the methods described in WO 2020/097012) + TX, methyl N-[[4-[1-(4-cyclopropyl-2,6-difluoro-phenyl)pyrazol-4-yl]-2-methyl-phenyl]methyl]carbamate (may be prepared from the methods described in WO 2020/097012) + TX, methyl N-[[5-[4-(2,4-dimethylphenyl)triazol-2-yl]-2-methyl-phenyl]methyl]carbamate + TX, methylchloroform + TX, methylene chloride + TX, methylneodecanamide + TX, metiram + TX, metolcarb + TX, metominostrobin + TX, metoxadiazone + TX, metrafenone + TX, metyltetraprole + TX, MGK 264 + TX, milbemycin oxime

+ TX, mipafox + TX, mirex + TX, monocrotophos + TX, morphothion + TX, morzid + TX, moxidectin + TX, muscalure + TX, myclobutanil + TX, myclozoline + TX, Myrothecium verrucaria composition + TX, N-((1R)-1-benzyl-3-chloro-1-methyl-but-3-enyl)-8-fluoro-quinoline-3-carboxamide (these compounds may be prepared from the methods described in WO2017/153380) + TX, N-((1S)-1-benzyl-3-chloro-1-methyl-but-3-enyl)-8-fluoro-quinoline-3-carboxamide (these compounds may be prepared from the methods described in WO2017/153380) + TX, N'-(2,5-dimethyl-4-phenoxy-phenyl)-N-ethyl-N-methyl-formamidine + TX, N'-(2-chloro-5-methyl-4-phenoxy-phenyl)-N-ethyl-N-methyl-formamidine + TX, N,2-dimethoxy-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide + TX, N,N-dimethyl-1-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-1,2,4-triazol-3-amine (THESE COMPOUNDS may be prepared from the methods described in WO 2017/055473 + TX, WO 2017/055469 + TX, WO 2017/093348 and WO 2017/118689) + TX, N-[(1R)-1-benzyl-1,3-dimethyl-butyl]-7,8-difluoro-quinoline-3-carboxamide + TX, N-[(1R)-1-benzyl-1,3-dimethyl-butyl]-8-fluoro-quinoline-3-carboxamide + TX, N-[(1R)-1-benzyl-3,3,3-trifluoro-1-methyl-propyl]-8-fluoro-quinoline-3-carboxamide + TX, N-[(1S)-1-benzyl-1,3-dimethyl-butyl]-7,8-difluoro-quinoline-3-carboxamide + TX, N-[(1S)-1-benzyl-1,3-dimethyl-butyl]-8-fluoro-quinoline-3-carboxamide + TX, N-[(1S)-1-benzyl-3,3,3-trifluoro-1-methyl-propyl]-8-fluoro-quinoline-3-carboxamide + TX, N-[(E)-methoxyiminomethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzamide + TX, N-[(Z)-methoxyiminomethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzamide + TX, N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide + TX, N-[2-[2,4-dichloro-phenoxy]phenyl]-3-(difluoromethyl)-1-methyl-pyrazole-4-carboxamide + TX, N-[2-[2-chloro-4-(trifluoromethyl)phenoxy]phenyl]-3-(difluoromethyl)-1-methyl-pyrazole-4-carboxamide + TX, N'-[2-chloro-4-(2-fluorophenoxy)-5-methyl-phenyl]-N-ethyl-N-methyl-formamidine (this compound may be prepared from the methods described in WO 2016/202742) + TX, N'-[4-(4,5-dichlorothiazol-2-yl)oxy-2,5-dimethyl-phenyl]-N-ethyl-N-methyl-formamidine + TX, N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine + TX, N'-[5-bromo-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-isopropyl-N-methyl-formamidine (these compounds may be prepared from the methods described in WO2015/155075) + TX, N'-[5-bromo-2-methyl-6-(2-propoxypropoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine (this compound may be prepared from the methods described in IPCOM000249876D) + TX, N'-[5-bromo-2-methyl-6-[(1R)-1-methyl-2-propoxy-ethoxy]-3-pyridyl]-N-ethyl-N-methyl-formamidine + TX, N'-[5-bromo-2-methyl-6-[(1S)-1-methyl-2-propoxy-ethoxy]-3-pyridyl]-N-ethyl-N-methyl-formamidine + TX, N'-[5-chloro-2-methyl-6-(1-methyl-2-propoxy-ethoxy)-3-pyridyl]-N-ethyl-N-methyl-formamidine + TX, N-[N-methoxy-C-methyl-carbonimidoyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzamide (these compounds may be prepared from the methods described in WO 2018/202428) + TX, N'-[4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxy-ethyl)-5-methoxy-2-methyl-phenyl]-N-isopropyl-N-methyl-formamidine (these compounds may be prepared from the methods described in WO2018/228896) + TX, nabam + TX, naftalofos + TX, naled + TX, naphthalene + TX, NC-170 + TX, Neodiprion sertifer NPV and N. lecontei NPV + TX, nerolidol + TX, N-ethyl-2-methyl-N-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]propanamide + TX, N-ethyl-N'-[5-methoxy-2-methyl-4-[(2-trifluoromethyl)oxetan-2-yl]phenyl]-N-methyl-formamidine + TX, nickel

bis(dimethyldithiocarbamate) + TX, niclosamide-olamine + TX, nicotine + TX, nicotine sulfate + TX, nifluridide + TX, nikkomycins + TX, N-isopropyl-N'-[5-methoxy-2-methyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenyl-ethyl)phenyl]-N-methyl-formamidine + TX, nithiazine + TX, nitrapyrin + TX, nitrilacarb + TX, nitrilacarb 1:1 zinc chloride complex + TX, nitrothal-isopropyl + TX, N-methoxy-N-[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]cyclopropanecarboxamide + TX, N-methyl-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzamide + TX, N-methyl-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]benzenecarbothioamide + TX, norbormide + TX, nuarimol + TX, O,O,O',O'-tetrapropy dithiopyrophosphate + TX, octadeca-2,13-dien-1-yl acetate + TX, octadeca-3,13-dien-1-yl acetate + TX, ochtilinone + TX, ofurace + TX, oleic acid + TX, omethoate + TX, orfralure + TX, Orius spp. + TX, orystalure + TX, orysastrobin + TX, ostramone + TX, oxadixyl + TX, oxamate + TX, oxathiapirolin + TX, oxine-copper + TX, oxolinic acid + TX, oxycarboxin + TX, oxydeprofos + TX, oxydisulfoton + TX, oxytetracycline + TX, paclobutrazole + TX, Paecilomyces fumosoroseus + TX, para-dichlorobenzene + TX, parathion + TX, parathion-methyl + TX, pefurazolate + TX, penconazole + TX, pencycuron + TX, penflufen + TX, penfluron + TX, pentachlorophenol + TX, pentachlorophenyl laurate + TX, penthiopyrad + TX, permethrin + TX, PH 60-38 + TX, phenamacril + TX, phenkapton + TX, phosacetim + TX, phosalone + TX, phosdiphen + TX, phosfolan + TX, phosglycin + TX, phosnichlor + TX, phosphamidon + TX, phosphine + TX, phosphorus + TX, phoxim-methyl + TX, phthalide + TX, Phytoseiulus persimilis + TX, picarbutrazox + TX, picardin + TX, picoxystrobin + TX, pindone + TX, piperazine + TX, piperonyl butoxide + TX, piprotal + TX, pirimetaphos + TX, polychlorodicyclopentadiene isomers + TX, polychloroterpenes + TX, polynactins + TX, polyoxins + TX, potassium arsenite + TX, potassium ethylxanthate + TX, potassium hydroxyquinoline sulfate + TX, potassium thiocyanate + TX, pp'-DDT + TX, precocene I + TX, precocene II + TX, precocene III + TX, primidophos + TX, probenazole + TX, prochloraz + TX, proclonol + TX, procymidone + TX, profluthrin + TX, promacyl + TX, promecarb + TX, propamocarb + TX, propiconazole + TX, propineb + TX, propoxur + TX, propyl isomer + TX, proquinazid + TX, prothidathion + TX, prothioconazole + TX, prothiofos + TX, prothoate + TX, pydiflumetofen + TX, pyraclostrobin + TX, pyrametostrobin + TX, pyraoxystrobin + TX, pyrapropoyne + TX, pyraziflumid + TX, pyrazophos + TX, pyresmethrin + TX, pyrethrin I + TX, pyrethrin II + TX, pyrethrins + TX, pyribencarb + TX, pyridachlometyl + TX, pyridaphenthion + TX, pyridin-4-amine + TX, pyrifenox + TX, pyrimethanil + TX, pyrimitate + TX, pyrimorph + TX, pyrinuron + TX, pyriofenone + TX, pyrisoxazole + TX, pyroquilon + TX, quassia + TX, quinalphos + TX, quinalphos-methyl + TX, quinochloramine + TX, quinofumelin + TX, quinonamid + TX, quinothion + TX, quinoxifen + TX, quintiofos + TX, quintozone + TX, R-1492 + TX, rafoxanide + TX, resmethrin + TX, Reynoutria sachalinensis extract + TX, ribavirin + TX, R-metalaxyl + TX, rotenone + TX, ryania + TX, ryanodine + TX, S421 + TX, sabadilla + TX, schradan + TX, scilliroside + TX, seboctylamine + TX, sebufos + TX, sedaxane + TX, selamectin + TX, sesamex + TX, sesasmolin + TX, SI-0009 + TX, siglure + TX, simazine + TX, simeconazole + TX, sodium arsenite + TX, sodium cyanide + TX, sodium fluoride + TX, sodium fluoroacetate + TX, sodium hexafluorosilicate + TX, sodium pentachlorophenoxide + TX, sodium selenate + TX, sodium tetrathiocarbonate + TX, sodium thiocyanate + TX, sophamide + TX, sordidin + TX, spiroxamine + TX, SSI-121 + TX, Steinernema bibionis + TX, Steinernema carpocapsae + TX, Steinernema feltiae + TX,

Steinernema glaseri + TX, Steinernema riobrave + TX, Steinernema riobavis + TX, Steinernema scapterisci + TX, Steinernema spp. + TX, streptomycin + TX, streptomycin sesquisulfate + TX, strychnine + TX, sulcatol + TX, sulcofuron + TX, sulcofuron-sodium + TX, sulfiram + TX, sulfluramid + TX, sulfotep + TX, sulfoxide + TX, sulfur + TX, sulfuryl fluoride + TX, sulprofos + TX, tar oils + TX, tau-fluvalinate + TX, tazimcarb + TX, TDE + TX, tebuconazole + TX, tebufloquin + TX, tebupirimfos + TX, tecloftalam + TX, temephos + TX, tepa + TX, TEPP + TX, terallethrin + TX, terbam + TX, tert-butyl N-[6-[[[(1-methyltetrazol-5-yl)-phenyl-methylene]amino]oxymethyl]-2-pyridyl]carbamate + TX, tetrachloroethane + TX, tetrachlorothiophene + TX, tetraconazole + TX, tetradec-11-en-1-yl acetate + TX, tetradifon + TX, tetramethylfluthrin + TX, tetrasul + TX, thallium sulfate + TX, thiabendazole + TX, thiafenox + TX, thiapronil + TX, thicrofos + TX, thifluzamide + TX, thiocarboxime + TX, thiocyclam + TX, thiocyclam hydrogen oxalate + TX, thiodiazole copper + TX, thiofanox + TX, thiohempa + TX, thiomersal + TX, thiometon + TX, thionazin + TX, thiophanate + TX, thiophanate-methyl + TX, thioquinox + TX, thiosultap + TX, thiosultap-sodium + TX, thiotepa + TX, thiram + TX, thuringiensin + TX, tiadinil + TX, tolclofos-methyl + TX, tolprocarb + TX, tolylfluanid + TX, tralomethrin + TX, transpermethrin + TX, tretamine + TX, triadimefon + TX, triadimenol + TX, triamiphos + TX, triarathene + TX, triazamate + TX, triazophos + TX, triazoxide + TX, triazuron + TX, tributyltin oxide + TX, trichlormetaphos-3 + TX, trichloronat + TX, Trichogramma spp. + TX, triclopyricarb + TX, tricyclazole + TX, tridemorph + TX, trifenmorph + TX, trifenofos + TX, trifloxystrobin + TX, triflumizole + TX, triforine + TX, trimedlure + TX, trimedlure A + TX, trimedlure B1 + TX, trimedlure B2 + TX, trimedlure C + TX, trimethacarb + TX, trinactin + TX, trinexapac + TX, triphenyltin acetate + TX, triphenyltin hydroxide + TX, triprene + TX, triticonazole + TX, trunc-call + TX, Typhlodromus occidentalis + TX, uredepa + TX, validamycin + TX, valifenalate + TX, vamidothion + TX, vaniliprole + TX, veratridine + TX, veratrine + TX, verbutin + TX, Verticillium lecanii + TX, vinclozoline + TX, warfarin + TX, XMC + TX, xlenols + TX, zeatin + TX, zetamethrin + TX, zhongshengmycin + TX, zinc naphthenate + TX, zinc phosphide + TX, zinc thiazole + TX, zineb + TX, ziram + TX, zolaprofos + TX, zoxamide + TX, α - (1 + TX, 1-dimethylethyl) - α - [4'- (trifluoromethoxy) [1 + TX, 1'- biphenyl] - 4- yl] -5- pyrimidinemethanol + TX;

Typhula phacorrhiza strain 94670 + TX, Acinetobacter lwoffii + TX, Acremonium alternatum + TX, Acremonium cephalosporium + TX, Acremonium diospyri + TX, Acremonium obclavatum + TX, Adoxophyes orana granulovirus (AdoxGV) (Capex®) + TX, Agrobacterium radiobacter strain K84 (Galltrol-A®) + TX, Alternaria alternate + TX, Alternaria cassia + TX, Alternaria destruens (Smolder®) + TX, Ampelomyces quisqualis (AQ10®) + TX, Aspergillus flavus AF36 (AF36®) + TX, Aspergillus flavus NRRL 21882 (Aflaguard®) + TX, Aspergillus spp. + TX, Aureobasidium pullulans + TX, Azospirillum (MicroAZ® + TX, TAZO B®) + TX, Azotobacter + TX, Azotobacter chroococcum (Azotomeal®) + TX, Azotobacter cysts (Bionatural Blooming Blossoms®) + TX, Bacillus amyloliquefaciens + TX, Bacillus cereus + TX, Bacillus chitosporus strain AQ746 + TX, Bacillus chitosporus strain CM-1 + TX, Bacillus circulans + TX, Bacillus firmus (BioSafe® + TX, BioNem-WP®) in particular strain CNMC 1-1582 (e.g. VOTIVO® from BASF SE) + TX, Bacillus licheniformis strain 3086 (EcoGuard® + TX, Green Releaf®) + TX, Bacillus licheniformis strain HB-2 (Biostart™

formerly Rhizoboost®) + TX, *Bacillus macerans* + TX, *Bacillus marismortui* + TX, *Bacillus megaterium* + TX, *Bacillus mycoides* strain AQ726 + TX, *Bacillus papillae* (Milky Spore Powder®) + TX, *Bacillus pumilus* spp. + TX, *Bacillus pumilus* strain AQ717 + TX, *Bacillus pumilus* strain GB34 (Yield Shield®) + TX, *Bacillus pumilus* strain QST 2808 (Sonata® + TX, Ballad Plus®) + TX, *Bacillus sphaericus* (VectoLex®) + TX, *Bacillus* spp. + TX, *Bacillus* spp. strain AQ175 + TX, *Bacillus* spp. strain AQ177 + TX, *Bacillus* spp. strain AQ178 + TX, *Bacillus subtilis* strain AQ153 + TX, *Bacillus subtilis* strain AQ743 + TX, *Bacillus subtilis* strain QST 713 (CEASE® + TX, Serenade® + TX, Rhapsody®) + TX, *Bacillus subtilis* strain QST 714 (JAZZ®) + TX, *Bacillus subtilis* strain QST3002 + TX, *Bacillus subtilis* strain QST3004 + TX, *Bacillus subtilis* var. *amyloliquefaciens* strain FZB24 (Taegro® + TX, Rhizopro®) + TX, *Bacillus thuringiensis aizawai* GC 91 (Agree®) + TX, *Bacillus thuringiensis* Cry 2Ae + TX, *Bacillus thuringiensis* Cry1Ab + TX, *Bacillus thuringiensis israelensis* (BMP123® + TX, Aquabac® + TX, VectoBac®) + TX, *Bacillus thuringiensis* kurstaki (Javelin® + TX, Deliver® + TX, CryMax® + TX, Bonide® + TX, Scutella WP® + TX, Turilav WP® + TX, Astuto® + TX, Dipel WP® + TX, Biobit® + TX, Foray®) + TX, *Bacillus thuringiensis* kurstaki BMP 123 (Baritone®) + TX, *Bacillus thuringiensis* kurstaki HD-1 (Bioprotec-CAF / 3P®) + TX, *Bacillus thuringiensis* strain AQ52 + TX, *Bacillus thuringiensis* strain BD#32 + TX, *Bacillus thuringiensis tenebrionis* (Novodor® + TX, BtBooster) + TX, *Bacillus thuringiensis* var. *aizawai* (XenTari® + TX, DiPel®) + TX, *bacteria* spp. (GROWMEND® + TX, GROWSWEET® + TX, Shootup®) + TX, bacteriophage of *Clavipacter michiganensis* (AgriPhage® + TX, Bakflor®) + TX, *Beauveria bassiana* (Beaugenic® + TX, Brocaril WP®) + TX, *Beauveria bassiana* GHA (Mycotrol ES® + TX, Mycotrol O® + TX, BotaniGuard®) + TX, *Beauveria brongniartii* (Engerlingspilz® + TX, Schweizer *Beauveria*® + TX, Melocont®) + TX, *Beauveria* spp. + TX, *Botrytis cinerea* + TX, *Bradyrhizobium japonicum* (TerraMax®) + TX, *Brevibacillus brevis* + TX, *Burkholderia cepacia* (Deny® + TX, Intercept® + TX, Blue Circle®) + TX, *Burkholderia gladii* + TX, *Burkholderia gladioli* + TX, *Burkholderia* spp. + TX, Canadian thistle fungus (CBH Canadian Bioherbicide®) + TX, *Candida butyri* + TX, *Candida famata* + TX, *Candida fructus* + TX, *Candida glabrata* + TX, *Candida guilliermondii* + TX, *Candida melibiosica* + TX, *Candida oleophila* strain O + TX, *Candida parapsilosis* + TX, *Candida pelliculosa* + TX, *Candida pulcherrima* + TX, *Candida reukauffii* + TX, *Candida saitoana* (Bio-Coat® + TX, Biocure®) + TX, *Candida sake* + TX, *Candida* spp. + TX, *Candida tenuis* + TX, *Cedecea davisae* + TX, *Cellulomonas flavigena* + TX, *Chaetomium cochliodes* (Nova-Cide®) + TX, *Chaetomium globosum* (Nova-Cide®) + TX, *Chromobacterium subtsugae* strain PRAA4-1T (Grandevo®) + TX, *Cladosporium chlorocephalum* + TX, *Cladosporium cladosporioides* + TX, *Cladosporium oxysporum* + TX, *Cladosporium* spp. + TX, *Cladosporium tenuissimum* + TX, *Clonostachys rosea* (EndoFine®) + TX, *Colletotrichum acutatum* + TX, *Coniothyrium minitans* (Cotans WG®) + TX, *Coniothyrium* spp. + TX, *Cryptococcus albidus* (YIELDPLUS®) + TX, *Cryptococcus humicola* + TX, *Cryptococcus infirmo-miniatus* + TX, *Cryptococcus laurentii* + TX, *Cryptophlebia leucotreta* granulovirus (Cryptex®) + TX, *Cupriavidus campinensis* + TX, *Cydia pomonella* granulovirus (CYD-X® + TX, Madex® + TX, Madex® Plus + TX, Madex Max + TX, Carpovirusine® + TX, *Cylindrobasidium laeve* (Stumpout®) + TX, *Cylindrocladium* + TX,

Debaryomyces hansenii + TX, Drechslera hawaiiensis + TX, Enterobacter cloacae + TX, Enterobacteriaceae + TX, Entomophthora virulenta (Vektor®) + TX, Epicoccum nigrum + TX, Epicoccum purpurascens + TX, Epicoccum spp. + TX, Filobasidium floriforme + TX, Fusarium acuminatum + TX, Fusarium chlamydosporum + TX, Fusarium oxysporum (Fusaclean® + TX, Biofox C®) + TX, Fusarium proliferatum + TX, Fusarium spp. + TX, Galactomyces geotrichum + TX, Gliocladium catenulatum (Primastop® + TX, Prestop®) + TX, Gliocladium roseum + TX, Gliocladium spp. (SoilGard®) + TX, Gliocladium virens (Soilgard®) + TX, Granulovirus (Granupom®) + TX, Halobacillus halophilus + TX, Halobacillus litoralis + TX, Halobacillus trueperi + TX, Halomonas spp. + TX, Halomonas subglaciescola + TX, Halovibrio variabilis + TX, Hanseniaspora uvarum + TX, Helicoverpa armigera nucleopolyhedrovirus (Helicovex®) + TX, Helicoverpa zea nuclear polyhedrosis virus (Gemstar®) + TX, Isaria fumosorosea (previously known as Paecilomyces fumosoroseus strain + TX, PFR-97® + TX, PreFeRa®) + TX, Isoflavone formononetin (Myconate®) + TX, Kloeckera apiculata + TX, Kloeckera spp. + TX, Lagenidium giganteum (Laginex®) + TX, Lecanicillium lecanii (formerly known as Verticillium lecanii (Mycotal®) conidia of strain KV01 (e.g. Vertalec® by Koppert/Arysta) + TX, Lecanicillium longisporum (Vertiblast®) + TX, Lecanicillium muscarium (Vertikil®) + TX, Lymantria Dispar nucleopolyhedrosis virus (Disparvirus®) + TX, Marinococcus halophilus + TX, Meira geulakonigii + TX, Metarhizium anisopliae (Destruxin WP®) + TX, Metarhizium anisopliae (Met52®) + TX, Metschnikowia fruticola (Shemer®) + TX, Metschnikowia pulcherrima + TX, Microdochium dimerum (Antibot®) + TX, Micromonospora coerulea + TX, Microsphaeropsis ochracea + TX, Muscodor albus 620 (Muscodor®) + TX, Muscodor roseus in particular strain A3-5 (Accession No. NRRL 30548) + TX, Mycorrhizae spp. (AMykor® + TX, Root Maximizer®) + TX, Myrothecium verrucaria strain AARC-0255 (DiTera® + TX, BROS PLUS®) + TX, Ophiostoma piliferum strain D97 (Sylvanex®) + TX, Paecilomyces farinosus + TX, Paecilomyces lilacinus strain 251 (MeloCon WG®) + TX, Paecilomyces linacinus (Biostat WP®) + TX, Paenibacillus polymyxa + TX, Pantoea agglomerans (BlightBan C9-1®) + TX, Pantoea spp. + TX, Pasteuria nishizawae in particular strain Pn1 (CLARIVA from Syngenta/ChemChina) + TX; + TX, Pasteuria spp. (Econem®) + TX, Penicillium aurantiogriseum + TX, Penicillium billai (Jumpstart® + TX, TagTeam®) + TX, Penicillium brevicompactum + TX, Penicillium frequentans + TX, Penicillium griseofulvum + TX, Penicillium purpurogenum + TX, Penicillium spp. + TX, Penicillium viridicatum + TX, Phlebiopsis gigantea (Rotstop®) + TX, phosphate solubilizing bacteria (Phosphomeal®) + TX, Phytophthora cryptogea + TX, Phytophthora palmivora (Devine®) + TX, Pichia anomala + TX, Pichia guilliermondii + TX, Pichia membranaefaciens + TX, Pichia onychis + TX, Pichia stipites + TX, Pseudomonas aeruginosa + TX, Pseudomonas aureofaciens (Spot-Less Biofungicide®) + TX, Pseudomonas cepacia + TX, Pseudomonas chlororaphis (AtEze®) + TX, Pseudomonas corrugate + TX, Pseudomonas fluorescens strain A506 (BlightBan A506®) + TX, Pseudomonas putida + TX, Pseudomonas reactans + TX, Pseudomonas spp. + TX, Pseudomonas syringae (Bio-Save®) + TX, Pseudomonas viridiflava + TX, Pseudomonas fluorescens (Zequanox®) + TX, Pseudozyma flocculosa strain PF-A22 UL (Sporodex L®) + TX, Puccinia canaliculata + TX, Puccinia thlaspeos (Wood Warrior®) + TX, Pythium paroecandrum + TX, Pythium oligandrum

(Polygandron® + TX, Polyversum®) + TX, Pythium periplocum + TX, Rhanella aquatilis + TX, Rhanella spp. + TX, Rhizobia (Dormal® + TX, Vault®) + TX, Rhizoctonia + TX, Rhodococcus globerulus strain AQ719 + TX, Rhodosporidium diobovatum + TX, Rhodosporidium toruloides + TX, Rhodotorula glutinis + TX, Rhodotorula graminis + TX, Rhodotorula mucilagnosa + TX, Rhodotorula rubra + TX, Rhodotorula spp. + TX, Saccharomyces cerevisiae + TX, Salinococcus roseus + TX, Sclerotinia minor + TX, Sclerotinia minor (SARRITOR®) + TX, Scytalidium spp. + TX, Scytalidium uredinicola + TX, Serratia marcescens + TX, Serratia plymuthica + TX, Serratia spp. + TX, Sordaria fimicola + TX, Spodoptera exigua nuclear polyhedrosis virus (Spod-X® + TX, Spexit®) + TX, Spodoptera littoralis nucleopolyhedrovirus (Littovir®) + TX, Sporobolomyces roseus + TX, Stenotrophomonas maltophilia + TX, Streptomyces hygroscopicus + TX, Streptomyces albaduncus + TX, Streptomyces exfoliates + TX, Streptomyces galbus + TX, Streptomyces griseoplanus + TX, Streptomyces griseoviridis (Mycostop®) + TX, Streptomyces lydicus (Actinovate®) + TX, Streptomyces lydicus WYEC-108 (ActinoGrow®) + TX, Streptomyces violaceus + TX, Tilletiopsis minor + TX, Tilletiopsis spp. + TX, Trichoderma asperellum (T34 Biocontrol®) + TX, Trichoderma atroviride (Plantmate®) + TX, Trichoderma gamsii (Tenet®) + TX, Trichoderma hamatum TH 382 + TX, Trichoderma harzianum rifai (Mycostar®) + TX, Trichoderma harzianum T-22 (Trianum-P® + TX, PlantShield HC® + TX, RootShield® + TX, Trianum-G® + TX, Trichoderma harzianum T-39 (Trichodex®) + TX, Trichoderma inhamatum + TX, Trichoderma koningii + TX, Trichoderma lignorum + TX, Trichoderma longibrachiatum + TX, Trichoderma polysporum (Binab T®) + TX, Trichoderma spp. LC 52 (Sentinel®) + TX, Trichoderma taxi + TX, Trichoderma virens + TX, Trichoderma virens (formerly Gliocladium virens GL-21) (SoilGuard®) + TX, Trichoderma viride + TX, Trichoderma viride strain ICC 080 (Remedier®) + TX, Trichosporon pullulans + TX, Trichosporon spp. + TX, Trichothecium roseum + TX, Trichothecium spp. + TX, Typhula phacorrhiza strain 94671 + TX, Ulocladium atrum + TX, Ulocladium oudemansii (Botry-Zen®) + TX, Ustilago maydis + TX, various bacteria and supplementary micronutrients (Natural II®) + TX, various fungi (Millennium Microbes®) + TX, Verticillium chlamydosporium + TX, Vip3Aa20 (VIPtera®) + TX, Virgibacillus marismortui + TX, Xanthomonas campestris pv. Poae (Camperico®) + TX, Xenorhabdus bovienii + TX, Xenorhabdus nematophilus + TX;

azadirachtin (Plasma Neem Oil® + TX, AzaGuard® + TX, MeemAza® + TX, Molt-X® e.g. AZATIN XL from Certis, US) + TX, Botanical IGR (Neemazad® + TX, Neemix®) + TX, canola oil (Lilly Miller Vegol®) + TX, Chenopodium ambrosioides near ambrosioides (Requiem®) + TX, Chrysanthemum extract (Crisant®) + TX, essentials oils of Labiatae (Botania®) + TX, extract of neem oil (Trilogy®) + TX, extracts of clove rosemary peppermint and thyme oil (Garden insect killer®) + TX, garlic + TX, Glycinebetaine (Greenstim®) + TX, kaolin (Screen®) + TX, lemongrass oil (GreenMatch®) + TX, Melaleuca alternifolia extract (also called tea tree oil) (Timorex Gold®) + TX, mixture of clove peppermint garlic oil and mint (Soil Shot®) + TX, mixture of clove rosemary and peppermint extract (EF 400®) + TX, mixture of rosemary sesame peppermint thyme and cinnamon extracts (EF 300®) + TX, neem oil + TX, Nepeta cataria (Catnip oil) + TX, Nepeta catarina + TX, nicotine + TX, oregano

oil (MossBuster®) + TX, Pedaliaceae oil (Nematon®) + TX, pine oil (Retenol®) + TX, pyrethrum + TX, Quillaja saponaria (NemaQ®) + TX, Reynoutria sachalinensis (Regalia® + TX, Sakalia®) + TX, rotenone (Eco Roten®) + TX, Rutaceae plant extract (Soleo®) + TX, soybean oil (Ortho ecosense®) + TX, storage glucan of brown algae (Laminarin®) + TX, thyme oil (AGNIQUE® MMF + TX, BugOil® + TX) + TX;

(E,Z)-7,9-Dodecadien-1-yl acetate + TX, (E,Z,Z)-3,8,11 Tetradecatrienyl acetate + TX, (Z,Z,E)-7,11,13-Hexadecatrienal + TX, 2-Methyl-1-butanol + TX, Biolure® + TX, blackheaded fireworm pheromone (3M Sprayable Blackheaded Fireworm Pheromone®) + TX, Calcium acetate + TX, Check-Mate® + TX, Codling Moth Pheromone (Paramount dispenser-(CM)/ Isomate C-Plus®) + TX, Entostat powder (extract from palm tree) (Exosex CM®) + TX, Grape Berry Moth Pheromone (3M MEC-GBM Sprayable Pheromone®) + TX, Lavandulyl senecioate + TX, Leafroller pheromone (3M MEC – LR Sprayable Pheromone®) + TX, Muscamone (Snip7 Fly Bait® + TX, Oriental Fruit Moth Pheromone (3M oriental fruit moth sprayable pheromone®) + TX, Peachtree Borer Pheromone (Isomate-P®) + TX, Scenturion® + TX, Starbar Premium Fly Bait®) + TX, Tomato Pinworm Pheromone (3M Sprayable pheromone®) + TX;

Fopius arisanus + TX, Acerophagus papaya + TX, Adalia bipunctata (Adalia-System®) + TX, Adalia bipunctata (Adaline®) + TX, Adalia bipunctata (Aphidalia®) + TX, Ageniaspis citricola + TX, Ageniaspis fuscicollis + TX, Amblyseius andersoni (Anderline®, or Andersoni-System®) + TX, Amblyseius californicus (Amblyline®, or Spical®) + TX, Amblyseius cucumeris (Thripex®, or Bugline cucumeris®) + TX, Amblyseius fallacis (Fallacis®) + TX, Amblyseius swirskii (Bugline swirskii®, or Swirskii-Mite®) + TX, Amblyseius womersleyi (WomerMite®) + TX, Amitus hesperidum + TX, Anagrus atomus + TX, Anagrus fusciventris + TX, Anagrus kamali + TX, Anagrus loeckii + TX, Anagrus pseudococci (Citripar®) + TX, Anicetus benefices + TX, Anisopteromalus calandrae + TX, Anthocoris nemoralis (Anthocoris-System®) + TX, Aphelinus abdominalis (Apheline® + TX, Aphiline®) + TX, + TX, Aphelinus asychis + TX, Aphidius colemani (Aphipar®) + TX, Aphidius ervi (Aphelinus-System®) + TX, Aphidius ervi (Ervipar®) + TX, Aphidius gifuensis + TX, Aphidius matricariae (Aphipar-M®) + TX, Aphidoletes aphidimyza (Aphidend® + TX, Aphidoline®) + TX, Aphytis lingnanensis + TX, Aphytis melinus + TX, Aprostocetus hagenowii + TX, Atheta coriaria (Staphyline®) + TX, Bombus spp. + TX, Bombus terrestris (Beeline® + TX, Tripol®) + TX, Bombus terrestris (Natupol Beehive®) + TX, Cephalonomia stephanoderis + TX, Chilocorus nigritus + TX, Chrysoperla carnea (Chrysoline® + TX, Chrysopa®) + TX, Chrysoperla rufilabris + TX, Cirrospilus ingenuus + TX, Cirrospilus quadristriatus + TX, Citrostichus phyllocnistoides + TX, Closterocerus chamaeleon + TX, Closterocerus spp. + TX, Coccidoxenoides perminutus (Planopar®) + TX, Coccophagus cowperi + TX, Coccophagus lycimnia + TX, Cotesia flavipes + TX, Cotesia plutellae + TX, Cryptolaemus montrouzieri (Cryptobug® + TX, Cryptoline®) + TX, Cybocephalus nipponicus + TX, Dacnusa sibirica (Minusa® + TX, DacDigline® + TX, Minex®) + TX, Delphastus catalinae (Delphastus®) + TX, Delphastus pusillus + TX, Diachasmimorpha krausii + TX, Diachasmimorpha

longicaudata + TX, Diaparsis jucunda + TX, Diaphorencyrtus aligarhensis + TX, Diglyphus isaea (Diminex® + TX, Miglyphus® + TX, Digline®) + TX, Diversinervus spp. + TX, Encarsia citrina + TX, Encarsia formosa (Encarsia max® + TX, Encarline® + TX, En-Strip®) + TX, Encarsia guadeloupae + TX, Encarsia haitiensis + TX, Episyrrhus balteatus (Syrphidend®) + TX, Eretmoceris siphonini + TX, Eretmoceris californicus + TX, Eretmoceris eremicus (Enermix® + TX, Ercal® + TX, Eretline e® + TX, Bemimix®) + TX, Eretmoceris hayati + TX, Eretmoceris mundus (Bemipar® + TX, Eretline m®) + TX, Eretmoceris siphonini + TX, Exochomus quadripustulatus + TX, Feltiella acarisuga (Feltiline®) + TX, Feltiella acarisuga (Spidend®) + TX, Fopius ceratitivorus + TX, Formononetin (Wirless Beehome®) + TX, Franklinothrips vespiformis (Vespop®) + TX, Galendromus occidentalis + TX, Goniozus legneri + TX, Habrobracon hebetor + TX, Harmonia axyridis (HarmoBeetle®) + TX, Heterorhabditis bacteriophora (NemaShield HB® + TX, Nemaseek® + TX, Terranem-Nam® + TX, Terranem® + TX, Larvanem® + TX, B-Green® + TX, NemAttack® + TX, Nematop®) + TX, Heterorhabditis megidis (Nemasys H® + TX, BioNem H® + TX, Exhibitline hm® + TX, Larvanem-M®) + TX, Heterorhabditis spp. (Lawn Patrol®) + TX, Hippodamia convergens + TX, Hypoaspis aculeifer (Aculeifer-System® + TX, Entomite-A®) + TX, Hypoaspis miles (Hypoline m® + TX, Entomite-M®) + TX, Lbalia leucospoides + TX, Lecanoideus floccissimus + TX, Lemophagus errabundus + TX, Leptomastidea abnormis + TX, Leptomastix dactylopii (Leptopar®) + TX, Leptomastix epona + TX, Lindorus lophanthae + TX, Lipolexis oregmae + TX, Lucilia caesar (NatuFly®) + TX, Lysiphlebus testaceipes + TX, Macrolophus caliginosus (Mirical-N® + TX, Macroline c® + TX, Mirical®) + TX, Mesoseiulus longipes + TX, Metaphycus flavus + TX, Metaphycus lounsburyi + TX, Micromus angulatus (Milacewing®) + TX, Microterys flavus + TX, Muscidifurax raptorellus and Spalangia cameroni (Biopar®) + TX, Neodryinus typhlocybae + TX, Neoseiulus californicus + TX, Neoseiulus cucumeris (THRYPEX®) + TX, Neoseiulus fallaxis + TX, Nesideocoris tenuis (NesidioBug® + TX, Nesibug®) + TX, Ophyra aenescens (Biofly®) + TX, Orius insidiosus (Thripor-I® + TX, Oriline i®) + TX, Orius laevigatus (Thripor-L® + TX, Oriline l®) + TX, Orius majusculus (Oriline m®) + TX, Orius strigicollis (Thripor-S®) + TX, Pauesia juniperorum + TX, Pediobius foveolatus + TX, Phasmarhabditis hermaphrodita (Nemaslug®) + TX, Phymastichus coffea + TX, Phytoseiulus macropilus + TX, Phytoseiulus persimilis (Spidex® + TX, Phytoline p®) + TX, Podisus maculiventris (Podisus®) + TX, Pseudacteon curvatus + TX, Pseudacteon obtusus + TX, Pseudacteon tricuspidatus + TX, Pseudaphycus maculipennis + TX, Pseudleptomastix mexicana + TX, Psyllaephagus pilosus + TX, Psytalia concolor (complex) + TX, Quadrastichus spp. + TX, Rhizobius lophanthae + TX, Rodolia cardinalis + TX, Rumina decollata + TX, Semielacher petiolatus + TX, Sitobion avenae (Ervibank®) + TX, Steinernema carpocapsae (Nematac C® + TX, Millenium® + TX, BioNem C® + TX, NemAttack® + TX, Nemastar® + TX, Capsanem®) + TX, Steinernema feltiae (NemaShield® + TX, Nemasys F® + TX, BioNem F® + TX, Steinernema-System® + TX, NemAttack® + TX, Nemaplus® + TX, Exhibitline sf® + TX, Scia-rid® + TX, Entonem®) + TX, Steinernema kraussei (Nemasys L® + TX, BioNem L® + TX, Exhibitline srb®) + TX, Steinernema riobrave (BioVector® + TX, BioVektor®) + TX, Steinernema scapterisci (Nematac S®) + TX, Steinernema spp. + TX, Steinernematid spp. (Guardian Nematodes®) + TX, Stethorus

punctillum (Stethorus®) + TX, Tamarixia radiata + TX, Tetrastichus setifer + TX, Thripobius semiluteus + TX, Torymus sinensis + TX, Trichogramma brassicae (Tricholine b®) + TX, Trichogramma brassicae (Tricho-Strip®) + TX, Trichogramma evanescens + TX, Trichogramma minutum + TX, Trichogramma ostrinae + TX, Trichogramma platneri + TX, Trichogramma pretiosum + TX, Xanthopimpla stemmator + TX;

abscisic acid + TX, Aminomite® + TX, BioGain® + TX, bioSea® + TX, Chondrostereum purpureum (Chontrol Paste®) + TX, Colletotrichum gloeosporioides (Collego®) + TX, Copper Octanoate (Cueva®) + TX, Delta traps (Trapline d®) + TX, Erwinia amylovora (Harpin) (ProAct® + TX, Ni-HIBIT Gold CST®) + TX, fatty acids derived from a natural by-product of extra virgin olive oil (FLIPPER®) + TX, Ferri-phosphate (Ferramol®) + TX, Funnel traps (Trapline y®) + TX, Gallex® + TX, Grower's Secret® + TX, Homo-brassonolide + TX, Iron Phosphate (Lilly Miller Worry Free Ferramol Slug & Snail Bait®) + TX, MCP hail trap (Trapline f®) + TX, Microctonus hyperodae + TX, Mycoleptodiscus terrestris (Des-X®) + TX, Nosema locustae (Semaspore Organic Grasshopper Control®) + TX, Pheromone trap (Thripline ams®) + TX, potassium bicarbonate (MilStop®) + TX, potassium iodide + potassiumthiocyanate (Enzicur®) + TX, potassium salts of fatty acids (Sanova®) + TX, potassium silicate solution (Sil-Matrix®) + TX, Spider venom + TX, Sticky traps (Trapline YF®) + TX, Rebell Amarillo®) + TX, SuffOil-X® + TX, Traps (Takitrapline y + b®) + TX, Zenox® + TX;

Bacillus mojavensis strain R3B (Accession No. NCAIM (P) B001389) (WO 2013/034938) from Certis USA LLC + TX, Bacillus pumilus, in particular strain BU F-33, having NRRL Accession No. 50185 (CARTISSA® from BASF, EPA Reg. No. 71840-19) + TX, Bacillus subtilis CX-9060 from Certis USA LLC + TX, Bacillus sp., in particular strain D747 (available as DOUBLE NICKEL® from Kumiai Chemical Industry Co, Ltd.), having Accession No. FERM BP-8234, (U.S. Patent No. 7,094,592) + TX, Bacillus subtilis strain BU1814 (VELONDIS® PLUS, VELONDIS® FLEX and VELONDIS® EXTRA from BASF SE) + TX, Bacillus subtilis var. amyloliquefaciens strain FZB24 having Accession No. DSM 10271 (available from Novozymes as TAEGRO® or TAEGRO® ECO (EPA Registration No. 70127-5)) + TX, Bacillus subtilis, in particular strain QST713/AQ713 (having NRRL Accession No. B-21661 and described in U.S. Patent No. 6,060,051, available as SERENADE® OPTI or SERENADE® ASO from Bayer CropScience LP, US) + TX, Paenibacillus polymyxa, in particular strain AC-1 (e.g. TOPSEED® from Green Biotech Company Ltd.) + TX, Paenibacillus sp. strain having Accession No. NRRL B-50972 or Accession No. NRRL B-67129 + TX, WO 2016/154297 + TX, Pantoea agglomerans, in particular strain E325 (Accession No. NRRL B-21856) (available as BLOOMTIME BIOLOGICAL™ FD BIOPESTICIDE from Northwest Agri Products) + TX, Pseudomonas proradix (e.g. PRORADIX® from Sourcon Padena) + TX;

Aureobasidium pullulans, in particular blastospores of strain DSM14940 + TX, blastospores of strain DSM 14941 or mixtures of blastospores of strains DSM14940 and DSM14941 (e.g., BOTECTOR® and BLOSSOM PROTECT® from bio-ferm, CH) + TX, Pseudozyma aphidis (as disclosed in

WO2011/151819 by Yissum Research Development Company of the Hebrew University of Jerusalem) + TX, *Saccharomyces cerevisiae*, in particular strains from Lesaffre et Compagnie (e.g. CNCM No. 1-393, CNCM No. 1-3937, CNCM No. 1-3938 or CNCM No. 1-3939 (WO 2010/086790) + TX;

bacteria including *Agrobacterium radiobacter* strain K84 (e.g. GALLTROL-A® from AgBioChem, CA) + TX, *Bacillus amyloliquefaciens* isolate B246 (e.g. AVOGREEN™ from University of Pretoria) + TX, *Bacillus amyloliquefaciens* strain F727 (also known as strain MBI110) (NRRL Accession No. B-50768 + TX, WO 2014/028521) (STARGUS® from Marrone Bio Innovations) + TX, *Bacillus amyloliquefaciens* strain FZB42 + TX, Accession No. DSM 23117 (available as RHIZOVITAL® from ABiTEP, DE) + TX, *Bacillus amyloliquefaciens*, in particular strain D747 (available as Double Nickel™ from Kumiai Chemical Industry Co., Ltd., having accession number FERM BP-8234, US Patent No. 7,094,592) + TX, *Bacillus licheniformis* FMCH001 and *Bacillus subtilis* FMCH002 (QUARTZO® (WG) and PRESENCE® (WP) from FMC Corporation) + TX, *Bacillus licheniformis*, in particular strain SB3086, having Accession No. ATCC 55406, WO 2003/000051 (available as ECOGUARD® Biofungicide and GREEN RELEAF™ from Novozymes) + TX, *Bacillus methylotrophicus* strain BAC-9912 (from Chinese Academy of Sciences' Institute of Applied Ecology) + TX, *Bacillus mycoides* + TX, isolate + TX, having Accession No. B-30890 (available as BMJ TGAi® or WG and LifeGard™ from Certis USA LLC) + TX, *Bacillus pumilus*, in particular strain GB34 (available as Yield Shield® from Bayer AG, DE) + TX, *Bacillus pumilus*, in particular strain QST2808 (available as SONATA® from Bayer CropScience LP, US, having Accession No. NRRL B-30087 and described in U.S. Patent No. 6,245,551) + TX, *Bacillus subtilis* CX-9060 from Certis USA LLC + TX, *Bacillus subtilis* IAB/BS03 (AVIV™ from STK Bio-Ag Technologies + TX, PORTENTO® from Idai Nature) + TX, *Bacillus subtilis* KTSB strain (FOLIACTIVE® from Donaghys) + TX, *Bacillus subtilis* strain BU1814 + TX, (available as VELONDIS® PLUS + TX, VELONDIS® FLEX and VELONDIS® EXTRA from BASF SE) + TX, *Bacillus subtilis* strain GB03 (available as Kodiak® from Bayer AG, DE) + TX, *Bacillus subtilis* strain MBI 600 (available as SUBTILEX from BASF SE) + TX, having Accession Number NRRL B-50595 + TX, U.S. Patent No. 5,061,495 + TX, *Bacillus subtilis* strain Y1336 (available as BIOBAC® WP from Bion-Tech + TX, Taiwan + TX, registered as a biological fungicide in Taiwan under Registration Nos. 4764 + TX, 5454 + TX, 5096 and 5277) + TX, *Bacillus subtilis* var. *amyloliquefaciens* strain FZB24 having Accession No. DSM 10271 (available from Novozymes as TAEGRO® or TAEGRO® ECO (EPA Registration No. 70127-5)) + TX, *Bacillus subtilis* Y1336 (available as BIOBAC® WP from Bion-Tech + TX, Taiwan + TX, registered as a biological fungicide in Taiwan under Registration Nos. 4764 + TX, 5454 + TX, 5096 and 5277) + TX, *Paenibacillus epiphyticus* (WO 2016/020371) from BASF SE + TX, *Paenibacillus polymyxa* ssp. *plantarum* (WO 2016/020371) from BASF SE + TX, *Paenibacillus* sp. strain having Accession No. NRRL B-50972 or Accession No. NRRL B-67129 + TX, WO 2016/154297 + TX, *Pseudomonas chlororaphis* strain AFS009 + TX, having Accession No. NRRL B-50897 + TX, WO 2017/019448 (e.g., HOWLER™ and ZIO® from AgBiome Innovations, US) + TX, *Pseudomonas*

chlororaphis, in particular strain MA342 (e.g. CEDOMON® , CERALL®, and CEDRESS® by Bioagri and Koppert) + TX, *Pseudomonas fluorescens* strain A506 (e.g. BLIGHTBAN® A506 by NuFarm) + TX, *Pseudomonas proradix* (e.g. PRORADIX® from Sourcon Padena) + TX, *Streptomyces griseoviridis* strain K61 (also known as *Streptomyces galbus* strain K61) (Accession No. DSM 7206) (MYCOSTOP® from Verdera, PREFERENCE® from BioWorks, cf. Crop Protection 2006, 25, 468-475) + TX, *Streptomyces lydicus* strain WYEC108 (also known as *Streptomyces lydicus* strain WYCD108US) (ACTINO-IRON® and ACTINOVATE® from Novozymes) + TX;

Trichoderma atroviride strain T11 (IMI352941/ CECT20498) + TX, *Ampelomyces quisqualis* strain AQ10, having Accession No. CNCM 1-807 (e.g. AQ 10® by IntrachemBio, Italia) + TX, *Ampelomyces quisqualis*, in particular strain AQ 10 (e.g. AQ 10® by IntrachemBio Italia) + TX, *Aspergillus flavus* strain NRRL 21882 (products known as AFLA-GUARD® from Syngenta/ChemChina) + TX, *Aureobasidium pullulans*, in particular blastospores of strain DSM 14941 + TX, *Aureobasidium pullulans*, in particular blastospores of strain DSM14940 + TX, *Aureobasidium pullulan*, in particular mixtures of blastospores of strains DSM14940 and DSM 14941 (e.g. Botector® by bio-ferm, CH) + TX, *Chaetomium cupreum* (Accession No. CABI 353812) (e.g. BLOKUPRUM™ by AgriLife) + TX, *Chaetomium globosum* (available as RIVADIOM® by Rivale) + TX, *Cladosporium cladosporioides*, strain H39, having Accession No. CBS122244, US 2010/0291039 (by Stichting Dienst Landbouwkundig Onderzoek) + TX, *Coniothyrium minitans*, in particular strain CON/M/91-8 (Accession No. DSM9660, e.g. Contans ® from Bayer CropScience Biologics GmbH) + TX, *Cryptococcus flavescens*, strain 3C (NRRL Y-50378) + TX, *Dactylaria candida* + TX, *Dilophosphora alopecuri* (available as TWIST FUNGUS®) + TX, *Fusarium oxysporum*, strain Fo47 (available as FUSACLEAN® by Natural Plant Protection) + TX, *Gliocladium catenulatum* (Synonym: *Clonostachys rosea* f. *catenulate*) strain J1446 (e.g. Prestop ® by Lallemand) + TX, *Gliocladium roseum* (also known as *Clonostachys rosea* f *rosea*) strain IK726 (Jensen DF, et al. Development of a biocontrol agent for plant disease control with special emphasis on the near commercial fungal antagonist *Clonostachys rosea* strain 'IK726, Australasian Plant Pathol. 2007,36(2):95-101) + TX, *Gliocladium roseum* (also known as *Clonostachys rosea* f *rosea*), in particular strain 321U from Adjuvants Plus, strain ACM941 as disclosed in Xue A.G. (Efficacy of *Clonostachys rosea* strain ACM941 and fungicide seed treatments for controlling the root rot complex of field pea, Can Jour Plant Sci 2003 + TX, 83(3): 519-524) + TX, *Metschnikowia fruticola*, in particular strain NRRL Y-30752 + TX, *Microsphaeropsis ochracea* + TX, *Penicillium steckii* (DSM 27859 + TX, WO 2015/067800) from BASF SE + TX, mixtures of *Trichoderma asperellum* strain ICC 012 (also known as *Trichoderma harzianum* ICC012) + TX, having Accession No. CABI CC IMI 392716 and *Trichoderma gamsii* (formerly *T. viride*) strain ICC 080 + TX, having Accession No. IMI 392151 (e.g., BIO-TAM™ from Isagro USA, Inc. or BIODERMA® by Agrobiosol de Mexico, S.A. de C.V.) + TX, *Penicillium vermiculatum* + TX, *Phlebiopsis gigantea* strain VRA 1992 (ROTSTOP® C from Danstar Ferment) + TX, *Pseudozyma flocculosa*, strain PF-A22 UL (available as SPORODEX® L by Plant Products Co., CA) + TX, *Saccharomyces cerevisiae* strain LAS117 cell

walls (CEREVISANE® from Lesaffre, ROMEO® from BASF SE) + TX, *Saccharomyces cerevisiae* strain from Lesaffre et Compagnie, FR (e.g. CNCM No. 1-3936, CNCM No. 1-3937, CNCM No. 1-3938, or CNCM No. 1-3939 (WO 2010/086790)) + TX, *Saccharomyces cerevisiae*, in particular strain LASO2 (from Agro-Levures et Dérivés) + TX, *Simplicillium lanosoniveum* strain T34 ((e.g. T34 Biocontrol by Biocontrol Technologies S.L., ES) or strain ICC 012 from Isagro, or strain WRL-076 (NRRL Y-30842), U.S. Patent No. 7,579,183) + TX, *Talaromyces flavus*, strain V117b + TX, *Trichoderma asperelloides* JM41R (Accession No. NRRL B-50759) (TRICHO PLUS® from BASF SE) + TX, *Trichoderma asperellum*, in particular strain SKT-1, having Accession No. FERM P-16510 (e.g. ECO-HOPE® from Kumiai Chemical Industry) + TX, *Trichoderma asperellum*, in particular strain kd (e.g. T-Gro from Andermatt Biocontrol) + TX, *Trichoderma atroviride* strain 77B (T77 from Andermatt Biocontrol) + TX, *Trichoderma atroviride* strain ATCC 20476 (IMI 206040) + TX, *Trichoderma atroviride* strain LC52 (e.g. Tenet by Agrimm Technologies Limited) + TX, *Trichoderma atroviride* strain LU132 (e.g. Sentinel from Agrimm Technologies Limited) + TX, *Trichoderma atroviride* strain NMI no. V08/002388 + TX, *Trichoderma atroviride* strain NMI no. V08/002389 + TX, *Trichoderma atroviride* strain NMI no. V08/002390 + TX, *Trichoderma atroviride* strain no. V08/002387 + TX, *Trichoderma atroviride* strain SKT-1 (FERM P-16510) + TX, JP Patent Publication (Kokai) 11-253151 A + TX, *Trichoderma atroviride* strain SKT-2 (FERM P-16511) + TX, JP Patent Publication (Kokai) 11-253151 A + TX, *Trichoderma atroviride* strain SKT-3 (FERM P-17021) + TX, JP Patent Publication (Kokai) 11-253151 A + TX, *Trichoderma atroviride*, in particular strain SC1 (Accession No. CBS 122089, WO 2009/116106 and U.S. Patent No. 8,431,120 (from Bi-PA)) + TX, *Trichoderma atroviride*, strain CNCM 1-1237 (e.g. Esquive® WP from Agrauxine + TX) + TX, *Trichoderma fertile* (e.g. product TrichoPlus from BASF) + TX, *Trichoderma gamsii* (formerly *T. viride*) + TX, *Trichoderma gamsii* (formerly *T. viride*) strain ICC 080 (IMI CC 392151 CABI) (available as BIODERMA® by AGROBIOSOL DE MEXICO, S.A. DE C.V.) + TX, + TX, *Trichoderma gamsii* strain ICC080 (IMI CC 392151 CABI + TX, e.g. BioDerma by AGROBIOSOL DE MEXICO, S.A. DE C.V.) + TX, + TX, *Trichoderma harzianum* + TX, *Trichoderma harzianum* + TX, having Accession No. ATCC 28012 + TX, *Trichoderma harzianum* + TX, *Trichoderma harzianum* rifai T39 (e.g. Trichodex® from Makhteshim, US) + TX, *Trichoderma harzianum* strain Cepa SimbT5 (from Simbiose Agro) + TX, + TX, *Trichoderma harzianum* strain DB 103 (available as T-GRO® 7456 by Dagutat Biolab) + TX, *Trichoderma harzianum* strain ITEM 908 (e.g. Trianum-P from Koppert) + TX, *Trichoderma harzianum* strain T-22 (e.g. Trianum-P from Andermatt Biocontrol or Koppert) + TX, *Trichoderma harzianum* strain TH35 (e.g. Root-Pro by Mycontrol) + TX, *Trichoderma polysporum* strain IMI 206039 (e.g. Binab TF WP by BINAB Bio-Innovation AB + TX, Sweden) + TX, *Trichoderma stromaticum* having Accession No. Ts3550 (e.g. Tricovab by CEPLAC, Brazil) + TX, *Trichoderma virens* (also known as *Gliocladium virens*) in particular strain GL-21 (e.g. SoilGard by Certis, US) + TX, *Trichoderma virens* strain G-41 + TX, formerly known as *Gliocladium virens* (Accession No. ATCC 20906) (e.g., ROOTSHIELD® PLUS WP and TURFSHIELD® PLUS WP from BioWorks, US) + TX, *Trichoderma viride* in particular strain B35 (Pietr et al. + TX, 1993 + TX, Zesz. Nauk. A R w Szczecinie 161: 125-137) + TX, *Trichoderma viride* strain TV1 (e.g. Trianum-

P by Koppert) + TX, *Ulocladium oudemansii* strain U3, having Accession No. NM 99/06216 (e.g., BOTRY-ZEN® by Botry-Zen Ltd, New Zealand and BOTRYSTOP® from BioWorks, Inc.) + TX, *Verticillium albo-atrum* (formerly *V. dahliae*) strain WCS850 having Accession No. WCS850, deposited at the Central Bureau for Fungi Cultures (e.g., DUTCH TRIG® by Tree Care Innovations) + TX, *Verticillium chlamydosporium* + TX;

bacteria including a mixture of *Azotobacter vinelandii* and *Clostridium pasteurianum* (available as INVIGORATE® from Agrinos) + TX, a mixture of *Bacillus licheniformis* FMCH001 and *Bacillus subtilis* FMCH002 (available as QUARTZO® (WG), PRESENCE® (WP) from FMC Corporation), *Azorhizobium caulinodans*, in particular strain ZB-SK-5 + TX, *Azospirillum brasilense* (e.g., VIGOR® from KALO, Inc.) + TX, *Azospirillum lipoferum* (e.g., VERTEX-IF™ from TerraMax, Inc.) + TX, *Azotobacter chroococcum*, in particular strain H23 + TX, *Azotobacter vinelandii*, in particular strain ATCC 12837 + TX, *Bacillus amyloliquefaciens* BS27 (Accession No. NRRL B-5015) + TX, *Bacillus amyloliquefaciens* in particular strain FZB42 (e.g. RHIZOVITAL® from ABiTEP, DE) + TX, *Bacillus amyloliquefaciens* in particular strain IN937a + TX, *Bacillus amyloliquefaciens* pm414 (LOLI-PEPTA® from Biofilm Crop Protection) + TX, *Bacillus amyloliquefaciens* SB3281 (ATCC # PTA-7542 + TX, WO 2017/205258) + TX, *Bacillus amyloliquefaciens* TJ1000 (available as QUIKROOTS® from Novozymes) + TX, *Bacillus cereus* family member EE128 (NRRL No. B-50917) + TX, *Bacillus cereus* family member EE349 (NRRL No. B-50928) + TX, *Bacillus cereus* in particular strain BP01 (ATCC 55675 + TX, e.g. MEPICHLOR® from Arysta Lifescience, US) + TX, *Bacillus mycoides* BT155 (NRRL No. B-50921) + TX, *Bacillus mycoides* BT46-3 (NRRL No. B-50922) + TX, *Bacillus mycoides* EE118 (NRRL No. B-50918) + TX, *Bacillus mycoides* EE141 (NRRL No. B-50916) + TX, *Bacillus pumilus* in particular strain GB34 (e.g. YIELD SHIELD® from Bayer Crop Science, DE) + TX, *Bacillus pumilus* in particular strain QST2808 (Accession No. NRRL No. B-30087) + TX, *Bacillus siamensis* in particular strain KCTC 13613T + TX, *Bacillus subtilis* in particular strain AQ30002 (Accession No. NRRL No. B-50421 and described in U.S. Patent Application No. 13/330,576) + TX, *Bacillus subtilis* in particular strain AQ30004 (NRRL No. B-50455 and described in U.S. Patent Application No. 13/330,576) + TX, *Bacillus subtilis* in particular strain MBI 600 (e.g. SUBTILEX® from BASF SE) + TX, *Bacillus subtilis* rm303 (RHIZOMAX® from Biofilm Crop Protection) + TX, *Bacillus subtilis* strain BU1814 (available as TEQUALIS® from BASF SE) + TX, *Bacillus tequilensis* in particular strain NII-0943 + TX, *Bacillus thuringiensis* BT013A (NRRL No. B-50924) also known as *Bacillus thuringiensis* 4Q7 + TX, *Bradyrhizobium japonicum* (e.g. OPTIMIZE® from Novozymes) + TX, *Delftia acidovorans* in particular strain RAY209 (e.g. BIOBOOST® from Brett Young Seeds) + TX, *Lactobacillus* sp. (e.g. LACTOPLANT® from LactoPAFI) + TX, *Mesorhizobium cicer* (e.g., NODULATOR from BASF SE) + TX, *Paenibacillus polymyxa* in particular strain AC-1 (e.g. TOPSEED® from Green Biotech Company Ltd.) + TX, *Pseudomonas aeruginosa* in particular strain PN1 + TX, *Pseudomonas proradix* (e.g. PRORADIX® from Sourcon Padena) + TX, *Rhizobium leguminosarium* biovar *viciae* (e.g., NODULATOR from BASF SE) + TX, *Rhizobium leguminosarum* in particular bv. *viciae* strain Z25 (Accession No. CECT 4585) + TX, *Serratia*

marcescens in particular strain SRM (Accession No. MTCC 8708) + TX, + TX, Sinorhizobium meliloti strain NRG-185-1 (NITRAGIN® GOLD from Bayer CropScience) + TX, Thiobacillus sp. (e.g. CROPAID® from Cropaid Ltd UK) + TX;

Myrothecium verrucaria strain AARC-0255 (e.g. DiTera™ from Valent Biosciences) + TX, Penicillium bilaii strain ATCC 22348 (e.g. JumpStart® from Acceleron BioAg) + TX, Penicillium bilaii strain ATCC ATCC20851 + TX, Purpureocillium lilacinum (previously known as Paecilomyces lilacinus) strain 251 (AGAL 89/030550 + TX, e.g. BioAct from Bayer CropScience Biologics GmbH) + TX, Pythium oligandrum strain DV74 + TX, Pythium oligandrum strain M1 (ATCC 38472 e.g. Polyversum from Bioprepaty, CZ) + TX, Rhizopogon amylopogon (Myco-Sol from Agri-Enterprise, LLC, formerly Helena Chemical Company) + TX, Rhizopogon fulvigleba (e.g. Myco-Sol from Agri-Enterprise, LLC, formerly Helena Chemical Company) + TX, Talaromyces flavus strain V117b + TX, Trichoderma asperellum strain (Eco-T from Plant Health Products + TX, ZA) + TX;

mercuric oxide + TX, octhlinone + TX, thiophanate-methyl + TX;

MGK 264 + TX, 2-(2-butoxyethoxy)ethyl piperonylate + TX, 2-isovalerylindan-1,3-dione + TX, 4-(quinoxalin-2-ylamino)benzenesulfonamide + TX, 5-(1,3-benzodioxol-5-yl)-3-hexylcyclohex-2-enone + TX, acibenzolar + TX, acibenzolar-S-methyl + TX, alpha-bromadiolone + TX, alpha-chlorohydrin + TX, aluminium phosphide + TX, anthraquinone + TX, antu + TX, arsenous oxide + TX, barium carbonate + TX, benoxacor + TX, bisthiosemi + TX, brodifacoum + TX, bromadiolone + TX, bromethalin + TX, calcium cyanide + TX, chloralose + TX, chlorophacinone + TX, cholecalciferol + TX, cloquintocet (including cloquintocet-mexyl) + TX, copper naphthenate + TX, copper oxychloride + TX, coumachlor + TX, coumafuryl + TX, coumatetralyl + TX, crimidine + TX, cyprosulfamide + TX, diazinon + TX, dichlormid + TX, dicyclopentadiene + TX, difenacoum + TX, difethialone + TX, diphacinone + TX, ergocalciferol + TX, farnesol + TX, farnesol with nerolidol + TX, fenchlorazole (including fenchlorazole-ethyl) + TX, fenclorim + TX, floccoumafen + TX, fluoroacetamide + TX, flupropadine + TX, flupropadine hydrochloride + TX, fluxofenim + TX, furilazole + TX, gamma-HCH + TX, guazatine + TX, guazatine acetates + TX, HCH + TX, hydrogen cyanide + TX, imanin + TX, iodomethane + TX, isoxadifen (including isoxadifen-ethyl) + TX, lindane + TX, magnesium phosphide + TX, MB-599 + TX, mefenpyr (including mefenpyr-diethyl) + TX, metcamifen + TX, methiocarb + TX, methyl bromide + TX, nerolidol + TX, norbormide + TX, petroleum oils + TX, phosacetim + TX, phosphine + TX, phosphorus + TX, pindone + TX, piperonyl butoxide + TX, piprotal + TX, potassium arsenite + TX, probenazole + TX, propyl isomer + TX, pyridin-4-amine + TX, pyrinuron + TX, Reynoutria sachalinensis extract + TX, ribavirin + TX, S421 + TX, scilliroside + TX, sesamex + TX, sesasmolin + TX, sodium arsenite + TX, sodium cyanide + TX, sodium fluoroacetate + TX, strychnine + TX, sulfoxide + TX, thallium sulfate + TX, thiram + TX, trimethacarb + TX, warfarin + TX, zinc naphthenate + TX, zinc phosphide + TX, ziram + TX.

The references in brackets behind the active ingredients, e.g. [3878-19-1] refer to the Chemical Abstracts Registry number. The above described mixing partners are known. Where the active ingredients are included in "The Pesticide Manual" [The Pesticide Manual - A World Compendium; Thirteenth Edition; Editor: C. D. S. Tomlin; The British Crop Protection Council], they are described

therein under the entry number given in round brackets hereinabove for the particular compound; for example, the compound "abamectin" is described under entry number (1). Where "[CCN]" is added hereinabove to the particular compound, the compound in question is included in the "Compendium of Pesticide Common Names", which is accessible on the internet via BCPC;

<http://www.bcpccpesticidecompendium.org/index.html>; for example, the compound "abamectin" is

described under the internet address http://www.bcpccpesticidecompendium.org/index_cn_frame.html.

Most of the active ingredients described above are referred to hereinabove by a so-called "common name", the relevant "ISO common name" or another "common name" being used in individual cases. If the designation is not a "common name", the nature of the designation used instead is given in round brackets for the particular compound; in that case, the IUPAC name, the IUPAC/Chemical Abstracts name, a "chemical name", a "traditional name", a "compound name" or a "development code" is used or, if neither one of those designations nor a "common name" is used, an "alternative name" is employed. "CAS Reg. No." means the Chemical Abstracts Registry Number.

The active ingredient mixture of the compounds of formula I selected from the compounds defined in the Tables A-1 to A-10 and P with active ingredients described above comprises a compound selected from one compound defined in the Tables A-1 to A-10 and P and an active ingredient as described above preferably in a mixing ratio of from 100:1 to 1:6000, especially from 50:1 to 1:50, more especially in a ratio of from 20:1 to 1:20, even more especially from 10:1 to 1:10, very especially from 5:1 to 1:5, special preference being given to a ratio of from 2:1 to 1:2, and a ratio of from 4:1 to 2:1 being likewise preferred, above all in a ratio of 1:1, or 5:1, or 5:2, or 5:3, or 5:4, or 4:1, or 4:2, or 4:3, or 3:1, or 3:2, or 2:1, or 1:5, or 2:5, or 3:5, or 4:5, or 1:4, or 2:4, or 3:4, or 1:3, or 2:3, or 1:2, or 1:600, or 1:300, or 1:150, or 1:35, or 2:35, or 4:35, or 1:75, or 2:75, or 4:75, or 1:6000, or 1:3000, or 1:1500, or 1:350, or 2:350, or 4:350, or 1:750, or 2:750, or 4:750. Those mixing ratios are by weight.

The compounds and mixtures as described above can be used in a method for controlling pests, which comprises applying a composition comprising a compound or mixture respectively as described above to the pests or their environment, with the exception of a method for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body.

The mixtures comprising a compound of formula I selected from the compounds defined in the Tables A-1 to A-10 and P and one or more active ingredients as described above can be applied, for example, in a single "ready-mix" form, in a combined spray mixture composed from separate formulations of the single active ingredient components, such as a "tank-mix", and in a combined use of the single active

ingredients when applied in a sequential manner, i.e. one after the other with a reasonably short period, such as a few hours or days. The order of applying the compounds of formula I and the active ingredients as described above is not essential for working the present invention.

5 The compositions according to the invention can also comprise further solid or liquid auxiliaries, such as stabilizers, for example unepoxidized or epoxidized vegetable oils (for example epoxidized coconut oil, rapeseed oil or soya oil), antifoams, for example silicone oil, preservatives, viscosity regulators, binders and/or tackifiers, fertilizers or other active ingredients for achieving specific effects, for example bactericides, fungicides, nematocides, plant activators, molluscicides or herbicides.

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The compositions according to the invention are prepared in a manner known per se, in the absence of auxiliaries for example by grinding, screening and/or compressing a solid active ingredient and in the presence of at least one auxiliary for example by intimately mixing and/or grinding the active ingredient with the auxiliary (auxiliaries). These processes for the preparation of the compositions and
15 the use of the compounds I for the preparation of these compositions are also a subject of the invention.

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The application methods for the compositions, that is the methods of controlling pests of the abovementioned type, such as spraying, atomizing, dusting, brushing on, dressing, scattering or
20 pouring - which are to be selected to suit the intended aims of the prevailing circumstances - and the use of the compositions for controlling pests of the abovementioned type are other subjects of the invention. Typical rates of concentration are between 0.1 and 1000 ppm, preferably between 0.1 and 500 ppm, of active ingredient. The rate of application per hectare is generally 1 to 2000 g of active ingredient per hectare, in particular 10 to 1000 g/ha, preferably 10 to 600 g/ha, especially 10 to 200 g/
25 ha.

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A preferred method of application in the field of crop protection is application to the foliage of the plants (foliar application), it being possible to select frequency and rate of application to match the danger of infestation with the pest in question. Alternatively, the active ingredient can reach the plants via the
30 root system (systemic action), by drenching the locus of the plants with a liquid composition or by incorporating the active ingredient in solid form into the locus of the plants, for example into the soil, for example in the form of granules (soil application). In the case of paddy rice crops, such granules can be metered into the flooded paddy-field.

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35 The compounds of formula I of the invention and compositions thereof are also suitable for the protection of plant propagation material, for example seeds, such as fruit, tubers or kernels, or nursery plants, against pests of the abovementioned type. The propagation material can be treated with the compound prior to planting, for example seed can be treated prior to sowing. Alternatively, the compound can be applied to seed kernels (coating), either by soaking the kernels in a liquid

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composition or by applying a layer of a solid composition. It is also possible to apply the compositions when the propagation material is planted to the site of application, for example into the seed furrow during drilling. These treatment methods for plant propagation material and the plant propagation material thus treated are further subjects of the invention. Typical treatment rates would depend on the plant and pest/fungi to be controlled and are generally between 1 to 200 grams per 100 kg of seeds, preferably between 5 to 150 grams per 100 kg of seeds, such as between 10 to 100 grams per 100 kg of seeds.

The term seed embraces seeds and plant propagules of all kinds including but not limited to true seeds, seed pieces, suckers, corns, bulbs, fruit, tubers, grains, rhizomes, cuttings, cut shoots and the like and means in a preferred embodiment true seeds.

The present invention also comprises seeds coated or treated with or containing a compound of formula I. The term "coated or treated with and/or containing" generally signifies that the active ingredient is for the most part on the surface of the seed at the time of application, although a greater or lesser part of the ingredient may penetrate into the seed material, depending on the method of application. When the said seed product is (re)planted, it may absorb the active ingredient. In an embodiment, the present invention makes available a plant propagation material adhered thereto with a compound of formula I. Further, it is hereby made available, a composition comprising a plant propagation material treated with a compound of formula I.

Seed treatment comprises all suitable seed treatment techniques known in the art, such as seed dressing, seed coating, seed dusting, seed soaking and seed pelleting. The seed treatment application of the compound formula I can be carried out by any known methods, such as spraying or by dusting the seeds before sowing or during the sowing/planting of the seeds.

The compounds of the invention can be distinguished from other similar compounds by virtue of greater efficacy at low application rates and/or different pest control, which can be verified by the person skilled in the art using the experimental procedures, using lower concentrations if necessary, for example 10 ppm, 5 ppm, 2 ppm, 1 ppm or 0.2 ppm; or lower application rates, such as 300, 200 or 100, mg of AI per m². The greater efficacy can be observed by an increased safety profile (against non-target organisms above and below ground (such as fish, birds and bees), improved physico-chemical properties, or increased biodegradability).

In each aspect and embodiment of the invention, "consisting essentially" and inflections thereof are a preferred embodiment of "comprising" and its inflections, and "consisting of" and inflections thereof are a preferred embodiment of "consisting essentially of" and its inflections.

The disclosure in the present application makes available each and every combination of embodiments disclosed herein.

It should be noted that the disclosure herein in respect of a compound of formula I applies equally in respect of a compound of each of formulae Ia, Ib, and Tables A-1 to A-10 and P.

The compounds of the invention can be distinguished from other similar compounds by virtue of greater efficacy at low application rates and/or different pest control, which can be verified by the person skilled in the art using the experimental procedures, using lower concentrations if necessary, for example 10 ppm, 5 ppm, 2 ppm, 1 ppm or 0.2 ppm; or lower application rates, such as 300, 200 or 100, mg of AI per m². The greater efficacy can be observed by an increased safety profile (against non-target organisms above and below ground (such as fish, birds and bees), improved physico-chemical properties, or increased biodegradability).

Biological Examples:

The Examples which follow serve to illustrate the invention. Certain compounds of the invention can be distinguished from known compounds by virtue of greater efficacy at low application rates, which can be verified by the person skilled in the art using the experimental procedures outlined in the Examples, using lower application rates if necessary, for example 50 ppm, 24 ppm, 12.5 ppm, 6 ppm, 3 ppm, 1.5 ppm, 0.8 ppm or 0.2 ppm.

The Resistance Factor (RF) is the ratio between BP80 (Break Point of at least 80% activity/mortality) of the resistant strain compared to susceptible strain
(note: resistance factor calculation is based on dilution rates indicated above when there is at least 80% control).

Resistant *Plutella xylostella* R1 (Diamond back moth) larvicide L3, feeding/contact

Chinese cabbage plants were sprayed with diluted test solutions in an application chamber. Cut off leaves were placed into petri dishes with wetted filter paper and infested 1 day after application with 10 L3 multi-resistant *Plutella xylostella* larvae having the G4946E resistance mutation. Samples were assessed 4 days after infestation for mortality and growth regulation. Chlorantraniliprole was used as standard and a resistance factor of 146 was obtained for this strain.

Origin:

Plutella xylostella resistant strain R1 originally collected from Taiwan in 2012 that carries the RyR mutation G4946E conferring resistance to diamides. The strain is reared on cabbage plants (*Brassica aleracea*) and selected approximately every two weeks with chlorantraniliprole.

The following compounds, according to the present invention, gave at least 80% control of the resistant strain of *Plutella xylostella* R1 at 200ppm or below: P12, P13, P14, P17, P21, P22, P23, P24, P25, P27, P34, P39, P40, P49, P57, P73, P74, P87, P114, P126, P129, P130.

Table below provides the RF (resistance factors) for the compounds

5

Compound of the invention		Comparative compound	
	RF		RF
P23	16	5-bromo-N-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide	146
P24	16	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide	63
P34	4	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide	63
P39	16	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide	63
P40	4	5-bromo-N-(2-carbamoyl-4-chloro-6-methyl-phenyl)-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide	63

Resistant *Plutella xylostella* R4 (Diamond back moth) larvicide L1, feeding/contact
24-well microtiter plates with artificial diet were treated with aqueous test solutions prepared from

10 10'000 ppm DMSO stock solutions by pipetting. After drying, around 30 *Plutella* eggs were pipetted through a plastic stencil onto a gel blotting paper and the plate was closed with it. The samples were assessed for mortality in comparison to untreated samples 8 days after infestation.

Chlorantraniliprole was used as standard and a resistance factor of 242 was obtained for this strain

15 **Origin:**

Plutella xylostella resistant strain R4 originated in the lab in 2021 from crossing the R1 strain with a lab-reared susceptible *P. xylostella* strain (SUS). R4 can be reared and tested on artificial diet and also carries the RyR mutation G4946E conferring resistance to diamides. The strain is selected approximately every two weeks with chlorantraniliprole.

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The following compounds, according to the present invention, gave at least 80% control of the resistant strain of *Plutella xylostella* R4 at 200ppm or below: P1, P4, P13, P14, P15, P20, P22, P23, P24, P27, P29, P34, P39, P40, P49, P58, P59, P60, P62, P68, P69, P79, P83, P94, P97, P109, P110, P126, P129, P130.

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In Vitro assay method description

Human embryonic kidney cells expressing the *Plutella xylostella* (Diamond back moth) ryanodine receptor, containing the G4946E resistance mutation, are loaded with Fluo-8 No Wash (NW) calcium-sensitive dye which responds by fluorescence to a change in intracellular calcium (e.g. stimulated by activation of ryanodine receptor). Test compounds are added in 10 rates to a 384-well plate containing dye-loaded cells and the fluorescent signal is measured using the Hamamatsu FDSS (Functional Drug Screening system). Dose-response curves are plotted to estimate the EC_{50} . EC_{50} are normalized against an in-assay reference standard (cyanthraniliprole: method 1, chlorantraniliprole: method 2) to address inter-assay variability. The ratio for a given compound is then obtained by the following formula:

- 10 $R_{EC50} = EC_{50} \text{ (compound)} / EC_{50} \text{ (reference standard)}$. Compounds for which the ratio R_{EC50} is inferior or equal to 1 are equally or more active than the standard.

The following compounds, according to the present invention, obtained a ratio $R_{EC50} \leq 1$ (method 1): P39, P40, P41, P45, P48.

- 15 The following compounds, according to the present invention, obtained a ratio $R_{EC50} \leq 1$ (method 2): P8, P13, P14, P15, P20, P22, P24, P27, P29, P30, P34, P49, P58, P59, P62, P68, P69, P70, P79, P82, P83, P109, P110, P120, P126, P129, P136.

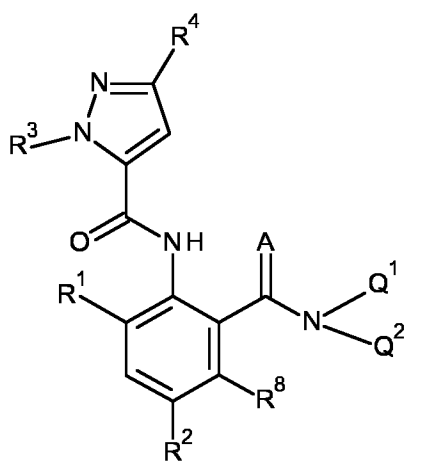
CLAIMS

1. A method for combating and controlling diamide-resistant insects to

(i) reduce damage on a plant, which comprises applying to the insect, to a locus of the insect, or to a plant susceptible to attack by the insect, an effective amount of a compound of formula I; or

(ii) protect plant propagation material, which comprises treating the propagation material or the site, where the propagation material is planted, with an effective amount of a compound of formula I;

wherein the compound of formula I is



wherein

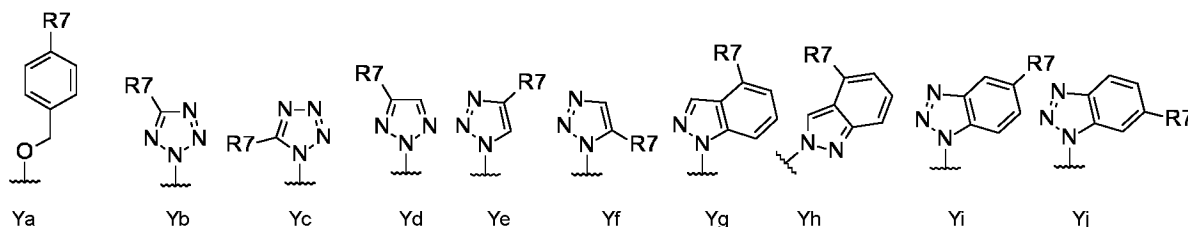
A is O or S;

R¹ is halogen, or C₁-C₆alkyl;

R² is halogen, cyano, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R³ is C₃-C₆cycloalkyl, C₃-C₆cycloalkyl substituted by one to three substituents (selected from halogen, cyano, and C₁-C₃-alkyl), C₄-C₆heterocycloalkyl, C₃-C₆cycloalkenyl, C₂-C₈-alkyl, C₁-C₃-alkoxy-C₂-C₈-alkyl, C₂-C₈haloalkyl, C₅-C₈-alkenyl, or CH₂-Z, where Z is C₃-C₆cycloalkyl, C₃-C₆halocycloalkyl, C₁-C₃-alkoxy-C₁-C₃-alkoxy, C₁-C₃-alkoxy, phenoxy, halophenoxy, or 5-membered heteroaromatic ring, which is unsubstituted or substituted with one to three groups independently selected from R⁶;

R⁴ is hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, C₃-C₆halocycloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, or CH₂-Y, where Y is C₃-C₆cycloalkyl, C₃-C₆halocycloalkyl, benzyloxy, halobenzyloxy, or any one of Ya to Yj;



R⁶ is independently selected from halogen, cyano, C₁-C₃alkyl, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy;

R⁷ is independently selected from halogen, cyano, C₁-C₃alkyl, C₁-C₃haloalkyl, C₃-C₆cycloalkyl, phenyl, and phenyl substituted with one to three independently selected substituents from halogen, cyano, C₁-C₃alkyl, and C₁-C₃haloalkyl;

R⁸ is hydrogen, or halogen;

Q¹ is hydrogen, C₁-C₄alkyl, C₃-C₆cycloalkyl, or C₁-C₃alkyl-C₃-C₆cycloalkyl;

Q² is hydrogen, C₁-C₄alkyl, or C₃-C₆cycloalkyl;

or an agronomically acceptable salt, isomer, enantiomer, tautomer and/or N-oxide of the compound of formula I.

2. The method according to claim 1, wherein the diamide-resistant insect is from the order Lepidoptera.

3. The method according to claim 1 or claim 2, wherein the diamide-resistant insect is resistant to least one compound selected from chlorantraniliprole, cyantraniliprole, cyclantraniliprole, fluchlordiniliprole, tetrachlorantraniliprole, tetraniliprole, flubendiamide and cyhalodiamide.

4. The method according to any one of claims 1 to 3, wherein A is oxygen, R¹ is halogen, or C₁-C₃alkyl; R² is halogen, cyano, C₁-C₃alkyl, or C₁-C₃haloalkyl; R³ as C₃-C₄cycloalkyl, C₃-C₄cycloalkyl substituted by one to three substituents selected from halogen, cyano, and C₁-C₃-alkyl, C₄-C₅heterocycloalkyl, C₃-C₄cycloalkenyl, C₂-C₆-alkyl, C₂-C₆haloalkyl, C₅-C₆-alkenyl, or CH₂-Z, where Z is C₃-C₄cycloalkyl, C₃-C₄halocycloalkyl, C₁-C₃-alkoxy, phenoxy, halophenoxy, or 5-membered heteroaromatic ring, which is unsubstituted or substituted with one to three groups independently selected from R⁶; R⁴ is halogen, C₁-C₃haloalkyl, C₁-C₃alkoxy, C₁-C₃haloalkoxy, or CH₂-Y, where Y is any one of from Ya1, Ya2, Ya3, Ya4 or Ya18; R⁶ is independently selected from chloro, fluoro, methyl, trifluoromethyl, and difluoromethyl; R⁸ is hydrogen; Q¹ is hydrogen, methyl, isopropyl, cyclopropyl, C₁-C₂alkyl-cyclopropyl; and Q² is hydrogen.

5. The method according to any one of claims 1 to 4, wherein the diamide-resistant insect is *Plutella xylostella* (Trocza et al. 2012; Steinbach et al. 2015; Guo et al. 2014), *Tuta absoluta* (Roiditakis et al. 2017; Zimmer et al. 2019), *Spodoptera frugiperda* (Bolzan et al. 2019) *Spodoptera exigua* (Zuo et al. 2020, 2017), or *Chilo suppressalis* (Yao et al. 2017; Yang et al. 2017).

6. The method according to any one of claims 1 to 5, wherein the diamide-resistant insect is in a defined area /field of plants where the ratio of diamide-resistant insects to their corresponding sensitive strains is greater than 1:20 (based on number of insects).

7. The method according to any one of claims 1 to 6, wherein the compound of formula I controls the diamide-resistant insect better compared to the secondary amide analog of the compound of formula I.

8. A compound as defined in claim 1 or claim 4.

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9. The compound according to claim 8, wherein R^1 is methyl, or chlorine; R^2 is chloro, bromo, fluoro, iodo, or cyano; R^3 is cyclopropyl, 4,4-difluorocyclohexyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, ethyl, isopropyl, 1,2-dimethylpropyl, 1,2-dimethylprop-1-enyl, cyclohexen-1-yl, cyclopropylmethyl, methoxymethyl, or isoxazol-4-ylmethyl; R^4 is bromine, chlorine, methoxy, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, or CH_2-Y , where Y is any one of from Y_{a1} , Y_{a2} , Y_{a3} , Y_{a4} or Y_{a18} ; R^8 is hydrogen; Q^1 is hydrogen, methyl, isopropyl, cyclopropylmethyl, or $CH(CH_3)$ -cyclopropyl; Q^2 is hydrogen.

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10. A composition comprising a compound of formula I as defined in either claim 8 or 9, one or more auxiliaries and diluent, and optionally one or more other active ingredient.

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11. A method of combating and controlling insects, acarines, nematodes or molluscs which comprises applying to a pest, to a locus of a pest, or to a plant susceptible to attack by a pest an insecticidally, acaricidally, nematocidally or molluscicidally effective amount of a compound of formula I as defined in either claim 8 or 9, or a composition as defined in claim 10.

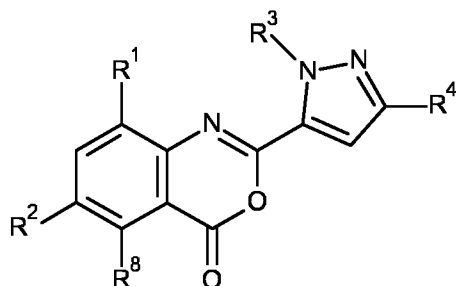
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12. A method for the protection of plant propagation material from the attack by insects, acarines, nematodes or molluscs, which comprises treating the propagation material or the site, where the propagation material is planted, with an effective amount of a compound of formula I as defined in either claim 8 or 9, or a composition as defined in claim 10.

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13. A plant propagation material, such as a seed, comprising, or treated with or adhered thereto, a compound of formula I as defined in either claim 8 or 9, or a composition as defined in claim 10.

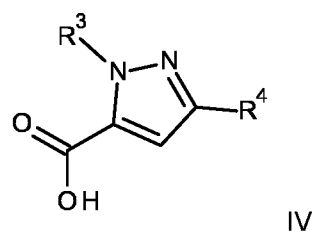
30 14. A compound of formula II



II

wherein R^1 , R^2 , R^3 , R^4 and R^8 are as defined in any one of claims 1, 4, and 9.

15. A compound of formula IV



wherein R^3 , and R^4 are as defined in any one of claims 1, 4, and 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/086893

A. CLASSIFICATION OF SUBJECT MATTER INV. A01N43/56 A01P7/00 C07D231/00 C07D413/14 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A01N A01P C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/015518 A1 (DU PONT [US]; LAHM GEORGE PHILIP [US] ET AL.) 27 February 2003 (2003-02-27) page 1, line 5 - page 4, line 4 claims 1,10,11 Test A-test H page 100 - page 123; table A -----	1-15
A	ANONYMOUS: "Pesticide resistance", INTERNET CITATION, 27 September 2012 (2012-09-27), pages 1-7, XP002715627, Retrieved from the Internet: URL: http://en.wikipedia.org/wiki/Pesticide_resistance [retrieved on 2013-10-29] the whole document ----- --/--	1-15
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
5 March 2024		14/03/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Zanobini, Alessandra

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2023/086893

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS: "Guidelines on Prevention and Management of Pesticide Resistance", INTERNET CITATION, 1 September 2013 (2013-09-01), pages I-II, XP002715628, Retrieved from the Internet: URL: http://www.eppo.int/PPPRODUCTS/resistance/FAO_RMG_Sept_12.pdf [retrieved on 2013-10-29] the whole document -----	1-15
A	RICHARDSON EWAN B ET AL: "Diamide resistance: 10 years of lessons from lepidopteran pests", JOURNAL OF PEST SCIENCE, SPRINGER BERLIN HEIDELBERG, BERLIN/HEIDELBERG, vol. 93, no. 3, 13 March 2020 (2020-03-13), pages 911-928, XP037112213, ISSN: 1612-4758, DOI: 10.1007/S10340-020-01220-Y [retrieved on 2020-03-13] abstract Target-site resistance; page 918 - page 920; table 1 -----	1-15
A	US 2016/205940 A1 (BRANSCOME DEANNA [US] ET AL) 21 July 2016 (2016-07-21) column 3, line 9 - line 62 examples 1-7 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2023/086893

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03015518	A1	27-02-2003	AR 038176 A1 05-01-2005
			BR 0212187 A 05-10-2004
			CA 2454302 A1 27-02-2003
			CN 1541063 A 27-10-2004
			CO 5550396 A2 31-08-2005
			EP 1416796 A1 12-05-2004
			IN 213177 B 25-01-2008
			JP 3689817 B2 31-08-2005
			JP 2004538327 A 24-12-2004
			KR 20040030069 A 08-04-2004
			MX 274785 B 26-03-2010
			MY 142967 A 31-01-2011
			NZ 530442 A 28-07-2006
			PL 208858 B1 30-06-2011
			RU 2262231 C1 20-10-2005
			TW I312274 B 21-07-2009
			TW 200930296 A 16-07-2009
			US 2005075372 A1 07-04-2005
			US 2008275061 A1 06-11-2008
			US 2010160307 A1 24-06-2010
			US 2013028879 A1 31-01-2013
			US 2014140973 A1 22-05-2014
			WO 03015518 A1 27-02-2003
			ZA 200400034 B 26-10-2005
US 2016205940	A1	21-07-2016	AU 2016206535 A1 27-07-2017
			BR 112017015054 A2 27-03-2018
			CO 2017007033 A2 10-10-2017
			EP 3244736 A1 22-11-2017
			ES 2792994 T3 12-11-2020
			JP 6772148 B2 21-10-2020
			JP 2018502134 A 25-01-2018
			US 2016205940 A1 21-07-2016
			WO 2016115466 A1 21-07-2016